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# Epidemiology, evidence-based care, and outcomes in spinal cord injury


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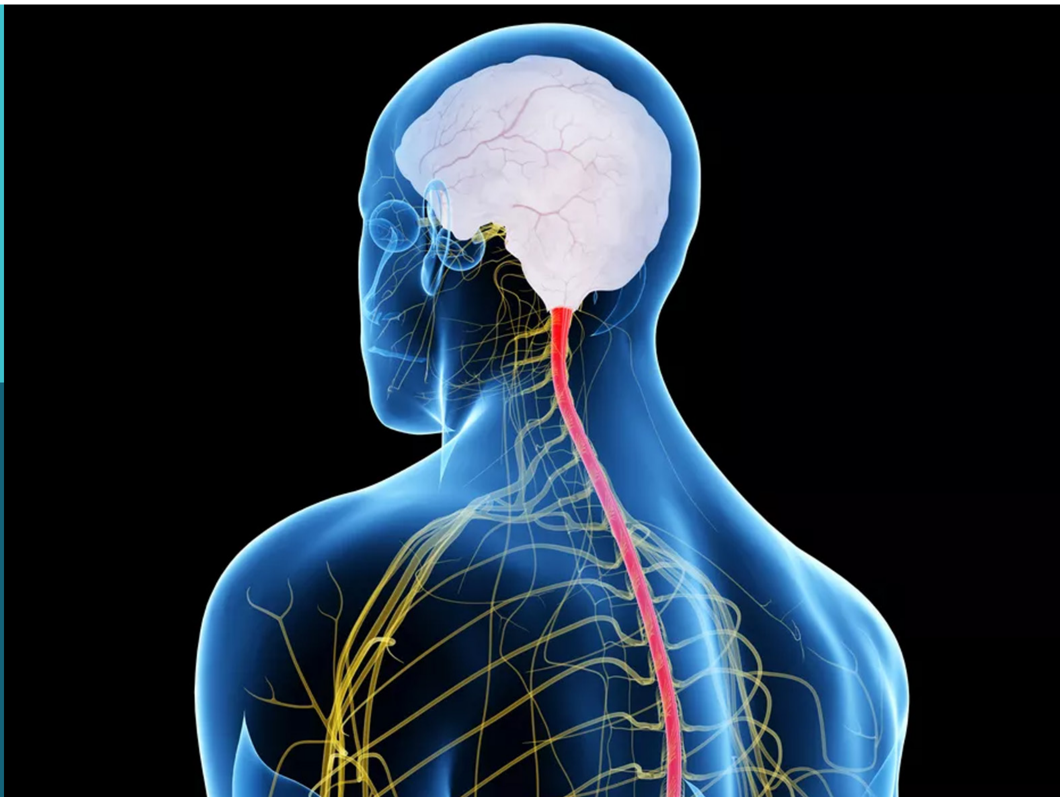

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# Epidemiology, evidence-based care, and outcomes in spinal cord injury

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# Editorial: Epidemiology, evidence-based care, and outcomes in spinal cord injury

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Editorial on the Research Topic
Epidemiology, evidence-based care, and outcomes in spinal cord injury

This edition of Frontiers in Neurology is dedicated to sharing progress in the epidemiology, evidence-based practice, and outcomes of spinal cord injury (SCI). The collection is divided into two parts: the first part describes the epidemiology of SCI, and the second part explores evidence-based approaches to care and patient outcomes. The increasing use of artificial intelligence and analytical methods such as machine learning, is also highlighted.

Spinal cord injury is a life altering condition that has a profound effect on an individual's motor, sensory and autonomic functions which impacts their ability to participate in society and can decrease their quality of life. With an aging population, there is a need to understand the epidemiology and economic implications as we plan for the future. Spinal cord injury interventions must be evaluated for effectiveness – not just economically, but to measure their impact on outcomes that are important to individuals living with SCI (such as neurology, function, mortality, and quality of life). Effective interventions and targeted implementation are required to ensure that individuals and the healthcare system benefit.

## Epidemiology of SCI

The first part of this Focus Issue includes six articles that describe the epidemiology of SCI in both pediatric and adult populations. There is also a article on the burden of Motor Neuron Disease.

In the first article by Thorogood et al. the incidence and prevalence of traumatic SCI were assessed for the Canadian population using ICD-10 codes. The reported incidence in 2019 was 1,199 cases (32/million), and the prevalence was 30,239. The study introduced a standardized method for calculating the incidence and prevalence of traumatic SCI in Canada through national-level health administrative data. Despite acknowledging the conservative nature of the estimates due to data limitations, the study represents a substantial Canadian sample over a 15-year period, providing insights into national trends.

Hu et al. undertook a systematic review and meta-analysis of epidemiology of traumatic SCI (from 1978 to 2022), including a total of 59 reports from 23 provinces in China. The random pooled incidence of traumatic SCI in China was reported as 65.15 per million population with a range of 6.7 to 569.7 per million population in their meta-analysis.

The co-occurrence of traumatic brain injury (TBI) and SCI, often termed "dual diagnosis," presents clinical and rehabilitation complexities. Gober et al. conducted a study with the aim of assessing the point prevalence of comorbid TBI among children hospitalized with SCI between 2016 and 2018 from U.S. hospitals participating in the Kids' Inpatient Database. Their findings revealed that 38.8% of children admitted with SCI also had a comorbid TBI. The study concluded that comorbid TBI is prevalent among United States children experiencing SCI, emphasizing the need for further research to better understand the impact of dual diagnosis on mortality, quality of life, and functional outcomes.

Jiang et al. conducted a study on the epidemiological characteristics of traumatic SCI in China, providing insights into the incidence, prevalence, and external causes. They determined that the point prevalence of traumatic SCI, standardized to the China census population of 2010, was 569.7 per 1,000,000 in the general population, 753.6 per 1,000,000 among men, and 387.7 per 1,000,000 among women. Additionally, the reported annual incidence of traumatic SCI was 49.8 per 1,000,000 in the overall population, 63.2 per 1,000,000 among men, and 36.9 per 1,000,000 among women. The study estimated a total of 759,302 prevalent cases of traumatic SCI and identified 66,374 new traumatic SCI cases annually in China for 2010.

Very little is known about the epidemiology of pediatric SCI. The study published by Crispo et al. is therefore an important contribution to fill this knowledge gap, reporting the annual rate of pediatric emergency department visits for traumatic SCI using the Healthcare Cost and Utilization Project -Nationwide Emergency Department Sample. The study found that the annual emergency visit rate has remained stable between 2016 and 2020, with ∼2,200 new all-cause pediatric emergency department visits with a diagnosis of traumatic SCI annually and that cervical injuries were most prevalent. Their findings also suggested that the proportion of sports-related traumatic SCI emergency department visits increased recently.

Park et al. assessed the global burden of MND from 1990 to 2019 as part of the Global Burden of Disease, Injuries, and Risk Factor study. They included various MNDs, including amyotrophic lateral sclerosis, progressive muscular atrophy, primary lateral sclerosis, pseudobulbar palsy, spinal muscular atrophy, and hereditary spastic paraplegia. The estimates indicated ∼63,700 incident cases annually and 268,673 prevalent cases of MND worldwide. In 2019, MND resulted in 39,081 deaths globally. The age-standardized rates for MND incidence, prevalence, and mortality in 2019 were calculated at 0.79 per 100,000 people, 3.37 per 100,000 people, and 0.48 per 100,000 people, respectively.

## Evidence-based care and outcomes following SCI

The second section of this Focus Issue includes articles on evidence-based care and outcomes following SCI. It has been reported that it takes an average of 17 years for research evidence to be translated into practice, which highlights the importance of timely knowledge translation (1, 2).

Previously, several articles have been published (3–5) to develop a clinical algorithm for use in the acute care setting to predict the probability that an individual will be able to walk at 1-year post injury. Hakimjavadi et al. described their efforts in launching a website (https://www.ambulation.ca/) to make an ambulation tool accessible to the public, and actively monitor end-user feedback to enhance its usability for the future. This tool serves as a valuable step in bridging the gap between knowledge and impact for clinicians, persons living with SCI and families and can serve as a model for other clinical algorithms.

The design and analysis of clinical trial data is challenging due to the heterogeneity of the injury (6). A solution to address this challenge is to identify similar subgroups based on patient demographics and baseline injury characteristics. Basiratzadeh et al. applied machine learning methodology to establish a more homogeneous group, illustrating how these patient subgroups could effectively discern differences in outcomes.

Furthermore, SCI studies often have small sample sizes due to the low incidence, resulting in under-powered results that can lead to inconclusive findings. This challenge can be addressed by optimizing the study design. Fallah, Noonan, Waheed et al. highlight the importance of stratifying or using an appropriate control group to obtain accurate conclusions about a treatment efficacy (in randomized controlled trial or observational studies), particularly when dealing with small sample sizes. This study demonstrates the importance of recording the baseline neurological examination date and time and ensuring the control and intervention groups are well-matched.

The Standing and Walking Assessment Tool (SWAT) serves as a standardized objective staging tool used in Canada to assess lower limb function in individuals with traumatic SCI. The use of SWAT was investigated in individuals with non-traumatic SCI or disease by Alavinia et al.. Specifically, the research aimed to evaluate the convergent validity of SWAT for inpatients with non-traumatic SCI. The study concluded that SWAT demonstrates sufficient evidence for convergent validity and responsiveness in persons with non-traumatic SCI or disease, making it a valuable tool for describing standing and walking recovery.

Physical activity among individuals with SCI is often decreased following injury. Olsen et al. assessed the intervention ProACTIVE SCI, evaluating its reach, effectiveness, adoption, implementation, and maintenance. This intervention led by physiotherapists and SCI peer coaches during the rehabilitation-to-community transition, successfully reached the majority of patients and has the potential to increase physical activity following SCI.

As the population ages, multi-morbidity is becoming a growing health concern, and individuals with SCI often have pre-existing comorbidities prior to their injury. The health conditions (comorbidities and secondary complications following SCI) can lead to increased healthcare utilization and diminished health outcomes. Fallah, Hong et al. utilized network models, a form of machine learning, on the Canadian SCI Community Survey dataset (7). They adapted the original 30 item Multi-morbidity Index (MMI) and created a concise version of the index, called the MMI-25. Their results demonstrated that multi-morbidity in persons with SCI is associated with higher healthcare utilization, as well as lower levels of physical and mental health and quality of life.

The global prevalence of people with disabilities is estimated to surpass 1 billion (2017), with over half residing in low- and middle-income nations (8). Cui et al. conducted a review encompassing the epidemiological features of stroke and SCI. They described the therapeutic outcomes and recent advancements in the utilization of both conventional and innovative orthotic devices for both stroke and SCI.

Finally, Fallah, Noonan, Thorogood et al. explored the association between body mass index (BMI) measured after acute traumatic SCI and the impact on mortality. Their study yielded two noteworthy findings. First, a higher BMI was identified as a mild protective factor linked to lower mortality in individuals with SCI, aligning with a modest "obesity paradox" that has been reported in health conditions such as stroke (9). Conversely, being underweight emerged as a significant risk factor for death during acute care and up to 7 years post-SCI. Second, the study did not use the World Health Organization criteria designed for able-bodied individuals, since it was found to have limitations for persons with SCI. The researchers employed a data-driven approach to define BMI ranges associated with distinct mortality risks following SCI. Future work will include understanding the underlying mechanisms and validating these results in other studies.

## Author contributions

NF: Writing—original draft, Writing—review & editing. VN: Writing—original draft, Writing—review & editing. LS: Writing—review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



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# Prevalence, Incidence, and External Causes of Traumatic Spinal Cord Injury in China: A Nationally Representative Cross-Sectional Survey

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**Background and Purpose:** The epidemiological characteristics of traumatic spinal cord injury (TSCI) in China are unclear. Thus, we aimed to study prevalence, incidence, and external causes of TSCI in China nationwide.

**Methods:** In 2013, we conducted a nationally representative, door-to-door epidemiological survey on TSCI in China using a complex, multistage, probability sampling design.

**Results:** In China, the point prevalence of TSCI standardized to the China census population 2010 was 569.7 (95% CI: 514.2–630.4) per 1,000,000 in the population, 753.6 (95% CI: 663.3–854.3) per 1,000,000 among men, and 387.7 (95% CI: 324.8–461.1) per 1,000,000 among women. The incidence of TSCI standardized to the China census population 2010 was 49.8 (95% CI: 34.4–70.7) per 1,000,000 per year in the population, 63.2 (95% CI: 38.9–98.5) per 1,000,000 among men, and 36.9 (95% CI: 19.5–65.9) per 1,000,000 among women. Among the 415 TSCI events in 394 prevalent cases, the top three injury causes were falls (55.2%), motor vehicle collisions (MVCs) (26.5%), and strike injuries (10.1%), while other injury causes including gunshot and explosion accounted for 8.2%. Among the 394 prevalent cases, the mean age of patients at the time of injury was 43.7 ± 17.1 years; the male-to-female ratio was 1.86:1.

**Conclusion:** It is estimated that there are 759,302 prevalent patients with TSCI in total and 66,374 new TSCI cases annually in China. Falls and MVCs are still 2 major external causes for TSCI in China.

**Keywords: prevalence, incidence, external causes, traumatic spinal cord injury, China**

## INTRODUCTION

Traumatic spinal cord injury (TSCI) once caused may lead to different degrees of paralysis, loss of sensory, and dysfunction of bladder or bowel. As one of the most devastating kinds of injury, TSCI not only affect one's health, but also generates a huge economic burden on the family and society. Since there is no curative hope for permanent spinal cord injury, prevention of TSCI is particular important (1). In previous studies, the global incidence of TSCI varied from 2.3 (2) to 150.6 (3) cases per million inhabitants per year, whereas the global prevalence varied from 236.0 (2, 4) to 1,800.0 (2) per million inhabitants. In contrast, due to the lack of national level monitoring data, the epidemiological data of TSCI in China are relatively scarce compared with other countries and regions (1, 2, 4). Previous studies are mainly confined to the incidence of TSCI sporadically in Beijing (5), Tianjin (6), Xi'an (7), and Taiwan (3, 8–10) and more focus is on clinical epidemiological investigation on TSCI in Beijing (11), Tianjin (12), Chongqing (13), Guangdong (14–16), Xi'an (7), and Heilongjiang (17). However, so far, not only there is no national representative data on the incidence of TSCI in China nationwide, but also little information is available with respect to the prevalence of TSCI in China. Therefore, we adopted a multistage, complex sampling method to investigate the prevalence and incidence of TSCI in China nationwide, based on the national epidemiological survey of cerebrovascular diseases in China (18, 19).

## METHODS

### Sampling Design, Quality Assurance, and Participants

The complex, multistage probability sampling design used to define the sampling frame and the participants has been described in detail in previous studies (18–20) (**Figure 1**). In brief, 2010 Chinese population census data and probability proportionate to population size (PPS) sampling were used to select 64 urban and 93 rural areas from 31 provinces of China [i.e., 157 disease surveillance points (DSPs) or survey sites shown in **Figure 2**]. In the first stage of sampling, PPS sampling was again used to select "neighborhoods" (Jiedao) within cities or "townships" (Xiang) in rural areas; the probability of selection was based on the population size of the neighborhood or township. In the second stage of sampling, one or more neighborhood committees (administrative villages) with a total population of at least 4,500 residents (∼1,500 households) were selected from the sampled neighborhoods (townships) at each site using random cluster sampling.

Detailed quality assurance methods have been described in previous studies (18–20). In brief, quality control was performed in all the phases of the survey and survey preparations, field work, and data processing were all supervised. Trained investigators visited these participants at least 3 times on different dates to ensure the response. Two of 157 DSPs were excluded from the final data analysis due to not meeting the requirements of the study design.

The participants included people who had lived in the county (or district) for at least 6 months in the past year. In this retrospective epidemiological survey, TSCI point prevalence was defined as the rate of patients with TSCI among the survival people prior to midnight on August 31, 2013 from the sampled families. TSCI incidence was defined as the rate of patients with TSCI occurred within a year among the survival population prior to midnight on August 31, 2012 from the sampled families. For prevalence and incidence analyses in this survey, 596,536 and 595,711 people from the 178,059 families were finally used (see **Figure 3**), respectively, with a response rate of about 81% (19).

### Diagnostic Criteria and Case Ascertainment

In this epidemiological study, a TSCI was defined as the occurrence of an acute lesion on the neural elements in the spinal canal (spinal cord and cauda equina), resulting in temporary or permanent sensory deficits, motor deficits, or bladder/bowel dysfunction (6). Other non-traumatic causes such as degenerative spinal change and surgical damage were excluded. From September 1 to December 31, 2013, the trained Centers for Disease Control and Prevention (CDC) investigators visited each eligible household, collected the signed informed consent forms of participants, and administered a structured questionnaire for TSCI data. The information on demographic characteristics including age, gender, education, occupation, and medical history of the individuals and data on times and dates, sites, symptoms and signs, external cause, and medical treatments of TSCI were also obtained and reviewed. Self-reported history of traumatic brain or spinal cord injury was further reviewed by our neurological reviewers. The validated verbal autopsy technique involving household members of people who died within the 12 months preceding the survey was used to identify TSCI as a possible cause of death.

### Statistical Analysis

In contrast to higher crude incidence in men than that in women in this survey, higher weighted incidence in women than that in men disapproved of using weighting during the analysis, although weighting is usually used to account for the complex sampling designs.

Sociodemographic characteristics of the study sample were categorized and presented as frequency and percent. Crude prevalence and incidence of TSCI were calculated by subgroups of age (0–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, and ≥ 75 years), sex (men/women), place of residence (urban/rural), and geographic location (eastern/central/western China). For comparison, the prevalence and incidence of overall age groups were directly standardized to the age distribution of the WHO world standard population and the China census population 2010, respectively. The 95% CIs for all the crude and age-standardized rates were also calculated. Prevalent and incident numbers of TISC in China nationwide were estimated based on the age-standardized rates of the China census population 2010. Furthermore, a Poisson regression analysis was used to compare the rate ratio of the prevalence and incidence of TSCI among different subgroups of population in China, 2013. Age group, sex,

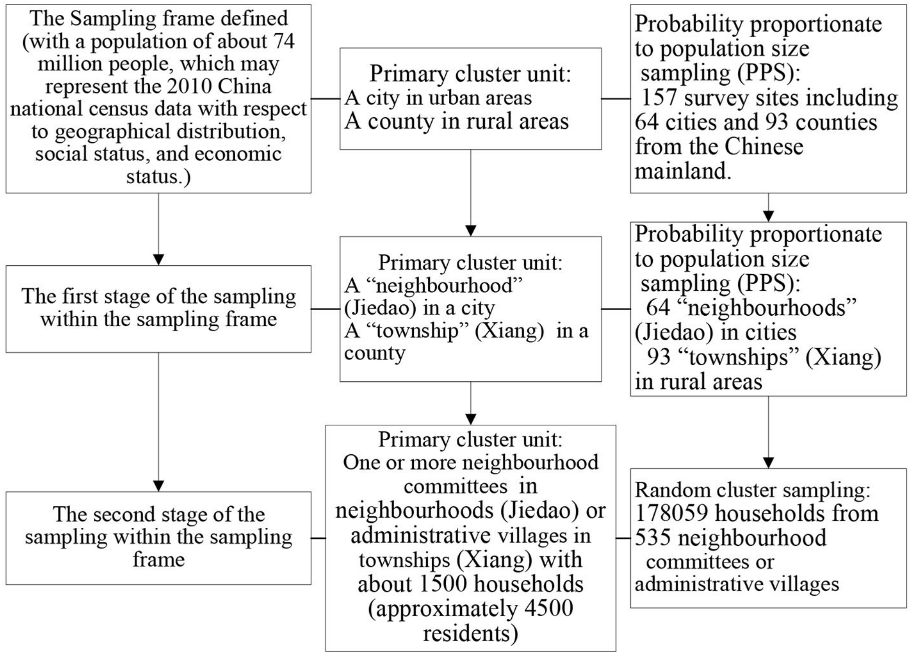


**FIGURE 1 |** Sampling flowchart.

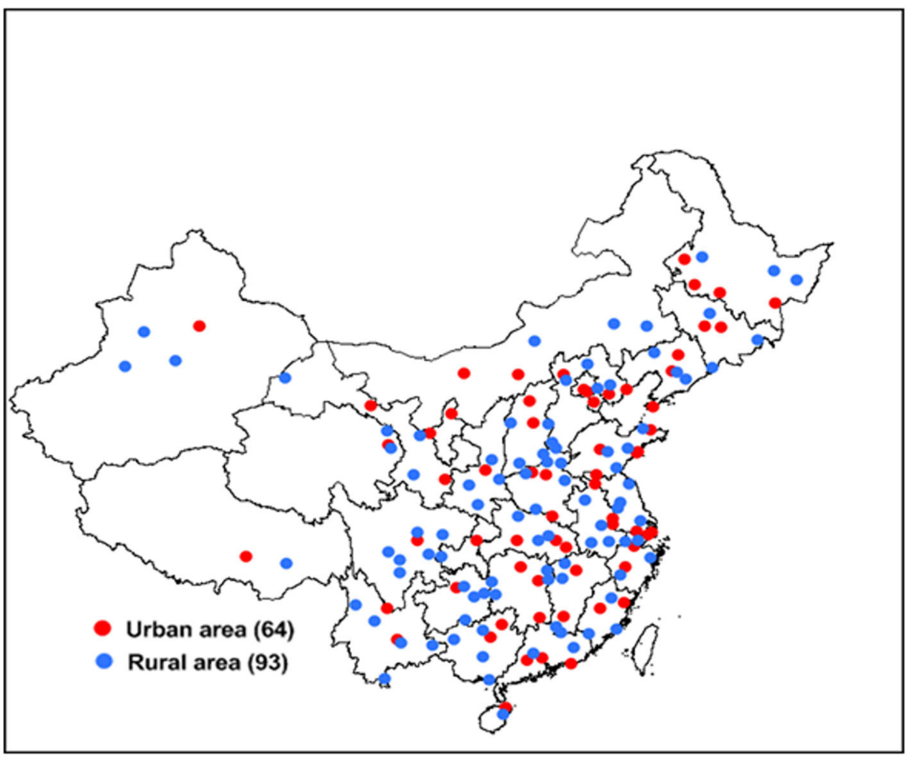


**FIGURE 2 |** Distribution of survey sites in 31 provinces of China.

place of residence, and geographic location were adjusted each other in all the Poisson regression analyses. The prognosis for TSCI in the population was estimated based on the prevalence and incidence of TSCI in the population, which was in fact a rate ratio of prevalence to incidence in the population different from the prognosis estimates in a cohort (19). Given that the number

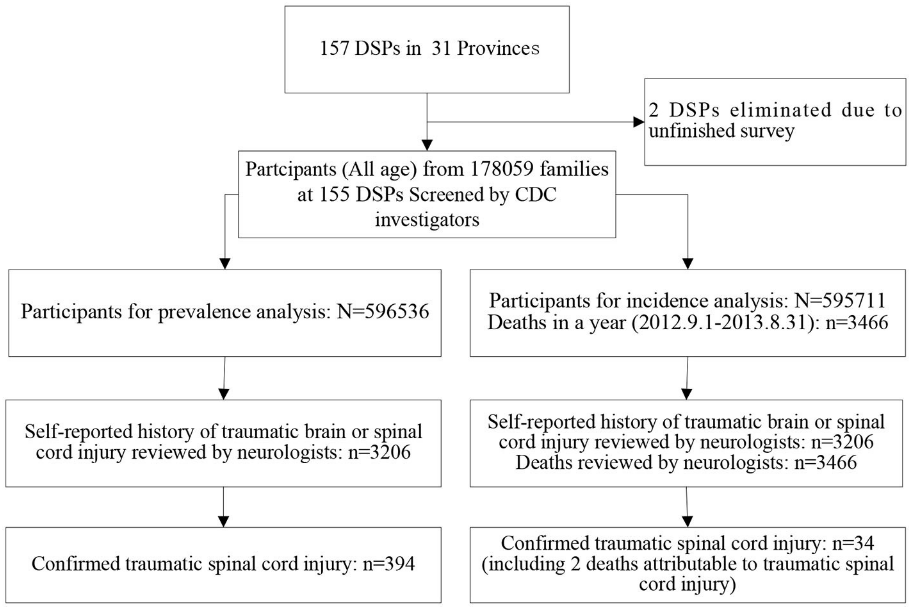


**FIGURE 3 |** Flowchart for traumatic spinal cord injury (TSCI) case ascertainment. DSPs, disease surveillance points; CDC, Centers for Disease Control and Prevention.

of incident cases was too small, the external causes and risky occupations for TSCI are also analyzed by prevalent cases. The comparison of rates between the different groups was performed by the chi-squared test. All of these statistical calculations on complex samples were performed using the SPSS version 15.0 software (SPSS Incorporation, Chicago, Illinois, USA). $p < 0.05$ was considered as statistically significant.

## RESULTS

The characteristics of the study sample from the national epidemiological survey of TSCI in China, 2013 are shown in **Table 1**. Among the 596,536 people evaluated for the prevalence analysis, 394 survival TSCI cases were identified on August 31, 2013 (see **Table 2**, **Figure 3**, and **Supplementary Table 1**). Among the 394 cases, 66.7% were confirmed with CT/MRI imaging; the mean age of patients at the time of injury was 43.7 ± 17.1 years; the male-to-female ratio was 1.86:1; there was 299 isolated TSCI events and 116 concomitant TSCI and traumatic brain injury (TBI) in total. Among the 595,711 people assessed for the incidence analysis, 34 TSCI cases (including 2 deaths) were found between September 1, 2012 and August 31, 2013 (see **Table 3**; **Figure 3**). Among the 34 cases, the mean age of patients at the time of injury was 56.0 ± 17.0 years; the male-to-female ratio was 1.62:1.

### Prevalence of TSCI

In China, the point prevalence of TSCI standardized to the China census population 2010 was 569.7 (95% CI: 514.2–630.4) per 1,000,000 in the population, 753.6 (95% CI: 663.3–854.3) per 1,000,000 among men, and 387.7 (95% CI: 324.8–461.1) per 1,000,000 among women; 567.7 (95% CI: 489.1–658.1) per 1,000,000 among urban residents and 541.3 (95% CI: 466.3–625.8) per 1,000,000 among rural residents; 335.4 (95% CI: 267.0–420.1) per 1,000,000 among eastern Chinese, 627.8 (95% CI: 536.6–732.5) per 1,000,000 among central Chinese, and 741.6 (95% CI: 616.4–886.1) per 1,000,000 among western Chinese (see **Table 2**; **Figure 4**). According to the above-estimated prevalence, there were an estimated 759,302 (95% CI: 685,331–840,204) patients with TSCI in the population with 514,203 (95% CI: 452,589–582,914) male patients with TSCI and 252,192 (95% CI: 211,277–299,937) female patients with TSCI in China.

After adjusting for other factors, the prevalence of TSCI increased with age (see **Table 4**). The prevalence of TSCI among men was significantly higher than that among women (rate ratio: 1.904; 95% CI: 1.548–2.342; see **Table 4**). The prevalence of TSCI among eastern Chinese was significantly lower than that among western Chinese (rate ratio: 0.462; 95% CI: 0.352–0.606; see **Table 4**). No difference in prevalence of TSCI was found between the urban and rural residents (see **Table 4**).

### Incidence of TSCI

In China, the incidence of TSCI standardized to the China census population 2010 was 49.8 (95% CI: 34.4–70.7) per 1,000,000 per year in the population, 63.2 (95% CI: 38.9–98.5) per 1,000,000 among men, and 36.9 (95% CI: 19.5–65.9) per 1,000,000 among women; 29.4 (95% CI: 14.0–58.1) per 1,000,000 among urban residents and 69.2 (95% CI: 44.2–104.3) per 1,000,000 among rural residents; 40.4 (95% CI: 18.9–80.3) per 1,000,000 among eastern Chinese, 52.0 (95% CI: 28.2–90.4) per 1,000,000 among central Chinese, and 58.8 (95% CI: 28.1–110.1) per 1,000,000 among western Chinese (see **Table 3**; **Figure 4**). According to the above-estimated

**TABLE 1 |** Characteristics of the study sample of the national epidemiological survey of traumatic spinal cord injury (TSCI) in China, 2013.

| | Prevalence | | Incidence | |
|---|---|---|---|---|
| **Characteristics** | **No.** | **%** | **No.** | **%** |
| **Age group** | | | | |
| 0∼ | 83,028 | 13.9% | 85,462 | 14.3% |
| 15∼ | 77,354 | 13.0% | 81,378 | 13.7% |
| 25∼ | 91,435 | 15.3% | 89,597 | 15.0% |
| 35∼ | 99,582 | 16.7% | 102,999 | 17.3% |
| 45∼ | 93,763 | 15.7% | 90,667 | 15.2% |
| 55∼ | 80,155 | 13.4% | 78,075 | 13.1% |
| 65∼ | 44,840 | 7.5% | 43,245 | 7.3% |
| 75∼ | 26,379 | 4.4% | 24,288 | 4.1% |
| **Sex** | | | | |
| Men | 30,0192 | 50.3% | 299,725 | 50.3% |
| Women | 296,344 | 49.7% | 295,986 | 49.7% |
| **Education** | | | | |
| Primary school or preschool | 248,916 | 41.7% | 245,192 | 41.1% |
| Middle school | 294,209 | 49.3% | 294,193 | 49.4% |
| College and higher | 51,730 | 8.7% | 51,721 | 8.7% |
| Unknown | 1,681 | 0.3% | 4,605 | 0.8% |
| **Occupation** | | | | |
| Student | 108,978 | 18.3% | 105,510 | 17.7% |
| Worker | 45,021 | 7.5% | 45,004 | 7.6% |
| Farmer or farmer worker | 271,068 | 45.4% | 270,916 | 45.5% |
| Employee | 46,676 | 7.8% | 46,674 | 7.8% |
| Self-employed | 52,518 | 8.8% | 52,516 | 8.8% |
| Retiree or homemaker | 66,169 | 11.1% | 66,145 | 11.1% |
| other | 4,439 | 0.7% | 4,356 | 0.7% |
| Unknown | 1,667 | 0.3% | 4,590 | 0.8% |
| **Place of residence** | | | | |
| Urban | 282,945 | 47.4% | 282,169 | 47.4% |
| Rural | 313,591 | 52.6% | 313,542 | 52.6% |
| **Geographic location** | | | | |
| Eastern China | 201,354 | 33.8% | 201,196 | 33.8% |
| Central China | 239,735 | 40.2% | 239,288 | 40.2% |
| Western China | 155,447 | 26.1% | 155,227 | 26.1% |

incidence, there were an estimated 66,374 (95% CI: 45,849–94,230) patients with TSCI annually in the population, with 43,123 (95% CI: 26,543–67,209) male patients with TSCI and 24,003 (95% CI: 12,684–42,867) female patients with TSCI in China.

After adjusting for other factors, the incidence of TSCI increased with age (see **Table 4**). The incidence of TSCI among urban residents was significantly lower than that among rural residents (rate ratio: 0.438; 95% CI: 0.208–0.921; see **Table 4**). No difference in incidence of TSCI was found between different subgroups of sex and geographic location (see **Table 4**).

## Prognosis for TSCI in the Population

In China, the average prognosis for TSCI in the population was estimated to be 11.57 (95% CI: 8.15–16.43) years based on estimates of point prevalence in a lifetime and the annual incidence of TSCI.

## External Cause and Risky Occupation for TSCI

Among the 415 TSCI events, the top three injury causes were falls (55.2%), motor vehicle collisions (MVCs) (26.5%), and strike injuries (10.1%), while other injury causes including gunshot and explosion accounted for 8.2%. The consistent injury causes (i.e., 64.7% for falls, 23.5% for MVCs, and 11.8% for strike injuries) were found in the 34 incident cases of TSCI. No difference in external cause was found between the 2 groups $\chi^2 = 3.484$; $p = 0.323$.

Among the 394 prevalent cases, the top four injury occupations were farmer or migrant workers from the villages (61.2%), retiree or homemaker (19.5%), the self-employed (9.9%), and worker (4.6%), while other classifications of occupation including employee or students accounted for 4.8%. The consistent risky occupation was found in the 34 incident cases of TSCI (data not shown). No difference in occupational risk was found between the 2 groups ($\chi^2 = 4.990$; $p = 0.288$). Among the 394 cases, primary school, middle school, college and higher, and preschool accounted for 49.2, 46.2, 3.3, and 1.3%, respectively.

# DISCUSSION

## Prevalence

**Supplementary Table 2** lists the study design, case definition, and findings of previous prevalence surveys of TSCI in different regions or countries (21–31). The prevalence of SCI was highest in the USA (1,800 per million population) (2) and lowest in Kashmir, India (236 per million population) (22). Obviously, different study designs and definitions have a great impact on the study results. According to the design, there are roughly two types: one is the cross-sectional point prevalence survey (21, 22, 24–26); the other is based on the estimation of incidence rate and duration of TSCI or other more complex estimation (23, 27–31). Except for individual model estimate (23), it seems that the prevalence estimated by models (27–31) is generally higher than the point prevalence in the cross-sectional surveys (21, 22, 24–26). In this survey, the prevalence of TSCI is higher than that in other cross-sectional surveys (21, 22, 24–26) and estimated by a model in a previous study (23), but lower than that estimated by a model in most studies (27–31) (**Figure 5**). In this survey, the average prognosis for TSCI in the population was estimated to be 11.57 years based on the point prevalence and annual incidence of TSCI. Obviously, the average prognosis in China was lower than the average life durations of about 20 years (23) and 40.35 years (27) adopted for prevalence estimations in previous studies. It is worth noting that most previous studies did not give a clear definition of TSCI (21–23, 27–31). Moreover, the ICD codes for TSCI given by two previous studies are also different (24, 26). Indeed, the prevalence of TSCI in this survey was higher than that in a previous study (25), although same design and definition of TSCI adopted in both the studies.

**TABLE 2 |** Prevalence* of TSCI in China, 2013 (1/1,000,000 person × life time).

| | Men | | | | Women | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age group | Population | Cases | Prevalence* | 95% CI* | Population | Cases | Prevalence* | 95% CI* | Prevalence* | 95% CI* |
| 0∼ | 443,64 | 1 | 22.5 | 0.6–125.6 | 38,664 | 1 | 25.9 | 0.7–144.1 | 24.1 | 2.9–87.0 |
| 15∼ | 39,589 | 6 | 151.6 | 55.6–329.9 | 37,765 | 2 | 53.0 | 6.4–191.3 | 103.4 | 44.6–203.8 |
| 25∼ | 45,020 | 21 | 466.5 | 288.7–713.0 | 46,415 | 9 | 193.9 | 88.7–368.1 | 328.1 | 221.4–468.4 |
| 35∼ | 50,759 | 37 | 728.9 | 513.2–1,004.7 | 48,823 | 15 | 307.2 | 172.0–506.7 | 522.2 | 390.0–684.8 |
| 45∼ | 46,879 | 62 | 1,322.6 | 1,014.0–1,695.5 | 46,884 | 28 | 597.2 | 396.8–863.1 | 959.9 | 771.8–1,179.8 |
| 55∼ | 39,366 | 62 | 1,575.0 | 1,207.5–2,019.0 | 40,789 | 42 | 1,029.7 | 742.1–1,391.8 | 1,297.5 | 1,060.1–1,572.1 |
| 65∼ | 21,902 | 49 | 2,237.2 | 1,655.1–2,957.7 | 22,938 | 23 | 1,002.7 | 635.6–1,504.5 | 1,605.7 | 1,256.4–2,022.1 |
| 75∼ | 12,313 | 18 | 1,461.9 | 866.4–2,310.4 | 14,066 | 18 | 1,279.7 | 758.4–2,022.4 | 1,364.7 | 955.8–1,889.4 |
| Total | 300,192 | 256 | 852.8 | 751.5–963.9 | 296,344 | 138 | 465.7 | 391.2–550.2 | 660.5 | 596.9–729.0 |
| Age-adjusted rates# | – | – | 645.4 | 567.4–735.1 | – | – | 332.2 | 277.7–400.0 | 487.9 | 439.9–541.9 |
| Age-adjusted rates$ | – | – | 753.6 | 663.3–854.3 | – | – | 387.7 | 324.8–461.1 | 569.7 | 514.2–630.4 |

*A point prevalence in a life time, on August 31, 2013. #Age standardized to the WHO world standard population. $Age standardized to the China census population 2010.*

**TABLE 3 |** Incidence* of TSCI in China, 2013 (1/1,000,000 person × years).

| | Men | | | | Women | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age group | Population | Cases | Incidence* | 95% CI* | Population | Cases | Incidence* | 95% CI* | Incidence* | 95% CI* |
| 0∼ | 45,548 | 0 | – | – | 39,914 | 1 | 25.1 | 0.6–139.6 | 11.7 | 0.3–65.2 |
| 15∼ | 41,209 | 1 | 24.3 | 0.6–135.2 | 40,169 | 0 | – | – | 12.3 | 0.3–68.5 |
| 25∼ | 44,351 | 1 | 22.6 | 0.6–125.6 | 45,246 | 1 | 22.1 | 0.6–123.1 | 22.3 | 2.7–80.6 |
| 35∼ | 52,561 | 3 | 57.1 | 11.8–166.8 | 50,438 | 1 | 19.8 | 0.5–110.5 | 38.8 | 10.6–99.4 |
| 45∼ | 45,289 | 4 | 88.3 | 24.1–226.1 | 45,378 | 0 | – | – | 44.1 | 12.0–113.0 |
| 55∼ | 38,189 | 7 | 183.3 | 73.7–377.7 | 39,886 | 5 | 125.4 | 40.7–292.5 | 153.7 | 79.4–268.5 |
| 65∼ | 21,283 | 3 | 141.0 | 29.1–411.9 | 21,962 | 4 | 182.1 | 49.6–466.3 | 161.9 | 65.1–333.5 |
| 75∼ | 11,295 | 2 | 177.1 | 21.4–639.6 | 12,993 | 1 | 77.0 | 1.9–428.8 | 123.5 | 25.5–361.0 |
| Total | 299,725 | 21 | 70.1 | 43.4–107.1 | 295,986 | 13 | 43.9 | 23.4–75.1 | 57.1 | 39.5–79.6 |
| Age-adjusted rates# | – | – | 53.3 | 32.7–87.5 | – | – | 34.9 | 17.3–69.1 | 43.8 | 29.8–64.7 |
| Age-adjusted rates$ | – | – | 63.2 | 38.9–98.5 | – | – | 36.9 | 19.5–65.9 | 49.8 | 34.4–70.7 |

*Annual incidence between September 1, 2012 and August 31, 2013. #Age standardized to the WHO world standard population. $Age standardized to the China census population 2010.*

## Incidence

**Supplementary Table 3** shows that the incidence of TSCI was significantly different across different countries, regions, and cities (3, 5–10, 21, 26, 32–48). This could be a reflection of actual differences in incidence or a result of differences in case ascertainment. For example, some studies have used information from death certificates, coroners, or the department of legal medicine to include TSCI victims who have died at the scene of the accident or during transport to acute care centers (32, 33, 40, 45). Other studies have excluded these patients from their estimates. In addition, identification of patients with acute SCI was done in different ways across studies. Some used ICD-9 or ICD-10 codes to detect relevant patients (3, 6, 7, 10, 26, 32–34, 40, 41, 44, 45), whereas others used a simple clinical definition, surveys, or questionnaires (5, 8, 10, 21, 35–39, 41, 43, 46–48). The low incidence of SCI from some countries may not be accurate, since data may be aggregated from hospitals or rehabilitation centers and not directly collected (49). In order to make comparisons between countries or to accurately estimate national or regional incidence, methodologies of data collection must be standardized (50). According to previous reports, the incidence rate of TSCI worldwide is 2.3 (2) to 150.6 (3) per million per year. In this survey, the incidence of TSCI was 49.8 per million per year in China, which was higher than that in most previous findings (6–8, 10, 21, 26, 35–44, 46, 47), but lower than that in other studies (3, 5, 9, 32–34, 45, 48). The incidence of TSCI in this survey increased with age before 75 years old. The incidence of TSCI reached a peak in the 65–74-year-old group. Previous studies have shown that the age of patients with SCI trends to be bimodal distribution, the first peak is 15–29 years, and the second peak is over 65 years (51). However, the first peak did not occur in this survey, probably attributable to the only child in a family being better protected during the period in China. In this study, nearly two-thirds of patients sustaining

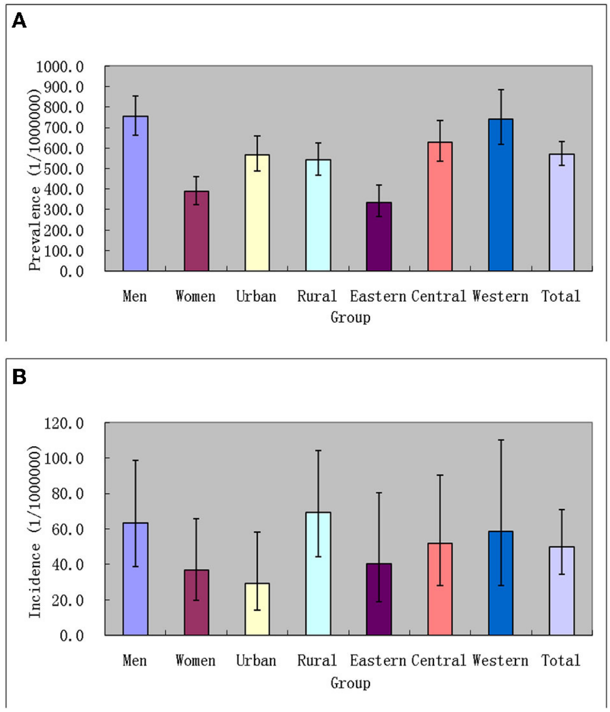


**FIGURE 4** | Prevalence [**(A)** 1/1,000,000 person × life time] and incidence [**(B)** 1/1,000,000 person × years] of TSCI in China, 2013.

TSCIs were over the age of 55 years. Similarly, in Japan, the majority of patients sustaining SCIs were over the age of 50 years (52). This is primarily due to early spinal degenerative changes such as stenosis, spondylolisthesis, and degenerative disk disease, specifically ossification of the posterior longitudinal ligament as well as an increased prevalence of congenital stenosis, causing a higher risk of SCI following a traumatic event (5, 50, 53). Degeneration of various components of the vertebra is common in the elderly population and may lead to narrowing of the spinal canal (5, 50, 53). In turn, these degenerative changes place people at a greater risk of suffering SCI following a fall or another traumatic event (5, 50, 53). In this study, fall was the primary cause of TSCI, which, in turn, supports this explanation.

Although the incidence of TSCI in this survey still showed weak male preponderance without statistical significance, the absolute male preponderance in other studies (5–10, 26, 32–39, 41–48) was likely to be weakened by aging and the one-child policy in China. In contrast, the prevalence of SCI in males was 1.9 times that in females, implying same risk of injury and different postinjury survival between sexes in China.

Indeed, from the perspective of injury occupations, farmers and migrant workers from the villages accounted for 61.2% of patients with TSCI injury. It was explained to some extent why incidence of TSCI in rural areas was higher than that in urban areas in China. On the contrary, the prevalence of TSCI in urban areas was slightly higher than that in rural areas. It could reflect the higher healthcare level for TSCI in urban China to a certain extent.

Interestingly, both the incidence and the prevalence of TSCI across western, central, and eastern areas keep a consistent order from high to low with the increasing economy. Likewise, the tetraplegia incidence of traumatic SCI in Taiwan decreases with good economic performance, which may be resulted from the provision of public goods and services, possibly through improvements in the infrastructure of transportation and construction (54).

Data from the previous incidence survey of TSCI in Taiwan showed that the incidence of TSCI increased from 14.6 in 1978–1981 (8) to 150.6 in 1998–2008 (3) in Taiwan. With the increase of aging and motor vehicle, the incidence of TSCI in China will be expected to increase in the future.

## External Causes

Generally, MVCs and falls are the two major causes of TSCI (3, 5–10, 21, 26, 32–48). Although both the MVCs and falls may swap each other in the top two in previous studies, MVCs were the largest cause of SCI in the majority of the previous studies (3, 8–10, 21, 26, 32, 34–37, 39, 43, 45, 46). In previous studies with TSCI in a bimodal distribution of age (10, 34, 37–39, 41, 43), a first peak for young adults was attributable to MVCs, while a second peak in elderly people aged 65 years and older can be mainly ascribed to falls. Consistent with other studies in the mainland of China (5–7), falls in this survey was the primary cause of TSCI, followed by MVCs. On the contrary, the primary cause of TSCI in Taiwan is MVCs, followed by falls (3, 8–10). A study from Tianjin testified that the leading cause of TSCI had shifted from MVCs during the period of 1997–2007 to falls during the period of 2008–2016 with the rapid aging of Chinese society and effectively traffic management. It was also observed that compared with the elderly, young and middle-aged people were more likely to become injured in traffic accidents (12). This shift in external cause of TSCI also contributed to the increase of the mean age at the time of injury. In this study, the mean age at the time of injury increased from 43.7 ± 17.1 years among the 394 prevalent cases to 56.0 ± 17.0 years among the 34 incident cases. In China, firearms are strictly controlled, so such injury was scarce. Compared with developed countries, sport injuries were also uncommon in China because of low prevalence of certain risky sports such as rugby, diving, and motor racing (6). The same findings were found in this survey.

## Strengths and Limitations

To the best of our knowledge, this is the first large-scale sampling survey on epidemiology of patients with TSCI with temporary or permanent sensory deficits, motor deficits, or bladder/bowel dysfunction in population in China including ∼600,000 people with better representativeness of the Chinese population. However, it also had many shortcomings. First, it may be difficult to assure the sufficient validity of TSCI epidemiological survey based on the sample calculation of the national cerebrovascular disease epidemiological survey, due to

**TABLE 4 |** Prevalence (1/1,000,000 person × life time), incidence (1/1,000,000 person × years), and rate ratio of TSCI among different subgroups of population in China, 2013.

| Factors | Prevalence | | | Incidence | | |
|---|---|---|---|---|---|---|
| | Rate (95%CI) | Rate ratio# (95%CI) | *P* value | Rate (95%CI) | Rate ratio# (95%CI) | *P* value |
| **Age group** | | | | | | |
| 0∼ | 24.1 (2.9–87.0) | 0.016 (0.004–0.067) | <0.001 | 11.7 (0.3–65.2) | 0.084 (0.009–0.808) | 0.032 |
| 15∼ | 103.4 (44.6–203.8) | 0.069 (0.032–0.149) | <0.001 | 12.3 (0.3–68.5) | 0.087 (0.009–0.842) | 0.035 |
| 25∼ | 328.1 (221.4–468.4) | 0.229 (0.141–0.372) | <0.001 | 22.3 (2.7–80.6) | 0.170 (0.028–1.017) | 0.052 |
| 35∼ | 522.2 (390.0–684.8) | 0.356 (0.232–0.544) | <0.001 | 38.8 (10.6–99.4) | 0.292 (0.065–1.309) | 0.108 |
| 45∼ | 959.9 (771.8–1,179.8) | 0.672 (0.456–0.989) | 0.044 | 44.1 (12.0–113.0) | 0.335 (0.075–1.496) | 0.152 |
| 55∼ | 1,297.5 (1,060.1–1,572.1) | 0.934 (0.640–1.365) | 0.725 | 153. 7 (79.4–268. 5) | 1.179 (0.333–4.179) | 0.799 |
| 65∼ | 1,605.7 (1,256.4–2,022.1) | 1.125 (0.754–1.679) | 0.563 | 161.9 (65.1–333.5) | 1.257 (0.325–4.865) | 0.741 |
| 75∼ | 1,364.7 (955.8–1,889.4) | Reference | | 123.5 (25.5–361.0) | Reference | |
| **Sex** | | | | | | |
| Men | 852.8 (751.5–963.9) | 1.904 (1.548–2.342) | <0.001 | 70.1 (43.4–107.1) | 1.640 (0.821–3.277) | 0.161 |
| Women | 465.7 (391.2–550.2) | Reference | | 43.9 (23.4–75.1) | Reference | |
| **Place of residence** | | | | | | |
| Urban | 682.1 (589.3–785.4) | 1.060 (0.868–1.294) | 0.565 | 35.4 (17.0–65.2) | 0.438 (0.208–0.921) | 0.029 |
| Rural | 605.9 (522.8–698.4) | Reference | | 76.5 (49.0–113.9) | Reference | |
| **Geographic location** | | | | | | |
| Eastern China | 427.1 (341.6–527.5) | 0.462 (0.352–0.606) | <0.001 | 49.7 (23.8–91.4) | 0.708 (0.294–1.704) | 0.441 |
| Central China | 721.6 (618.1–837.5) | 0.816 (0.649–1.026) | 0.082 | 58.5 (32.0–98.2) | 0.937 (0.414–2.121) | 0.876 |
| Western China | 797.7 (663.5–951.1) | Reference | | 64.4 (30.9–118.5) | Reference | |

#*Age group, sex, place of residence, and geographic location were adjusted each other in all the Poisson regression analyses.*

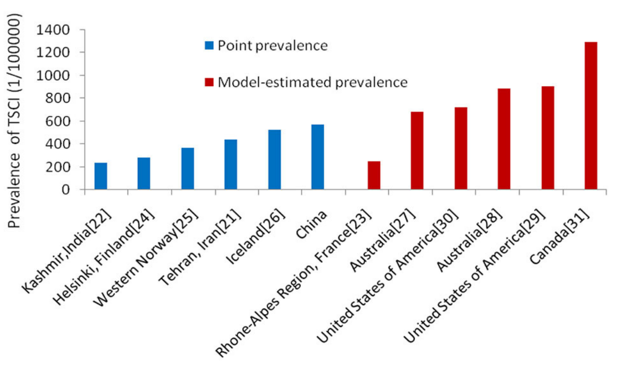


**FIGURE 5 |** Point prevalence (blue) and model-estimated prevalence (red) of TSCI from different regions and countries.

the relatively low incidence of TSCI. Fewer TSCI cases also limit further subgroup analysis. Second, nearly a third of the 394 cases with diagnosis of TSCI were not confirmed with CT/MRI imaging. Third, a recall bias existed in this cross-sectional survey because we could not obtain accurate information of TSCI on dead cases within the defined period of incidence, even though we examined all the deaths in the period. In our survey on incidence of TSCI, only 2 cases of incident TSCI were from deaths from 66 road traffic accidents and 31 falls; therefore, the incidence of TSCI may be underestimated. Finally, this population-based study is based on medical records from hospitals of different grades as well as injury history. Considering the feasibility in population, we could not collect scores at injury of the America Spinal Injury Association Impairment Scale (AIS)/Frankel grade, especially for cases not accessing to hospital. Accordingly, we are unable to differentiate whether a patient is a complete or incomplete SCI.

## CONCLUSION

In summary, it is estimated that there are 759,302 prevalent patients with TSCI in total and 66,374 new TSCI cases annually in China. Falls and MVCs are still 2 major external causes for TSCI in China. The burden of TSCI in China will be expected to rise with increasing falls in the elderly and increasing use of motor vehicles. These findings may provide a data reference for relevant health administrative departments or professional associations tasked with healthcare policymaking, resources allocation, or disease management in patients with TSCI.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Beijing Tiantan Hospital affiliated with the Capital Medical University (Ethic ID: KY2013-006-01). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

BJ and WW were the principal investigators responsible for the survey, as such, had full access to all the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis. BJ performed the statistical analysis and manuscript writing. All authors contributed to the study conception and design, its implementation and field works, data collection and analysis, discussed the findings, and approved the final version for publication.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.784647/full#supplementary-material

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# The Global Burden of Motor Neuron Disease: An Analysis of the 2019 Global Burden of Disease Study

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Up-to-date, accurate information on the disease burden of motor neuron disease (MND) is the cornerstone for evidence-based resource allocation and healthcare planning. We aimed to estimate the burden of MND globally from 1990 to 2019, as part of the Global Burden of Disease, Injuries and Risk Factor (GBD) study. Amyotrophic lateral sclerosis, progressive muscular atrophy, primary lateral sclerosis, pseudobulbar palsy, spinal muscular atrophy and hereditary spastic paraplegia- were included for analysis as MNDs. We measured age-standardized incidence, prevalence, death, and disability-adjusted life-years (DALYs) in 204 countries and territories worldwide from 1990 to 2019 using spatial Bayesian analyses. The effects of age, sex, and the sociodemographic index (measures of income per capita, education, and fertility) on incidence, prevalence, death, and disability-adjusted life-years due to MNDs were explored. According to 2019 GBD estimates, there were ∼268,673 [95% uncertainty interval (UI), 213,893–310,663] prevalent cases and 63,700 (95% UI, 57,295–71,343) incident cases of MND worldwide. In 2019, MND caused 1,034,606 (95% UI, 979,910–1,085,401) DALYs and 39,081 (95% UI, 36,566–41,129) deaths worldwide. The age-standardized rates of prevalence, incidence, death, and DALYs for MNDs in 2019 were 3.37 (95% UI, 2.9–3.87) per 100,000 people, 0.79 (95% UI, 0.72–0.88) per 100,000 people, 0.48 (95% UI, 0.45–0.51) per 100,000 people, and 12.66 (95% UI, 11.98–13.29) per 100,000 people, respectively. The global prevalence and deaths due to MND in 2019 were increased (1.91% [95% UI, 0.61–3.42] and 12.39% [95% UI, 5.81–19.27], respectively) compared to 1990, without significant change in incidence. More than half of the prevalence and deaths due to MND occurred in three high-income regions (North America, Western Europe, and Australasia). In most cases, the prevalence, incidence, and DALYs of MNDs were high in regions with high sociodemographic index; however, in high-income East Asia, these were relatively low compared to similar sociodemographic index groups elsewhere. The burden of MND increased between 1990 and 2019. Its expected increase in the future highlights the importance of global and national healthcare planning using more objective evidence. Geographical heterogeneity in the MND burden might suggest the influences of sociodemographic status and genetic background in various regions.

**Keywords: motor neuron disease, amyotrophic lateral sclerosis, incidence, prevalence, disease burden**



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# INTRODUCTION

Motor neuron diseases (MNDs) are rare neurological disease groups of neurodegenerative disorders associated with the degeneration of motor neurons in the upper and lower extremities (1). They include amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, hereditary spastic paraplegia, progressive muscular atrophy, spinal muscular atrophy, and pseudobulbar palsy (2). Among MNDs, ALS—the most common disease entity—causes respiratory failure in 50% of patients within 2 years of diagnosis. Other MNDs also have poor long-term prognoses, imposing a socioeconomic burden on patients and care givers (1, 2).

Although epidemiologic studies on MNDs have been published in the United States and Europe, their incidence, prevalence, and burden are not well known because the diseases are rare (3–6). Although it varies according to age, sex, and region, the peak incidence of ALS is at ∼70 years, the incidence rate is 1.7 per 100,000 person-years, and the prevalence is 4.5 per 100,000 people (7, 8). Moreover, according to the 2016 Global Burden of Diseases (GBD) estimates, the incidence rate of all age was 0.78 per 100 000 person-years for MNDs (9). In addition, the age-standardized prevalence was high in high-income Europe, Australasia, and North America, excluding the Asia-Pacific region (9). Despite this high prevalence, there are few recent global epidemiologic studies of MNDs.

The purpose of this study was to investigate the global burden of MNDs, including the incidence, prevalence, death, disability-adjusted life-years (DALYs), years lived with disability (YLDs), and years of life lost (YLLs) between 1990 and 2019 from GBD information according to age, sex, regions, and the estimates from individual countries. Furthermore, we investigated the GBD of MNDs based on the sociodemographic index (SDI) reflecting the development of each country.

# METHODS

## Overview

The GBD Study is a systematic and comprehensive study of diseases worldwide. Based on the estimates of this study, it is possible to compare and analyze the current status of the global, regional, and national burden of diseases (10). The GBD Study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting statement (11). Based on the Institute for Health Metrics and Evaluation (IHME) of the University of Washington, which is in charge of the GBD Study, only anonymous information is used in the GBD Study, resulting in the waiver of informed consent.

Our study used the estimates from the GBD's public website. All the results related to GBD research on MNDs can be freely accessed and downloaded from the GBD Compare website and the Global Health Data Exchange website (GBD Compare, available at: https://vizhub.healthdata.org/gbd-compare/; Global Health Data Exchange, available at: http://ghdx.healthdata.org/) (10). GBD 2019 methods are described in detail on the GBD website and in a previous study (12). The GBD 2019 is a multinational collaborative study conducted by worldwide countries that is updated every year. The most recent version provides the burden of diseases according to age, sex, and region (369 diseases and injuries in 204 countries and territories) from 1990 to 2019. The estimates acquisition and analysis of our study followed the methodology detailed on the GBD website. Our dataset from 1990 to 2019 for MNDs was provided on the GBD website, and the estimates were extracted from the GBD standards. For comparison of the temporal change by region and country, the variations of the estimates were presented as the percentage change in age-standardized rates between 1990 and 2019.

## Case Definition

MNDs are a set of chronic, degenerative, and progressive neurological conditions typified by the destruction of motor neurons and the subsequent deterioration of voluntary muscle activity. The most common MND is ALS. The International Statistical Classification of Diseases and Related Health Problems (ICD)-10 code corresponding to MNDs is G12. The GBD Study's gold standard diagnostic criteria are the El Escorial Criteria, combined with other similar criteria (e.g., the original set from World Federation of Neurology) if necessary (9, 13, 14).

## Search Terms

Detailed methods for obtaining information for nonfatal estimates and death have been described in previous research (12). Considering DALYs, YLDs, and YLLs, these estimates for MNDs were acquired from surveillance systems of diseases, registries, survey microdata, health claims data, and systematic reviews of published and unpublished reports (12). The IHME searched PubMed, Medline, CINAHL®, Embase, World Health Organization Library Information System, CAP abstracts, and System for Information on Gray Literature in Europe databases for Global Burden of Disease Study data, regardless of language, age, and sex. The terms, "motor neuron disease," "amyotrophic lateral sclerosis," "primary lateral sclerosis," "spinal muscular atrophy," "progressive muscular atrophy," and "pseudobulbar palsy" were searched individually. These terms were re-searched with combinations of the following terms, "epidemiology," "population sample," "population study," "population-based," "cross-sectional," "cross sectional," "prevalen*," and "inciden*." (12) Systematic reviews from the above data sources and the National Health Interview Survey, National Health and Nutrition Examination Survey in United States and other nationwide claim data were reviewed for the GBD Study (12, 15). The studies or dataset complied with small sample size (<150), review article, not a population sample study, studies in which the subpopulation of the national population was not clearly explained were excluded by IHME (12, 15). These datasets are repositioned to the Global Health Data Exchange, and data of different characteristics are analyzed using DisMod-MR 2.1, a Bayesian meta-regression tool (16). All rates were age-standardized using the GBD standard. Data were described using 95% uncertainty intervals (UIs) and changes from 1990 to 2019 as percentages (95% UIs) provided by the GBD website.

## Sociodemographic Index

The SDI was used to investigate the association of the level of development of regions or countries with the GBD of MNDs (12). The SDI is a composite indicator that measures the development of individual countries. It is defined as 0 in the lowest case and 1 in the highest case and calculated based on the lag-distributed income per capita, the total fertility rate for those under 25, and the average educational level of the population over the age of 15 (17). In our study, the age-standardized prevalence and DALYs for each region and DALYs for each country were estimated according to the SDI.

# RESULTS

## 2019 GBD of Motor Neuron Diseases by Region

Prevalence, incidence, DALYs, YLDs, YLLs, and death due to MNDs in counts and age-standardized rates for both sexes for 2019 are listed in **Table 1**. The age-standardized rates of DALYs of MNDs in the 21 GBD world regions generally increased with SDI (**Figure 1**).

Globally, 268,674 individuals (95% UI, 231893.92–310663.85) had MND in 2019. The number of patients with MND in 2019 was 1.7 times higher than in 1990 (159074.07 [95% UI, 134173.93–187017.72]). The age-standardized incidence of MND in 2019 was 0.79 (95% UI, 0.72–0.88), and the number of patients was 63,700 (95% UI, 57295.90–71343.33). The global age-standardized DALYs value of MND was 12.66 (95% UI, 11.98–13.29), and the count was 1034606.59 (95% UI, 979910.92–1085401.11). The YLD and YLL values of MND were 57,068.01 (95% UI, 39981.62–76338.40) and 977538.58 (95% UI, 926348.26–1025429.87), respectively. The global death count of MND in 2019 was 39081.23 (95% UI, 36566.69–41129.62).

High-income North America, Western Europe, Australasia, and Asia Pacific, as well as Southern Latin America had higher age-standardized prevalence rates. The age-standardized prevalence rates were low in the following regions: Oceania, Central sub-Saharan Africa, Western sub-Saharan Africa, Eastern sub-Saharan Africa, and Southeast Asia.

The age-standardized incidence rates were high in Australasia, high-income North America, Western Europe, Southern Latin America, and high-income Asia Pacific and low in Southeast Asia, South Asia, Oceania, Andean Latin America, and Central Asia.

The age-standardized DALY rates were high in Australasia, high-income North America, Western Europe, Southern Latin America, and Tropical Latin America. Central sub-Saharan Africa, Eastern sub-Saharan Africa, Western sub-Saharan Africa, Southern sub-Saharan Africa, and Central Asia had lower age-standardized DALY rates. The global age-standardized DALY rates of motor neuron diseases by age and sex are shown in **Figure 2**.

The age-standardized rates of deaths caused by MND showed a similar pattern as DALYs. Australasia, high-income North America, Western Europe, Southern Latin America, and Tropical Latin America were the top five regions with high age-standardized death rates. Central sub-Saharan Africa, Eastern sub-Saharan Africa, Western sub-Saharan Africa, Southern sub-Saharan Africa, and Central Asia had relatively low age-standardized death rates.

## Regional Trend of Motor Neuron Disease Between 1990 and 2019

Changes in the age-standardized prevalence rates between 1990 and 2019 were most prominent in Australasia and Western Europe but lowest in Oceania and Central sub-Saharan Africa.

Changes in the age-standardized DALYs and death rates between 1990 and 2019 showed a similar pattern. The highest increase in the DALY and death were observed in Southern Latin America and the Caribbean. The lowest changes in the DALY and death were observed in Oceania and East Asia.

## 2019 GBD of Motor Neuron Diseases by Country

Prevalence, incidence, DALYs, YLDs, YLLs, and death due to MNDs by country in counts and age-standardized rates for both sexes for 2019 are listed in **Supplementary Table 1**. The age-standardized prevalence rates were high in Canada, Andorra, Finland, Ireland, and Sweden. In contrast, Kiribati, Somalia, Burundi, Central African Republic, and Solomon Islands had lower age-standardized prevalence of MND than other countries.

In 2019, the age-standardized incidence of MND was low in Malaysia, Seychelles, Indonesia, Maldives, and Philippines. In contrast, Ireland, Finland, Australia, United Kingdom, and Andorra had high age-standardized incidence of MND.

Age-standardized DALYs and death were high in the following countries: Ireland, Australia, Andorra, New Zealand, and Finland. The age-standardized DALYs and death were low in the following countries: Somalia, Central African Republic, Burundi, and Democratic Republic of the Congo South.

## National Trend of Motor Neuron Disease Between 1990 and 2019

Between 1990 and 2019, the DALYs rates were increased to the greatest extent in Barbados, Costa Rica, and Uruguay. The DALYs rates decreased in the following countries: Slovenia, Guam, Bosnia and Herzegovina, and Republic of Korea. Portugal, Italy, Lithuania, and Costa Rica showed the highest increase in age-standardized prevalence and incidence rates over the examined period. Sudan showed low DALY but an increased death rate in 2019 compared to 1990.

## Association Between Prevalence and DALYs of MNDs According to the SDI

The age-standardized prevalence rate (per 100,000) was relatively high in high-income North America, Western Europe, Australasia, and high-income Asia-Pacific regions with high SDI levels but was low in the sub-Saharan African region (**Figure 3**). The age-standardized DALY rate (per 100,000) for MNDs was also relatively high in Australasia, high-income North America, Western Europe, and high-income Asia-Pacific regions. In contrast, the age-standardized DALY rate of the sub-Saharan African region was the lowest among all countries (**Figure 4**). **Figure 5** shows the age-standardized DALY rate for each country according to SDI. Ireland, Australia, New Zealand, Finland,

**TABLE 1 |** Prevalence, incidence, DALYs, YLD, YLL, and death of motor neuron diseases in counts and age-standardized rate for both sexes combined in 1990 and 2019, with percentage change between 1990 and 2019 by GBD region.

| | 1990 | | 2019 | | Percentage change in age-standardized rates between 1990 and 2019 (%) |
|---|---|---|---|---|---|
| | **Counts (95% UI)** | **Age-standardized rate (per 100k)** | **Counts (95% UI)** | **Age-standardized rate (per 100k)** | |
| **Prevalence** | | | | | |
| Global | 159074.07 (134173.93, 187017.72) | 3.31 (2.83, 3.85) | 268673.82 (231893.92, 310663.85) | 3.37 (2.90, 3.87) | 1.91 (0.61, 3.42) |
| East Asia | 30416.42 (24265.40, 37552.45) | 2.47 (2, 3.02) | 43368.36 (35365.62, 53087.77) | 2.81 (2.28, 3.42) | 14.01 (11.92, 16.55) |
| Southeast Asia | 6976.22 (5524.27, 8766.2) | 1.56 (1.26, 1.90) | 11553.01 (9320.49, 14150.96) | 1.70 (1.37, 2.07) | 8.81 (7.37, 10.41) |
| Central Asia | 1763.87 (1427.23, 2136.48) | 2.61 (2.15, 3.16) | 2482.75 (2010.03, 3034.69) | 2.66 (2.17, 3.22) | 1.81 (−0.08, 3.63) |
| High-income Asia Pacific | 8184.62 (6975.14, 9505.28) | 4.37 (3.71, 5.10) | 13685.11 (11728.72, 15889.95) | 4.96 (4.21, 5.73) | 13.50 (10.20, 17.06) |
| South Asia | 16889.59 (13251.61, 21327.56) | 1.60 (1.28, 2.01) | 32423.68 (25648.91, 40699.06) | 1.77 (1.41, 2.21) | 10.32 (8.69, 12.11) |
| Central Europe | 4732.18 (3963.39, 5604.84) | 3.78 (3.13, 4.46) | 5114.87 (4353.92, 6023.38) | 4.16 (3.46, 4.91) | 10.11 (7.77, 12.54) |
| Eastern Europe | 7394.11 (6051.33, 8952.39) | 3.28 (2.67, 3.97) | 7226.55 (6019.61, 8647.80) | 3.43 (2.81, 4.11) | 4.31 (2.55, 6.30) |
| Western Europe | 32546.71 (28367.54, 37168.89) | 6.65 (5.83, 7.62) | 56841.52 (48862.68, 64813.67) | 8.33 (7.24, 9.54) | 25.29 (22.14, 28.44) |
| Southern Latin America | 1903.01 (1608.70, 2235.20) | 3.90 (3.31, 4.57) | 3446.54 (2961.42, 3967.82) | 4.77 (4.08, 5.53) | 22.33 (17.63, 26.30) |
| High-income North America | 24268.48 (21294.92, 27403.77) | 7.69 (6.74, 8.72) | 43939.61 (40591.11, 47456.48) | 8.86 (8.19, 9.51) | 15.16 (6.95, 25.60) |
| Andean Latin America | 618.51 (499.81, 765.97) | 1.76 (1.45, 2.12) | 1195.76 (986.3, 1444.28) | 1.90 (1.57, 2.29) | 8.13 (4.99, 10.95) |
| Central Latin America | 3582.30 (2860.72, 4423.03) | 2.28 (1.86, 2.76) | 6259.06 (5183.23, 7537.21) | 2.49 (2.06, 2.99) | 9.41 (7.15, 12.11) |
| Tropical Latin America | 3578.71 (2864.26, 4373.53) | 2.43 (1.99, 2.92) | 6577.87 (5550.97, 7804.33) | 2.84 (2.39, 3.37) | 16.94 (13.06, 21.43) |
| North Africa and Middle East | 7659.13 (6139.90, 9397.60) | 2.49 (2.03, 3.01) | 15573.91 (12657.01, 19025.23) | 2.58 (2.11, 3.10) | 3.55 (2.01, 5.10) |
| Central Sub-Saharan Africa | 640.30 (508.60, 805.50) | 1.41 (1.14, 1.74) | 1574.70 (1246.39, 1974.15) | 1.42 (1.16, 1.73) | 0.75 (−1.69, 3.26) |
| Eastern Sub-Saharan Africa | 2258.65 (1776.01, 2848.39) | 1.44 (1.16, 1.77) | 5243.76 (4117.62, 6614.97) | 1.49 (1.21, 1.83) | 3.86 (2.86, 4.92) |
| Southern Sub-Saharan Africa | 902.47 (715.56, 1136.22) | 1.81 (1.47, 2.22) | 1455.91 (1164.75, 1808.32) | 1.89 (1.53, 2.32) | 4.45 (3.13, 5.94) |
| Western Sub-Saharan Africa | 2386.40 (1875.05, 3002.83) | 1.44 (1.16, 1.77) | 5937.72 (4650.94, 7517.55) | 1.49 (1.19, 1.83) | 3.42 (2.58, 4.23) |
| Oceania | 86.03 (68.61, 107.11) | 1.43 (1.17, 1.73) | 175.43 (139.94, 217.28) | 1.40 (1.14, 1.69) | −1.95 (−4.69, 0.84) |
| Australasia | 1426.95 (1245.42, 1648.03) | 6.35 (5.57, 7.32) | 3341.02 (2886.63, 3856.43) | 8.03 (6.99, 9.18) | 26.40 (19.56, 33.03) |
| Caribbean | 859.40 (714.72, 1029.32) | 2.53 (2.14, 3.02) | 1256.66 (1070.71, 1478.73) | 2.59 (2.20, 3.04) | 2.31 (−0.17, 4.80) |
| **Incidence** | | | | | |
| Global | 35589.21 (31621.30, 40068.04) | 0.79 (0.71, 0.89) | 63700.04 (57295.90, 71343.33) | 0.79 (0.72, 0.88) | 0.28 (−0.37, 0.94) |
| East Asia | 6278.11 (5218.62, 7576.54) | 0.59 (0.50, 0.72) | 9432.66 (7816.94, 11699.79) | 0.54 (0.46, 0.65) | −9.02 (−10.92,−6.96) |
| Southeast Asia | 1475.31 (1218.21, 1780.07) | 0.41 (0.34, 0.50) | 2610.84 (2121.40, 3208.19) | 0.40 (0.33, 0.49) | −1.44 (−2.49,−0.44) |
| Central Asia | 303.68 (255.62, 359.75) | 0.49 (0.42, 0.60) | 431.58 (355.63, 525.64) | 0.49 (0.41, 0.59) | −0.63 (−2.04, 0.91) |

*(Continued)*

**TABLE 1 |** Continued

| | 1990 | | 2019 | | Percentage change in age-standardized rates between 1990 and 2019 (%) |
|---|---|---|---|---|---|
| | Counts (95% UI) | Age-standardized rate (per 100k) | Counts (95% UI) | Age-standardized rate (per 100k) | |
| High-income Asia Pacific | 1546.95 (1383.49, 1718.90) | 0.81 (0.72, 0.89) | 3114.27 (2840.71, 3436.45) | 0.87 (0.78, 0.97) | 8.26 (5.65, 11.08) |
| South Asia | 3903.90 (3204.06, 4756.93) | 0.42 (0.35, 0.52) | 6855.22 (5615.30, 8401.31) | 0.42 (0.34, 0.51) | −1.92 (−3.40,−0.29) |
| Central Europe | 826.68 (716.85, 956.76) | 0.63 (0.55, 0.72) | 1098.89 (968.04, 1253.9) | 0.69 (0.61, 0.79) | 10.29 (8.12, 12.69) |
| Eastern Europe | 1239.63 (1035.78, 1495.5) | 0.52 (0.44, 0.62) | 1499.10 (1284.01, 1760.28) | 0.58 (0.50, 0.68) | 11.46 (8.25, 14.71) |
| Western Europe | 7787.23 (7325.06, 8273.72) | 1.55 (1.45, 1.64) | 13796.97 (13037.65, 14494.46) | 1.85 (1.73, 1.95) | 19.51 (17.68, 21.37) |
| Southern Latin America | 402.63 (355.60, 449.83) | 0.84 (0.75, 0.94) | 734.86 (664.39, 806.44) | 0.96 (0.87, 1.06) | 14.01 (10.52, 17.64) |
| High-income North America | 5685.47 (5372.57, 6019.86) | 1.75 (1.64, 1.85) | 11322.79 (10817.90, 11839.31) | 1.97 (1.88, 2.06) | 12.83 (9.85, 16.22) |
| Andean Latin America | 125.78 (104.87, 147.14) | 0.42 (0.35, 0.49) | 268.04 (228.69, 312.01) | 0.45 (0.38, 0.52) | 7.84 (5.06, 10.82) |
| Central Latin America | 704.93 (595.06, 814.16) | 0.51 (0.44, 0.59) | 1414.86 (1230.26, 1621.14) | 0.59 (0.51, 0.67) | 15.36 (12.06, 18.73) |
| Tropical Latin America | 779.70 (672.64, 897.89) | 0.62 (0.54, 0.71) | 1915.61 (1705.55, 2132.61) | 0.83 (0.74, 0.91) | 32.92 (27.11, 38.88) |
| North Africa and Middle East | 1862.19 (1577.27, 2168.99) | 0.61 (0.52, 0.72) | 3409.38 (2880.66, 4056.06) | 0.62 (0.53, 0.73) | 1.92 (0.29, 3.56) |
| Central Sub-Saharan Africa | 225.47 (183.85, 275.70) | 0.62 (0.51, 0.78) | 539.21 (437.93, 660.28) | 0.64 (0.53, 0.81) | 3.20 (0.55, 5.66) |
| Eastern Sub-Saharan Africa | 812.17 (667.31, 988.29) | 0.67 (0.55, 0.84) | 1735.36 (1424.63, 2131.85) | 0.66 (0.55, 0.83) | −0.89 (−1.78,−0.03) |
| Southern Sub-Saharan Africa | 213.43 (178.65, 257.52) | 0.53 (0.44, 0.65) | 376.93 (311.48, 465.51) | 0.55 (0.46, 0.68) | 3.38 (1.97, 4.86) |
| Western Sub-Saharan Africa | 721.11 (593.72, 867.07) | 0.51 (0.42, 0.63) | 1634.14 (1349.80, 1970.13) | 0.51 (0.42, 0.63) | 0.01 (−0.78, 0.78) |
| Oceania | 21.21 (17.65, 25.04) | 0.45 (0.38, 0.53) | 45.65 (37.71, 54.73) | 0.43 (0.36, 0.52) | −3.05 (−5.39,−0.43) |
| Australasia | 471.97 (449.22, 495.56) | 2.09 (1.99, 2.19) | 1108.53 (1056.79, 1154.97) | 2.47 (2.36, 2.58) | 18.42 (15.85, 20.95) |
| Caribbean | 201.66 (175.29, 229.01) | 0.66 (0.57, 0.75) | 355.13 (314.48, 400.05) | 0.73 (0.64, 0.81) | 10.40 (8, 12.89) |
| **DALYs** | | | | | |
| Global | 624364.36 (594254.18, 665295.3) | 13.20 (12.70, 13.92) | 1034606.59 (979910.92, 1085401.11) | 12.66 (11.98, 13.29) | −4.50 (−10.09, 1.87) |
| East Asia | 152285.99 (135032.40, 170843.37) | 13.01 (11.54, 14.55) | 113080.73 97726.25, 128867.40) | 6.83 (6.05, 7.70) | −47.53 (−55.99,−37.57) |
| Southeast Asia | 11458.45 (10039.59, 13066.93) | 3.09 (2.69, 3.48) | 20690.9 (17170.16, 24504.33) | 3.01 (2.51, 3.56) | −2.64 (−18.56, 13.88) |
| Central Asia | 1187.31 (1007.70, 1426.9) | 1.98 (1.69, 2.40) | 2207.82 (1926.05, 2531.33) | 2.40 (2.10, 2.75) | 21.56 (0.77, 40.61) |
| High-income Asia Pacific | 36131.48 (34218.25, 38298.73) | 21.06 (19.40, 23.14) | 53490.14 (48237.91, 57800.70) | 14.66 (13.45, 15.74) | −30.35 (−38.57,−22.21) |
| South Asia | 27013.59 (20867.31, 33597.14) | 3.08 (2.28, 4.04) | 72624.17 (58024.33, 88717.91) | 4.49 (3.57, 5.51) | 45.83 (18.05, 78.76) |
| Central Europe | 16722.43 (16036.79, 17499.34) | 14.08 (13.39, 14.90) | 22124.33 (19284.68, 25046.48) | 14.33 (12.37, 16.36) | 1.82 (−11.75, 16.63) |
| Eastern Europe | 11952.50 (10375.70, 15679.64) | 4.85 (4.25, 6.26) | 30570.79 (27335.72, 33943.33) | 10.69 (9.64, 11.77) | 120.46 (66.55, 162.88) |

*(Continued)*

**TABLE 1 |** Continued

| | 1990 | | 2019 | | Percentage change in age-standardized rates between 1990 and 2019 (%) |
|---|---|---|---|---|---|
| | Counts (95% UI) | Age-standardized rate (per 100k) | Counts (95% UI) | Age-standardized rate (per 100k) | |
| Western Europe | 169362.09 (165230.78, 173320.48) | 36.52 (35.58, 37.51) | 283150.27 (262769.68, 301431.82) | 39.39 (36.60, 41.89) | 7.86 (0.25, 15.15) |
| Southern Latin America | 3956.35 (3724.62, 4193.44) | 8.26 (7.78, 8.75) | 17187.38 (15694.86, 18385.60) | 22.30 (20.38, 23.94) | 170.04 (145.72, 193.32) |
| High-income North America | 115678.28 (112284.79, 118971.11) | 37.32 (36.20, 38.44) | 252573.77 (242925.55, 260048.76) | 46.91 (45.25, 48.37) | 25.69 (21.4, 29.91) |
| Andean Latin America | 1624.72 (1433.85, 1823.69) | 5.81 (5.16, 6.57) | 4723.74 (3757.67, 5888.11) | 8.02 (6.38, 9.96) | 38.04 (8.38, 75.25) |
| Central Latin America | 9302.06 (8828.52, 9825.84) | 7.35 (7.07, 7.66) | 31333.12 (26157.22, 36995.01) | 12.74 (10.62, 15.02) | 73.35 (43.60, 105.07) |
| Tropical Latin America | 14370.77 (13490.43, 15459.08) | 11.51 (10.93, 12.2) | 44751.24 (40955.11, 47744.19) | 18.58 (16.98, 19.87) | 61.43 (40.45, 77.07) |
| North Africa and Middle East | 33985.19 (22089.94, 57107.66) | 9.40 (7.06, 13.85) | 41628.31 (33815.43, 50605.43) | 7.84 (6.36, 9.54) | −16.63 (−44.77, 17.91) |
| Central Sub-Saharan Africa | 503.65 (390.60, 696.80) | 1.05 (0.80, 1.54) | 1065.5 (847.45, 1333.19) | 0.98 (0.76, 1.27) | −6.01 (−28.77, 17.51) |
| Eastern Sub-Saharan Africa | 1739.75 (1403.49, 2223.76) | 1.02 (0.77, 1.44) | 3725.92 (3107.29, 4408.37) | 1.02 (0.81, 1.25) | −0.41 (−18.27, 15.35) |
| Southern Sub-Saharan Africa | 1021.90 (888.99, 1161.36) | 2.64 (2.26, 3.02) | 1687.40 (1392.86, 2091.32) | 2.40 (1.99, 2.98) | −9.14 (−28.18, 19.85) |
| Western Sub-Saharan Africa | 3411.76 (2655.83, 4296.15) | 2.57 (1.92, 3.30) | 6169.26 (5024.46, 7541.74) | 1.95 (1.59, 2.41) | −23.98 (−44.73, 2.11) |
| Oceania | 182.01 (129.88, 246.33) | 4.49 (3.11, 6.21) | 256.61 (187.75, 348.56) | 2.60 (1.86, 3.60) | −42.14 (−54.72,−26.07) |
| Australasia | 10073.49 (9630.45, 10508.85) | 46.16 (43.92, 48.28) | 23113.79 (21006.39, 25198.22) | 55.16 (50.13, 60.39) | 19.51 (7.51, 32.2) |
| Caribbean | 2400.61 (2034.38, 2946.3) | 7.57 (6.72, 8.87) | 8451.39 (6865.67, 10354.28) | 16.93 (13.7, 20.92) | 123.77 (79.18, 179.23) |
| **YLD** | | | | | |
| Global | 33800.6 (23550.19, 45745.61) | 0.70 (0.49, 0.940) | 57068.01 (39981.62, 76338.40) | 0.72 (0.50, 0.96) | 1.86 (0.57, 3.35) |
| East Asia | 6461.53 (4357.38, 8992.43) | 0.52 (0.36, 0.73) | 9213.77 (6322.25, 12911.4) | 0.60 (0.40, 0.83) | 14.02 (11.92, 16.55) |
| Southeast Asia | 1482.08 (1008.87, 2089.48) | 0.33 (0.23, 0.46) | 2454.48 (1672.07, 3425.34) | 0.36 (0.25, 0.50) | 8.81 (7.37, 10.41) |
| Central Asia | 374.75 (256.68, 515.69) | 0.56 (0.38, 0.77) | 527.5 (359.41, 735) | 0.57 (0.39, 0.79) | 1.81 (−0.08, 3.63) |
| High-income Asia Pacific | 1739.51 (1198.60, 2333.35) | 0.93 (0.65, 1.25) | 2909.13 (1991.34, 3943.44) | 1.05 (0.73, 1.41) | 13.5 (10.20, 17.06) |
| South Asia | 3587.87 (2412.77, 5024.02) | 0.34 (0.23, 0.48) | 6887.60 (4692.36, 9654.53) | 0.38 (0.26, 0.53) | 10.32 (8.69, 12.11) |
| Central Europe | 1005.45 (696.71, 1373.12) | 0.80 (0.56, 1.10) | 1086.98 (746.37, 1460.78) | 0.89 (0.61, 1.21) | 10.12 (7.77, 12.54) |
| Eastern Europe | 1570.87 (1077.89, 2181.94) | 0.70 (0.48, 0.97) | 1535.46 (1049.49, 2121.1) | 0.73 (0.50, 1.01) | 4.32 (2.55, 6.30) |
| Western Europe | 6916.85 (4790.61, 9100.59) | 1.41 (0.98, 1.86) | 12063.70 (8288.2, 15935.77) | 1.77 (1.22, 2.33) | 25.18 (22.01, 28.29) |
| Southern Latin America | 404.41 (278.3, 543.93) | 0.83 (0.57, 1.12) | 732.52 (509.39, 974.33) | 1.01 (0.71, 1.36) | 22.34 (17.63, 26.30) |
| High-income North America | 5158.58 (3599.96, 6824.02) | 1.64 (1.14, 2.16) | 9333.71 (6642.86, 12243.18) | 1.88 (1.34, 2.47) | 15.11 (6.92, 25.50) |
| Andean Latin America | 131.41 (89.10, 183.88) | 0.37 (0.26, 0.52) | 254.08 (174.61, 349.50) | 0.40 (0.28, 0.56) | 8.14 (4.99, 10.95) |

*(Continued)*

**TABLE 1** | Continued

| | 1990 | | 2019 | | Percentage change in age-standardized rates between 1990 and 2019 (%) |
|---|---|---|---|---|---|
| | Counts (95% UI) | Age-standardized rate (per 100k) | Counts (95% UI) | Age-standardized rate (per 100k) | |
| Central Latin America | 761.13 (516.31, 1053.70) | 0.48 (0.33, 0.67) | 1329.94 (915.54, 1828.29) | 0.53 (0.36, 0.73) | 9.42 (7.15, 12.11) |
| Tropical Latin America | 760.34 (517.12, 1061.99) | 0.52 (0.35, 0.71) | 1397.76 (969.35, 1907.94) | 0.60 (0.42, 0.82) | 16.95 (13.06, 21.43) |
| North Africa and Middle East | 1626.98 (1102.95, 2254.79) | 0.53 (0.36, 0.73) | 3308.29 (2269.07, 4603.9) | 0.55 (0.38, 0.76) | 3.55 (2.01, 5.10) |
| Central Sub-Saharan Africa | 136.03 (92.65, 191.01) | 0.30 (0.21, 0.42) | 334.54 (227.59, 470.20) | 0.30 (0.21, 0.42) | 0.76 (−1.69, 3.26) |
| Eastern Sub-Saharan Africa | 479.87 (324.06, 671.58) | 0.31 (0.21, 0.43) | 1113.98 (752.18, 1554.22) | 0.32 (0.22, 0.44) | 3.86 (2.86, 4.92) |
| Southern Sub-Saharan Africa | 191.73 (130.30, 266.67) | 0.38 (0.27, 0.53) | 309.29 (212.52, 431.30) | 0.40 (0.28, 0.56) | 4.45 (3.13, 5.94) |
| Western Sub-Saharan Africa | 506.99 (342.18, 708.31) | 0.31 (0.21, 0.43) | 1261.42 (853.55, 1773.88) | 0.32 (0.22, 0.44) | 3.42 (2.58, 4.23) |
| Oceania | 18.28 (12.34, 25.69) | 0.3 (0.21, 0.42) | 37.27 (25.46, 52.52) | 0.30 (0.21, 0.41) | −1.96 (−4.69, 0.84) |
| Australasia | 303.33 (208.63, 404.58) | 1.35 (0.93, 1.80) | 709.57 (490.27, 941.35) | 1.71 (1.19, 2.26) | 26.30 (19.37, 33) |
| Caribbean | 182.61 (126.57, 248.5) | 0.54 (0.37, 0.73) | 267.03 (186.61, 361.73) | 0.55 (0.38, 0.75) | 2.31 (−0.17, 4.80) |
| **YLL** | | | | | |
| Global | 590563.76 (562254.06, 628441.15) | 12.55 (12.05, 13.19) | 977538.58 (926348.26, 1025429.87) | 11.94 (11.30, 12.53) | −4.86 (−10.71, 1.88) |
| East Asia | 145824.46 (128648.03, 164532.34) | 12.49 (11.07, 14.05) | 103866.96 (89445.70, 119783.67) | 6.23 (5.45, 7.09) | −50.11 (−58.65,−39.99) |
| Southeast Asia | 9976.37 (8684.10, 11565.76) | 2.76 (2.39, 3.13) | 18236.42 (14925.97, 22196.65) | 2.65 (2.18, 3.22) | −4.02 (−21.83, 14.57) |
| Central Asia | 812.55 (700.25, 1013.13) | 1.42 (1.24, 1.79) | 1680.33 (1467.58, 1933.98) | 1.84 (1.61, 2.11) | 29.27 (0.41, 57.26) |
| High-income Asia Pacific | 34391.98 (32598.18, 36483.71) | 20.13 (18.48, 22.29) | 50581.01 (45452.57, 54772.78) | 13.61 (12.43, 14.57) | −32.38 (−41.04,−24.05) |
| South Asia | 23425.72 (17514.04, 29950.16) | 2.74 (1.97, 3.68) | 65736.57 (51380.09, 81332.34) | 4.12 (3.21, 5.11) | 50.24 (18.95, 89.09) |
| Central Europe | 15716.99 (15154.80, 16413.13) | 13.27 (12.66, 14.06) | 21037.36 (18144.93, 24002.57) | 13.45 (11.49, 15.51) | 1.32 (−12.94, 17.03) |
| Eastern Europe | 10381.62 (9050.47, 13849.17) | 4.15 (3.65, 5.46) | 29035.33 (25781.93, 32248.89) | 9.96 (8.91, 11.02) | 139.98 (74.76, 191.90) |
| Western Europe | 162445.24 (158821.11, 165324.18) | 35.1 (34.29, 35.97) | 271086.57 (251170.14, 289081.57) | 37.62 (34.88, 40.06) | 7.16 (−0.81, 14.73) |
| Southern Latin America | 3551.94 (3360.44, 3753) | 7.43 (7.04, 7.84) | 16454.87 (14917.84, 17662.02) | 21.29 (19.32, 22.94) | 186.53 (159.09, 212.06) |
| High-income North America | 110519.7 (107667.40, 113278.24) | 35.69 (34.76, 36.64) | 243240.06 (234099.78, 249719.10) | 45.03 (43.51, 46.25) | 26.18 (21.67, 30.60) |
| Andean Latin America | 1493.30 (1311.10, 1694.55) | 5.44 (4.79, 6.18) | 4469.66 (3520.72, 5594.46) | 7.62 (6.01, 9.52) | 40.1 (8.41, 80.44) |
| Central Latin America | 8540.92 (8126.66, 8984.78) | 6.86 (6.63, 7.11) | 30003.18 (24869.81, 35597.06) | 12.21 (10.13, 14.51) | 77.86 (45.85, 111.83) |
| Tropical Latin America | 13610.42 (12785.64, 14665.37) | 10.99 (10.46, 11.69) | 43353.48 (39612.65, 46355.59) | 17.98 (16.40, 19.30) | 63.51 (41.51, 79.84) |
| North Africa and Middle East | 32358.21 (20550.87, 55563.11) | 8.87 (6.52, 13.39) | 38320.02 (30629.59, 47074.26) | 7.29 (5.82, 8.97) | −17.84 (−47.13, 19.10) |
| Central Sub-Saharan Africa | 367.62 (264.20, 546.24) | 0.75 (0.52, 1.20) | 730.96 (549.08, 963.01) | 0.68 (0.48, 0.95) | −8.74 (−37.30, 25) |

*(Continued)*

**TABLE 1 |** Continued

| | 1990 | | 2019 | | Percentage change in age-standardized rates between 1990 and 2019 (%) |
|---|---|---|---|---|---|
| | Counts (95% UI) | Age-standardized rate (per 100k) | Counts (95% UI) | Age-standardized rate (per 100k) | |
| Eastern Sub-Saharan Africa | 1259.88 (984.53, 1664.58) | 0.72 (0.50, 1.10) | 2611.94 (2137.47, 3162.18) | 0.70 (0.53, 0.90) | −2.23 (−24.82, 21.49) |
| Southern Sub-Saharan Africa | 830.17 (717.97, 947.57) | 2.26 (1.92, 2.59) | 1378.11 (1113.30, 1740.13) | 2 (1.61, 2.53) | −11.45 (−32.94, 22.62) |
| Western Sub-Saharan Africa | 2904.78 (2192.13, 3727.32) | 2.26 (1.63, 2.95) | 4907.83 (3849.77, 6230.45) | 1.64 (1.29, 2.10) | −27.67 (−50.27, 1.83) |
| Oceania | 163.73 (111.25, 226.23) | 4.19 (2.82, 5.88) | 219.34 (152.77, 311.34) | 2.3 (1.59, 3.32) | −45.06 (−57.93,−27.91) |
| Australasia | 9770.16 (9330.12, 10207.42) | 44.81 (42.66, 47.01) | 22404.22 (20249.28, 24424.65) | 53.46 (48.23, 58.57) | 19.30 (6.98, 32.37) |
| Caribbean | 2218 (1858.03, 2766.82) | 7.03 (6.18, 8.30) | 8184.36 (6603.55, 10106.40) | 16.38 (13.20, 20.43) | 133.07 (84.79, 192.48) |
| **Death** | | | | | |
| Global | 17653.17 (17010.69, 18269.68) | 0.43 (0.41, 0.44) | 39081.23 (36566.69, 41129.62) | 0.48 (0.45, 0.51) | 12.39 (5.71, 19.27) |
| East Asia | 2663.02 (2377.81, 2945.9) | 0.25 (0.22, 0.27) | 3072.55 (2627.3, 3569.17) | 0.16 (0.14, 0.18) | −35.31 (−46.51,−22.89) |
| Southeast Asia | 248.99 (214.58, 282.63) | 0.08 (0.07, 0.09) | 544.44 (443.3, 663.93) | 0.08 (0.07, 0.10) | 1.72 (−19.22, 23.69) |
| Central Asia | 21.64 (18.66, 27.74) | 0.04 (0.04, 0.05) | 49.13 (43.22, 56.06) | 0.06 (0.05, 0.06) | 37.79 (4.77, 67.94) |
| High-income Asia Pacific | 1141.94 (1098.81, 1179.04) | 0.6 (0.57, 0.62) | 2606.37 (2267.78, 2857.88) | 0.59 (0.53, 0.64) | −0.99 (−10.5, 7.93) |
| South Asia | 581 (415.94, 785.87) | 0.08 (0.06, 0.12) | 1945.55 (1498.29, 2432.51) | 0.13 (0.10, 0.16) | 54.31 (18.99, 101.97) |
| Central Europe | 393.57 (382.73, 405.58) | 0.29 (0.29, 0.30) | 756.25 (653.93, 860.78) | 0.40 (0.35, 0.46) | 36.7 (18.54, 55.35) |
| Eastern Europe | 297.33 (254.99, 408.05) | 0.11 (0.10, 0.15) | 971.69 (860.18, 1084.05) | 0.30 (0.27, 0.34) | 173.01 (92.82, 240.55) |
| Western Europe | 6315.26 (6109.95, 6446.10) | 1.17 (1.13, 1.19) | 12606.56 (11547.44, 13506.02) | 1.48 (1.37, 1.58) | 26.95 (17.95, 35.13) |
| Southern Latin America | 104.31 (98.98, 110.03) | 0.22 (0.21, 0.23) | 611.29 (554.79, 655.45) | 0.75 (0.68, 0.81) | 242.23 (210.3, 271.37) |
| High-income North America | 4175.26 (4034.67, 4285.74) | 1.22 (1.19, 1.26) | 10697.33 (10121.78, 11091.36) | 1.77 (1.68, 1.82) | 44.19 (38.81, 49.30) |
| Andean Latin America | 39.18 (34.63, 44.36) | 0.17 (0.15, 0.19) | 154.03 (121.92, 190.99) | 0.27 (0.21, 0.33) | 63.45 (27.76, 107.07) |
| Central Latin America | 206.03 (199.25, 212.88) | 0.20 (0.20, 0.21) | 987.61 (823.04, 1166.85) | 0.41 (0.34, 0.48) | 102.23 (67, 139.48) |
| Tropical Latin America | 339.4 (326.45, 356.83) | 0.32 (0.31, 0.34) | 1490.06 (1364.14, 1590.49) | 0.61 (0.56, 0.66) | 90.03 (68.72, 104.27) |
| North Africa and Middle East | 560.77 (414.24, 841.72) | 0.20 (0.16, 0.28) | 1067.64 (855.02, 1318.24) | 0.22 (0.18, 0.28) | 9.26 (−26.75, 51.11) |
| Central Sub-Saharan Africa | 7.23 (5.08, 11.68) | 0.02 (0.01, 0.04) | 14.83 (10.65, 20.57) | 0.02 (0.01, 0.03) | −11.41 (−40.72, 28.01) |
| Eastern Sub-Saharan Africa | 23.31 (16.85, 34.40) | 0.02 (0.01, 0.03) | 47.72 (36.74, 60.85) | 0.02 (0.01, 0.02) | −8.80 (−30.36, 15.93) |
| Southern Sub-Saharan Africa | 21.69 (18.36, 25.06) | 0.07 (0.06, 0.08) | 37.45 (30.16, 47.43) | 0.06 (0.05, 0.07) | −13.55 (−35.57, 21.73) |
| Western Sub-Saharan Africa | 75.18 (54.79, 97.51) | 0.07 (0.05, 0.09) | 120.67 (95.65, 154.05) | 0.05 (0.04, 0.06) | −29.89 (−52.67, 0.04) |
| Oceania | 4.87 (3.28, 6.84) | 0.14 (0.10, 0.20) | 6.21 (4.26, 9.02) | 0.08 (0.05, 0.11) | −47.87 (−59.78,−32.31) |
| Australasia | 379.17 (360.49, 395.74) | 1.63 (1.55, 1.70) | 1023.71 (914.65, 1126.65) | 2.13 (1.91, 2.34) | 30.60 (18.06, 42.89) |
| Caribbean | 54.02 (49.50, 60.30) | 0.19 (0.18, 0.21) | 270.14 (223.52, 321.49) | 0.53 (0.44, 0.63) | 179.60 (129.52, 239.82) |

*Data in parentheses are 95% uncertainty intervals (UI). MND, motor neuron disease; GBD, global burden of disease; DALY, disability-adjusted life-year; YLD, years lived with disability; YLL, years of life lost.*

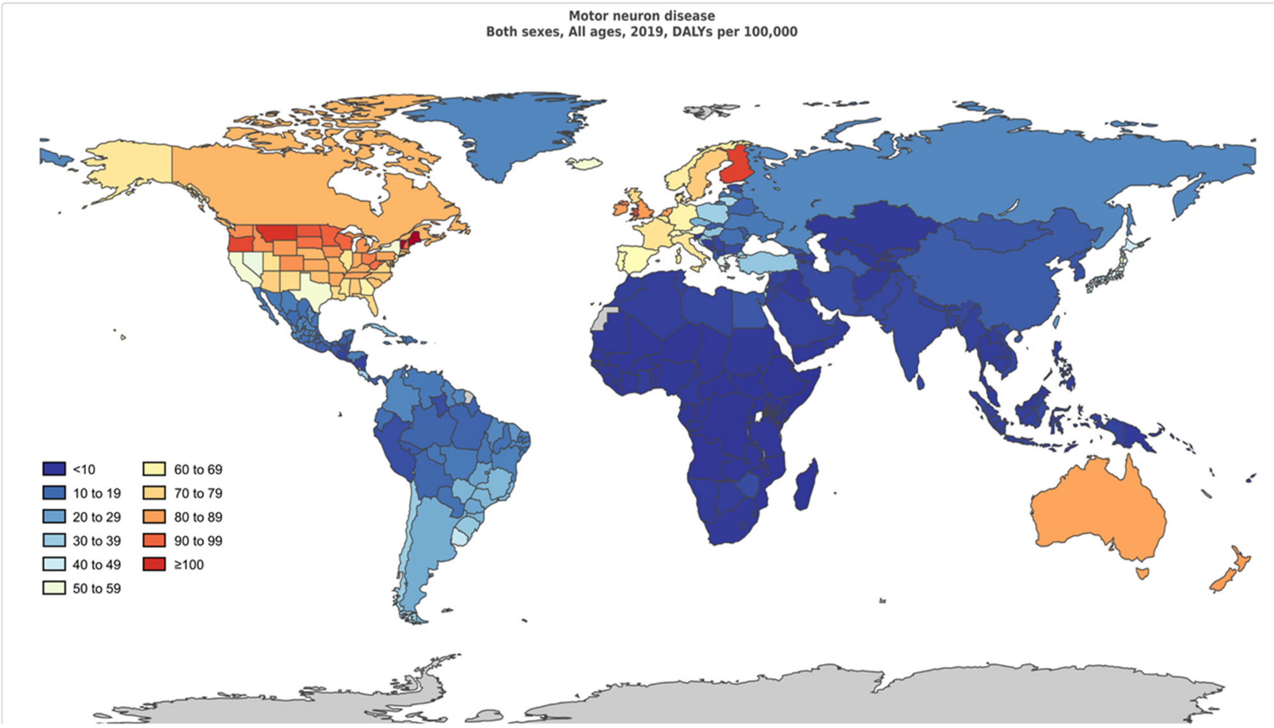


**FIGURE 1 |** Age-standardized disability-adjusted life-years per 100,000 population of motor neuron diseases by region for both sexes, 2019.

United Kingdom, the Netherlands, United States, and Canada showed relatively high age-standardized DALY rates and SDIs (**Figure 5**).

## DISCUSSION

We evaluated the burden of MNDs (estimated as incidence, prevalence, and DALYs) worldwide in 204 countries and territories from 1990 to 2019 using spatial Bayesian analyses. According to 2019 GBD estimates, age-standardized prevalence were 3.37 (95% UI, 2.9–3.87) per 100,000 population and age-standardized incidence were 0.79 (95% UI, 0.72–0.88) per 100,000 person-years for MND worldwide. In 2019, age-standardized DALY rate were 12.66 (95% UI, 11.98–13.29) per 100,000 population and age-standardized death rate were 0.48 (95% UI, 0.45–0.51) per 100,000 person-years associated with MND around the world. Global prevalence and deaths related to MNDs increased every year without significant changes in incidence. More than half of the prevalence and deaths due to MNDs occurred in three high-income regions (North America, Western Europe, and Australasia). In general, the prevalence, incidence, and DALYs value of MND were high in regions with high SDI, except in high-income East Asia where these values were relatively low despite similar SDI. These findings might suggest that not only sociodemographic development but also the genetic background might be responsible for the MND burden. Compared with the previous 2016 GBD MND results (9), our results showed that the global prevalence and DALYs of MNDs continued to increase similar to those in 2016, and the regional change of prevalence, DALYs showed a similar patterns as in 2016.

The age-standardized prevalence of MND seems to be increasing globally, a phenomenon that is more obvious in high-income countries. In contrast, the global age-standardized incidence of MND did not seem to increase to the same extent. However, when categorized by subcontinent in 2019, most of the age-standardized incidence increased significantly in the middle, high-middle, and high SDI regions. In the low and low-middle SDI regions, the age-standardized incidence either decreased or did not change significantly from 2009 to 2019. This phenomenon could be affected by whether accurate or early diagnosis is possible in the area where the incidence is analyzed. Since the El Escorial criteria were established in 1994 (14), the ALS diagnostic criteria were revised in 2000 (revised El Escorial criteria) and in 2008 (Awaji criteria) for early diagnosis and inclusion of more harmonized patients suitable for clinical trials (18, 19). The application of the latest diagnostic criteria for more accurate case ascertainment and access to specialists or medical institutions are largely affected by regional income levels. Similar geographical differences in MND incidence according to socioeconomic status or access to healthcare systems were also reported in the United States and Europe (20, 21). The non-significant changes in age-standardized incidence of MNDs in the low and low-middle SDI regions may indicate that the incidence is actually small in these region, but may be an underestimated number. The remarkable growth in prevalence

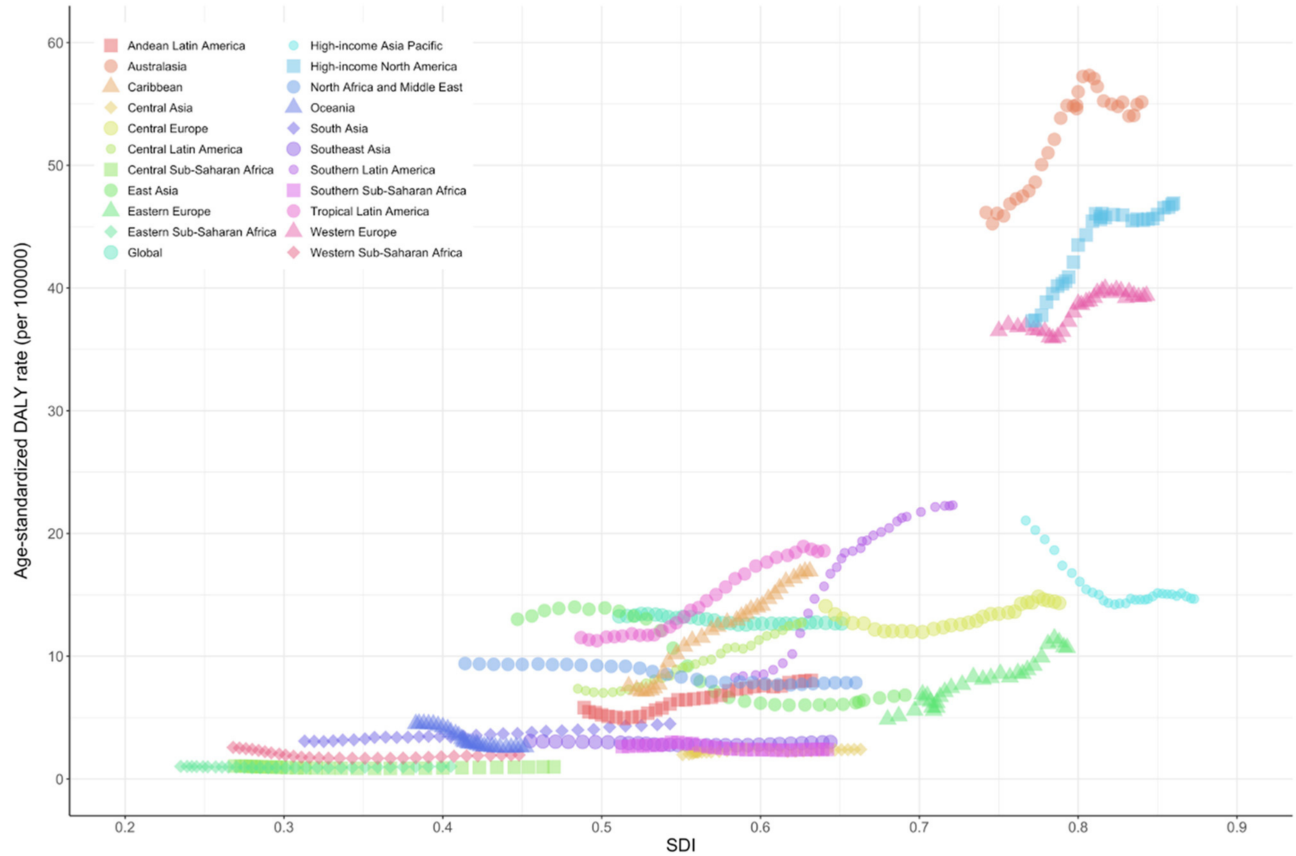


**FIGURE 2 |** Global disability-adjusted life-years and its age-standardized rate of motor neuron diseases by age and sex. Values are dotted at the midpoints of 5-year age categories. Shaded areas represent 95% uncertainty intervals of the age-standardized DALY rates. DALY, disability-adjusted life-years; UI, uncertainty interval.

with relatively stable or mild increment in incidence in the above regions could have been influenced by the increase in survival due to the development of therapies, such as the universal use of noninvasive ventilators in ALS or application of novel drugs (e.g., nusinersen for spinal muscular atrophy) in clinical practice (22, 23).

Racial diversity and geographic gradients regarding MND incidence were reported in several epidemiology studies. One study performed in New Jersey showed that the risk of ALS was higher in White patients than in Black and Asian patients (23). Mortality due to ALS, which is a surrogate marker of incidence, was the lowest in people of mixed ancestry compared to Black and White patients in Cuba (24). Because Cuba offers free national healthcare to all citizens, socioeconomic status was not the main factor for this discrepancy. In the meta-analysis pooled from 45 geographic areas, ALS incidence rates of populations with European ancestry (North America, Europe, New Zealand) showed homogeneous rates [1.81 (1.66–1.97)/100,000 person-years], which are higher than those of the populations of East Asia and South Asia [0.83 (0.42–1.24)/100,000 person-years; 0.73 (0.58–0.89)/100,000 person-years, respectively] (8). As observed in the previous 2016 GBD Study, our results showed that these geographical heterogeneities were independent of SDI in high-income East Asia, which supports the risk associated with genetic background and ancestry (18). *C9ORF72*, the most common causative gene for ALS (40% of familial ALS and 8% of sporadic), may be one possible reason for the high ALS incidence in North American and European populations (25). The frequency of *C9ORF72* mutation was much lower in South and East Asia (5.9% in familial and 1.6% in sporadic ALS in Iran; <4% in Japan and Korea) (26–28). However, as we observed in Guam and Kii Peninsula cases, where the extremely high ALS incidence rates dropped rapidly with westernization, both genetic and environmental factors might influence ALS incidence (29).

We analyzed the GBD project-specific measurement "DALY" to summarize the overall burden of a disease. The patterns of DALY and MND-associated death showed somewhat similar trend to that of prevalence in each continents: high age-standardized DALY number and rate in high SDI regions (except in the high-income Asia-Pacific region) and relatively low age-standardized DALY number and rate in middle and low SDI regions. The exception of reduced DALY in the high-income Asia-Pacific region might be partially due to different frequencies of ALS subtypes, different ratio of familial ALS and the coincidence of non-motor phenotypes (e.g., frontotemporal dementia) compared to other subcontinents. Bulbar-onset ALS,

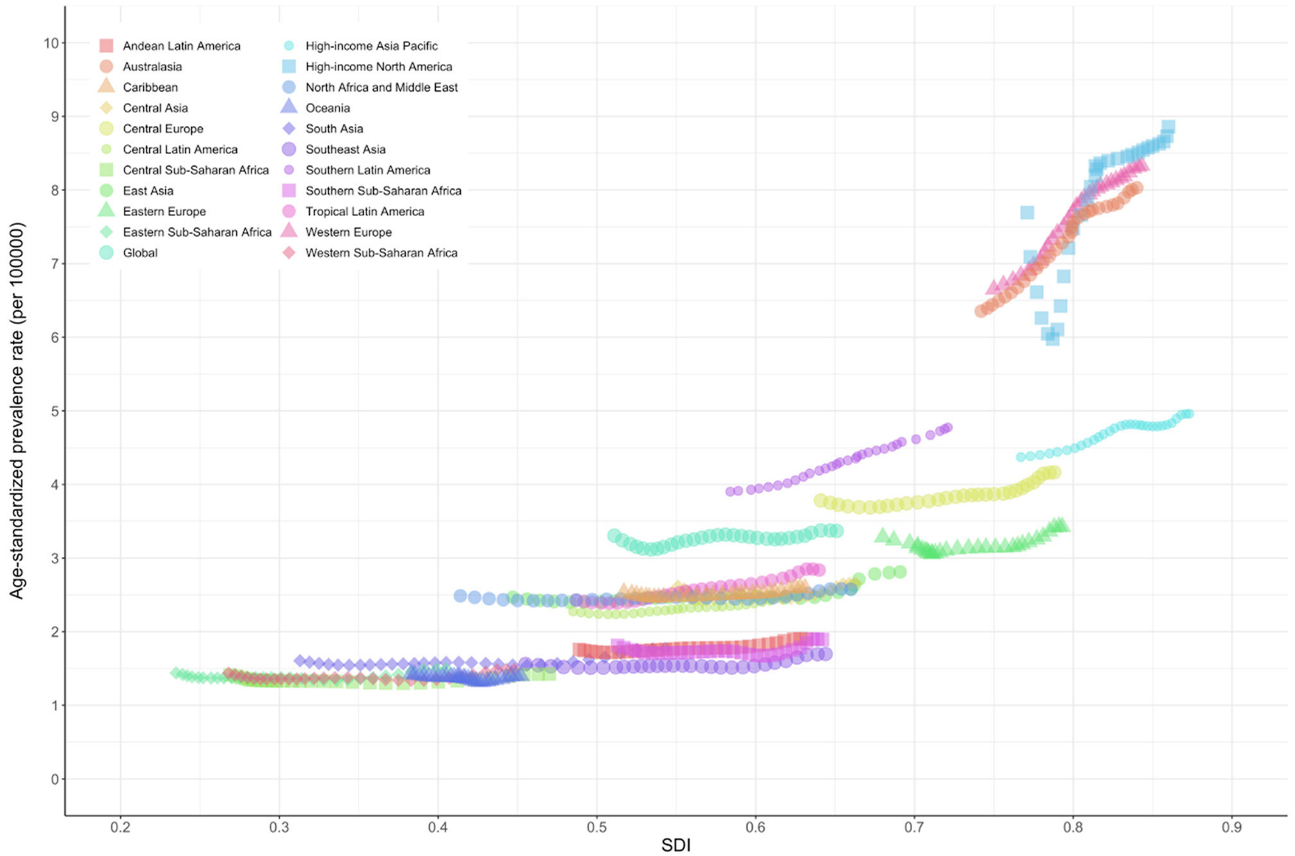


**FIGURE 3 |** Age-standardized prevalence rates of motor neuron diseases by Global Burden of Disease regions by sociodemographic index, 1990–2019. Age-standardized prevalence rates are presented as number affected by motor neuron diseases per 100,000 population. SDI, sociodemographic index.

which is well-known for its poor prognosis compared to limb-onset ALS, is more common in regions of European ancestry than in Asia (30). Similarly, frontotemporal dementia, highly connected with the presence of *C9ORF72* mutations, is more common in regions of European ancestry and might be the cause of high disability and death (25–28).

The number of DALY and age-standardized rates were consistently higher in males than in females in all age groups between 1990 and 2019. Because the effects of sex on survival were not dominant, this male preponderance of DALY might explain by the difference in prevalence between the sexes. The male preponderance in MND, especially in limb-onset ALS, was consistent with previous reports (8, 9, 31). Possible causes of the difference between males and females include the differences in exposure to environmental risk factors, response to exogenous toxins, and the nervous system structure and damage correction ability (31).

The age-standardized rate of DALYs of MND dramatically increased after age of 50, with a peak at 70–79 years followed by a rapid decline in both males and females. Given that ALS, which accounts for the largest proportion of MND, has a very short mean or median survival of 24–50 months from symptom onset, the changes in DALYs according to age in our results are consistent with the previous results showing the highest incidence between 70 and 74 years of age (20, 32). The rapid decline in DALYs and prevalence after the age of 80 requires caution in interpreting the phenomenon in that diagnostic ascertainment is not easy in the elderly. In elderly patients, it is generally more difficult to differentiate ALS mimic syndromes, and other comorbidities that can cause death are common. Moreover, elderly patients are less frequently referred to tertiary centers (because their weakness is more easily considered as due to aging and not pathological). The higher frequency of the bulbar-onset ALS with poor prognosis in older patients than in young patients may also be other causes of the rapid decline in DALYs and prevalence in people over 80 years of age. Another small peak of DALY occurs in the postneonatal period and this rate/number decreases until age 4. The high DALY rate in early childhood is considered to be a phenomenon from MNDs other than ALS—occurring mainly in childhood such as spinal muscular atrophy and hereditary spastic paraplegia—are included in the analysis.

This study has the same general limitations that inevitably occur in the design of GBD studies (33). First, although global epidemiology data were analyzed, relatively less data from regions other than Europe or North America were included in this study. The relatively small number of epidemiology studies in South and Central Asia, sub-Saharan Africa, and Latin America,

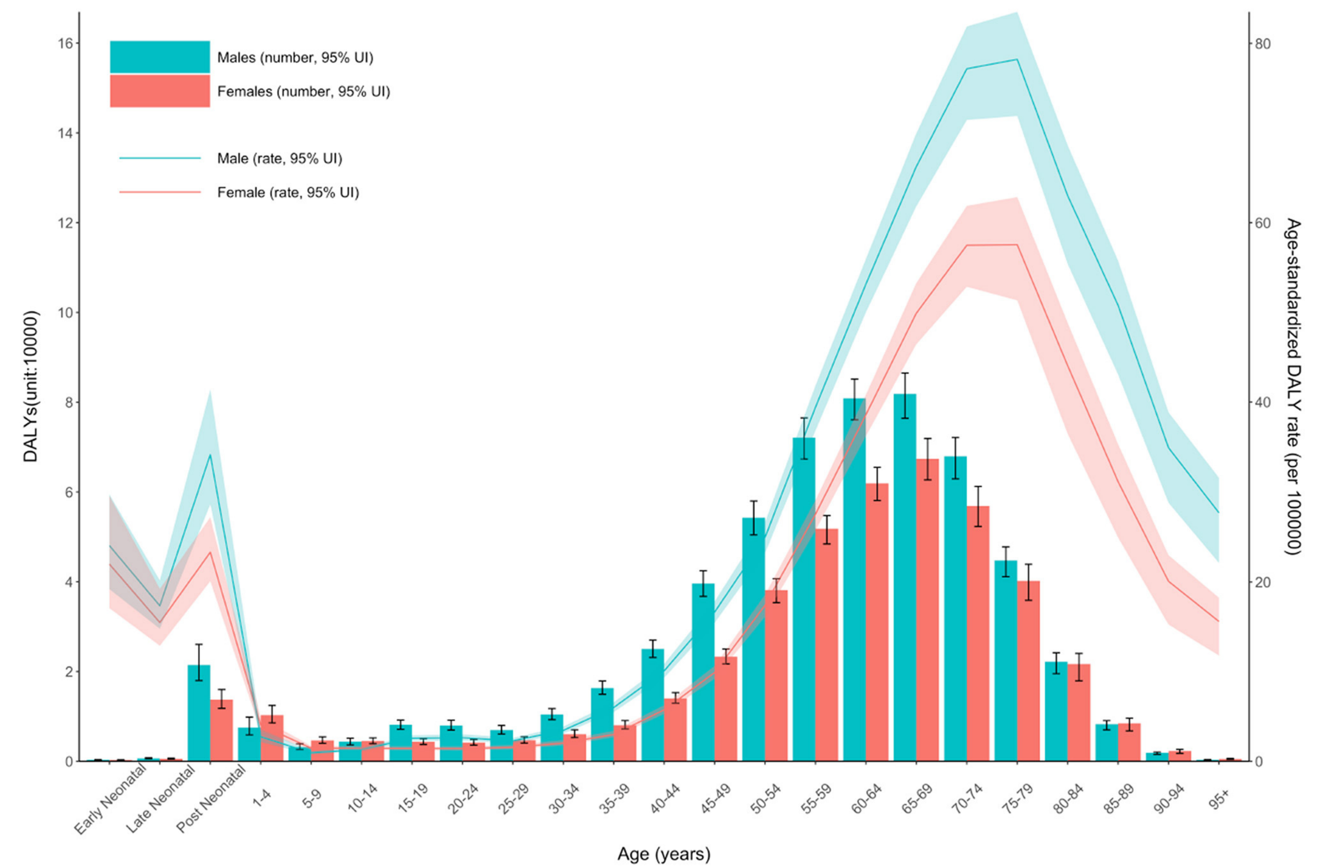


**FIGURE 4 |** Age-standardized DALY rate of motor neuron diseases by Global Burden of Disease regions by sociodemographic index, 1990–2019. Age-standardized DALY rates are presented as rates per 100,000 population. DALY, disability-adjusted life-years; SDI, sociodemographic index.

and the lack of access to medical facilities for diagnosing MNDs in these regions might be factors contributing to the relative low prevalence or incidence of MNDs in these regions. Second, the ICD version used for evaluating the death rate was changed from ICD-9 to ICD-10 during the study period. This evolution in the classification may have influenced the results. Third, the diagnosis of MND is known to be clinically challenging, and there is a possibility that certain categories, especially older individuals or ethnic minorities, may be underdiagnosed. In addition, the diagnostic criteria for MNDs have changed between 1990 and 2019, leading to differences in diagnostic sensitivity. However, the systematic bias of GBD estimates due to changes in diagnostic criteria during this study period was unclear (9). Fourth, because prevalence and DALYs are values related to incidence, disease duration, and survival, they are affected by the treatment methods or abilities of each region. Prevalence and DALYs may be high in high-income regions as access to and quality of treatment provision is high, and survival and disease duration are increased. In addition, treatment is affected not only by income level but also by the experience and preference of the local medical staff or the social climate for allowing treatment. This difference in treatment affects disease duration and survival. For example, in Japan, the rate of tracheostomy is 30%, whereas it is only 0–10% in Europe and the United States (34, 35). In contrast, non-invasive ventilators are used in 15–35% of patients in the United States, which is much higher than in Japan or Europe (36). Fifth, the prevalence rate confirmed in this study is slightly lower than the rates for ALS or early-childhood-onset MND (spinal muscular atrophy, hereditary spastic paraplegia) analyzed in other regional or meta-analysis studies. This is because this study analyzed diverse MNDs as one disease group and included the estimates of various races and regions.

In conclusion, the GBD of MND provides information on worldwide epidemiology, social influence, and risk factors of MNDs by using a standardized protocol. The global burden of MNDs is continuously increasing, especially in middle- and high-income areas. Because the number of epidemiology studies conducted in South and Central Asia, sub-Saharan Africa, and Latin America is small, and there is a high possibility that MNDs are underdiagnosed in the local system, the actual burden is expected to be higher than the presented results. In addition, the aging of the global population is expected to increase the share of the social burden of, for example, ALS, a neurodegenerative disease that mainly occurs in old age. The results of our analysis of the 2019 GBD 2019 Study may offer objective, recent information

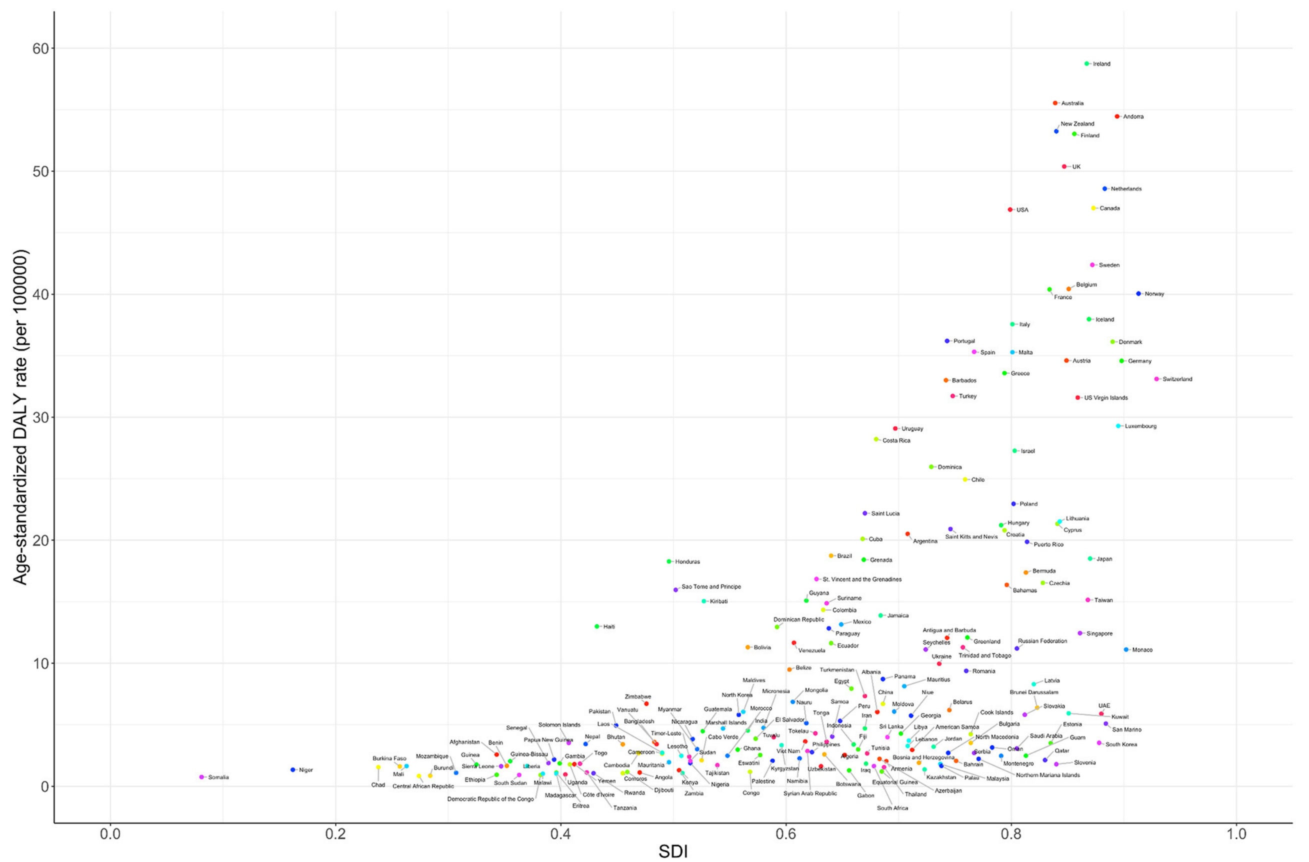


**FIGURE 5 |** Age-standardized DALY rate of motor neuron diseases according to country-specific sociodemographic index. Age-standardized DALY rates are presented as rates per 100,000 population. DALY, disability-adjusted life-years; SDI, sociodemographic index.

for resource allocation and healthcare planning related to MNDs at global and national levels.

## DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: the Institute for Health Metrics and Evaluation (IHME) Global Health Data Exchange (GHDx), http://ghdx.healthdata.org/gbd-results-tool.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

T-JS: concept and design, statistical analysis, administrative, technical, or material support, final approval of the version to be published, and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JP, J-EK, and T-JS: analysis and/or interpretation of data, drafting of the manuscript, critical writing or revising the intellectual content. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.864339/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Advances in the clinical application of orthotic devices for stroke and spinal cord injury since 2013

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Stroke and spinal cord injury are common neurological disorders that can cause various dysfunctions. Motor dysfunction is a common dysfunction that easily leads to complications such as joint stiffness and muscle contracture and markedly impairs the daily living activities and long-term prognosis of patients. Orthotic devices can prevent or compensate for motor dysfunctions. Using orthotic devices early can help prevent and correct deformities and treat muscle and joint problems. An orthotic device is also an effective rehabilitation tool for improving motor function and compensatory abilities. In this study, we reviewed the epidemiological characteristics of stroke and spinal cord injury, provided the therapeutic effect and recent advances in the application of conventional and new types of orthotic devices used in stroke and spinal cord injury in different joints of the upper and lower limbs, identified the shortcomings with these orthotics, and suggested directions for future research.

KEYWORDS
**orthotics, 3D-printing, motor dysfunction, stroke, spinal cord injury**

## 1. Introduction

Stroke and spinal cord injury (SCI) are common neurological disorders that can cause neurological dysfunctions (1, 2). Motor dysfunction is a common complication often accompanied by low muscle strength, muscular hypertonia, and limited joint activities. Serious complications, such as joint stiffness and muscle contracture, can easily occur if left untreated, significantly impacting the activities of daily living (ADL) and the long-term prognosis of patients (3).

Orthotic devices are special or general products developed using rehabilitation engineering technology that can prevent or compensate for the dysfunction in motor activities caused by neurological disorders. Orthotic devices can effectively reduce or overcome motor dysfunction and support rehabilitation training to improve movement and participation (4). Early use of orthotic devices with rehabilitation skills can rectify limb deformities and avoid secondary damage. The ADL and self-care ability of patients can be improved by improving their motor function and compensatory ability. Functional improvement may ease the burden on family and society and shorten rehabilitation (5, 6).

## 2. Methods

The first part briefly summarizes the epidemiological characteristics of stroke and SCI and shows the necessity for orthosis. The second section reviews progress with the clinical application of orthotic devices in stroke and SCI. In the second section, a literature search was conducted in November 2022, based on a selective search in the PubMed/MEDLINE databases to search the literature from January 1, 2013, up to September 30, 2022. We used search terms related to "stroke", "spinal cord injury", "orthosis", "orthoses", "orthotics", "orthotic device", "brace", "splint", and "arm sling". The literature search was limited to articles published in English in which the full text was available. This manuscript mainly included prospective and retrospective research articles of upper or lower limb orthotic devices for patients with stroke and SCI. Studies that involved spinal orthoses, devices implanted in the body, orthoses with electrical/electronic components (or involving electrical stimulation devices), robotic devices, and orthoses unrelated to limb joints were not included. Studies not related to the improvement of motor function or ADL were also excluded. Fifty seven articles were selected to be included in this study.

# 3. Discussion

## 3.1. Epidemiological characteristics of stroke and spinal cord injury and the need for orthotic devices

Stroke is a common cause of hemiplegia. It is a group of acute cerebrovascular diseases that can induce many complications, including motor and cognitive dysfunction, aphasia/dysarthria, and psychological problems, which affect survivors' social activities and quality of life (7, 8). Motor dysfunction was the most common complication associated with stroke (9). It often has manifestations, such as low muscle strength, dystonia, and limited joint activities, which seriously affect the patient's balance, walking ability, and ADL (8). Stroke is characterized by a high prevalence in disability, recurrence, and mortality and is the second leading cause of death worldwide (10). In the United States, ∼795,000 people experience a new or recurrent stroke each year. Approximately 7.0 million people over 20 years of age have experienced a stroke. The overall prevalence of stroke was ∼2.5%. It is estimated that by 2030, there will be an increase of 3.4 million people with stroke in people over 18 years, and the prevalence will increase by 20.5% compared to 2012(11).

SCI is also a common central nervous system injury caused by traffic crashes, falls, and violence. SCI usually results in severe disruption of sensorimotor and autonomic nerve functions and may lead to severe physical and psychological problems in survivors. Tetraplegia and paraplegia are the most common sequelae of SCI (12), indicating that motor dysfunction occurs in the injury plane and is accompanied by abnormal muscle tension and pathological reflexes. Survivors may face permanent impairments, and only a few have completed neurological recovery. This can impose a heavy burden on individuals, families, and society. SCI can lead to severe morbidity and mortality and is estimated to affect 250,000–500,000 people annually (13). In Western Europe, the incidence of new cases of SCI is ∼16–19.4 per million people annually (14).

In these neurological disorders, if spasticity, joint range of motion, and motor dysfunction are not reduced and corrected early, complications such as limited joint movement and stiffness, and muscle contracture will occur that can affect patients' quality of life. It is estimated that the global population of people with disabilities may exceed one billion, and more than half of them live in low- and middle-income countries (15). Although assistive devices may improve the function of people with disabilities, only 5–15% of people in need currently have access to assistive devices (16). Orthotics and prosthetics are important assistive devices. The orthotic device is an external application device used to restore and maintain anatomical and functional position and to assist the functions of the human body (17, 18). Common orthoses include upper limb orthosis, lower limb orthosis, and spinal orthosis according to the part of the body it is used. In addition, the main function of compression/containment orthosis is to improve limb stability by stabilizing the joints, and functional orthosis can control limb activities by stabilizing, supporting, strengthening, and protecting limbs based on joint stabilization and can also correct deformities and relieve pain (17, 19). Studies indicate that orthotics can effectively improve patients' function and prognoses and should be widely popularized (4–6).

## 3.2. Advances in the use of common orthotic devices

To prevent contracture, limbs with motor dysfunction must maintain a joint range of motion. Methods to maintain the joint range of motion of limbs include normal limb position, stretching and standing training, and the use of orthotic devices. Early use of orthotic devices can play a role in early prevention, improve therapeutic effect, lay a stable foundation for later rehabilitation, and prevent joint deformities. It also helps control muscle tension, improve joint range of motion, prevent muscle contracture, and maintain physical alignment of the limbs. The classification of orthotic devices reviewed in this article is shown in Figure 1. The characteristics of the articles are summarized in Table 1.

### 3.2.1. Upper limb orthotic devices

Hemiplegia due to stroke and quadriplegia due to SCI can cause upper limb motor dysfunction. Upper-limb orthotic devices are widely used in stroke and SCI. They can prevent and correct upper limb deformities, keep the limbs in functional position, provide traction to prevent joint contracture, partially compensate for the function of disabled muscles, and help to treat upper limb motor dysfunction.

#### 3.2.1.1. Shoulder orthotic devices

Shoulder orthotic devices are commonly used to treat glenohumeral subluxation (GHS). GHS, also known as shoulder subluxation, is a common complication in hemiplegia. GHS can cause loss of range of motion due to the instability of the shoulder joint. Approximately 80% of stroke patients with hemiplegia may experience GHS (20), and if left untreated may cause shoulder pain, upper extremity edema, and limited shoulder joint movement. A study compared the efficacy of hemi-sling to a lap-tray combined with a triangle sling in GHS among acute stroke survivors. The

Abbreviations: GHS, glenohumeral subluxation; SCI, spinal cord injury; ADL, activities of daily living; 3D, three-dimensional; 3D-DHD, 3D printed dynamic hand device; HKAFO, hip-knee-ankle-foot orthosis; HESWO, hip energy storage walking orthosis; RGO, reciprocating-gait orthosis; ARGO, advanced RGO; IRGO, isocentric RGO; KAFO, knee-ankle-foot orthosis; KO, knee orthosis; KIB, knee immobilization brace; FLO, Foot Lifter Orthosis®; AFO, ankle-foot orthosis; AFO-OD, AFO with oil damper; PLS AFO, posterior leaf spring AFO.

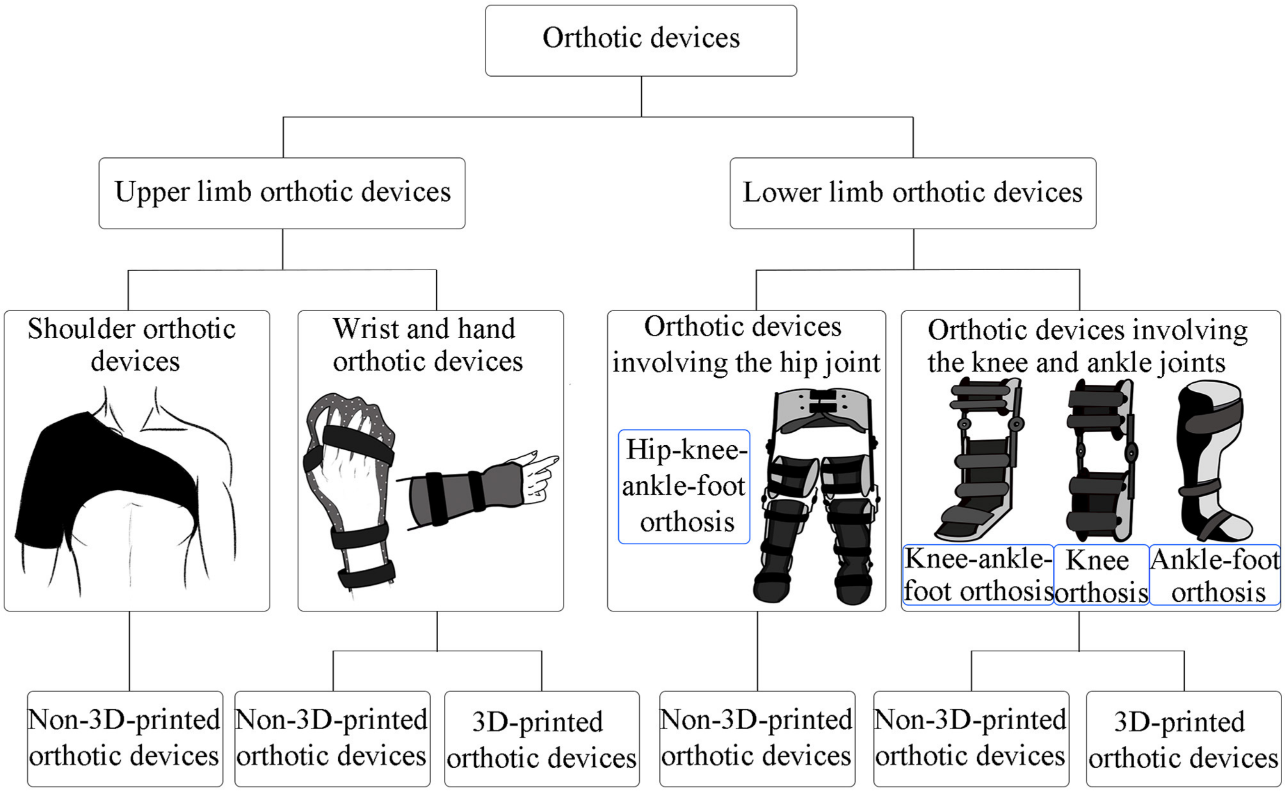


FIGURE 1
Classification of orthotic devices in the article.

result showed no significant difference between the two groups in preventing subluxation, pain, contracture, or movement limitation (21). This suggests that further studies may be needed to find effective shoulder support devices for patients with GHS. Van et al. (22) also compared different arm slings and found that the shoulderlift that directly supports the shoulder joint was more efficient than the Actimove® sling in reducing pain. However, subluxation was reduced only in the control group without slings, suggesting that orthoses may affect active correction. Although studies have shown that wearing orthoses is helpful for recovery in GHS, they should be removed promptly if necessary. The selection of orthotics and the appropriate time for wearing them may require further research.

X-ray findings suggest an improvement in GHS in some studies (23, 24). In a study, radiography revealed that wearing an orthosis reduced the vertical displacement of the glenohumeral joint in stroke patients (23). In another study using an elastic dynamic shoulder sling in stroke patients with GHS, radiography showed that the horizontal distance from the humeral head to the glenoid fossa improved compared to the control group (Bobath sling) (24). Considering that orthoses provide immediate improvement of GHS, and different orthoses have different effects on GHS recovery, it is necessary to adapt the best orthotic devices. Meanwhile, the results showed that the improvement in motor function was more pronounced after 8 weeks than after 4 weeks in the group (24). This suggests that the length of wearing time affects the functional improvement. However, the results also indicated no significant difference in motor and ADL functions between the groups (24). Studies suggest that improving motor function is an important method to recover from GHS, and further studies may be needed to consider suitable orthoses and GHS improvement methods for patients.

Interestingly, wearing shoulder orthotics also affected gait efficiency. Some studies have shown that patients with GHS after stroke wore shoulder support arm slings, which could reduce energy consumption and increase walking distance (25, 26). This suggests that posture correction may improve motor function. Dysfunction of different parts may affect each other, and rehabilitation after stroke should be comprehensive.

#### 3.2.1.2. Wrist and hand orthotic devices

Depending on the disorders, the wrist and hand orthotic devices can take various forms, such as wrist stabilization, wrist-hand stabilization, and wrist-finger stabilization. The biomechanical principle is to assist in the extension of the wrist and finger joints (77). Hemiplegic spasm is a common complication; the incidence of hemiplegic spasm in the 1st year after stroke is between 33 and 78%, and the incidence of contracture is at least 50% (78). Early prevention and treatment, such as passive stretching, can increase muscle extensibility and effectively reduce muscle spasms to improve the recovery of upper limb function. Wrist and hand orthotic devices assist in the stabilization of the wrist and hand in a functional position and may be considered an effective method of passive stretching to reduce wrist flexor spasticity. Wrist and hand orthotic devices often prevent wrist and finger contractures in hemiplegic survivors, but their effectiveness is unclear (79). A study using task-specific training combined with wrist-finger extension splints in hemiplegic

TABLE 1 Characteristics of included studies.

| Limbs | Joints | Reference | Participants | Type of orthoses | Applied orthoses | Major findings |
|---|---|---|---|---|---|---|
| Upper limb | Shoulder | Ada et al. (21) | ($n = 46$) Stroke | Non-3D-printed | Triangular sling, hemi-sling | Modified lap-tray combined with triangular sling showed no significant difference compared to hemi-sling in preventing GHS. |
| | | Van et al. (22) | ($n = 28$) Stroke | Non-3D-printed | Shoulderlift, Actimove® sling | Actimove® sling: more pain at rest ($P = 0.036$). No sling: decrease in subluxation (-37.59% or 3.30mm). |
| | | Hesse et al. (23) | ($n = 40$) Stroke | Non-3D-printed | New shoulder orthosis | Using orthosis significantly decreased the vertical distance between acromion point and the central point of the humeral head by an average of 0.8cm. |
| | | Kim et al. (24) | ($n = 41$) Stroke | Non-3D-printed | Elastic dynamic sling, Bobath sling | Horizontal distance significantly decreased in the elastic dynamic sling group compared with the Bobath sling group ($P = 0.006$). No significant difference in motor and ADL functions between the groups. |
| | | Jeong et al. (25) | ($n = 57$) Stroke | Non-3D-printed | Arm sling | Using arm sling could reduce the energy cost compared to no sling ($P < 0.05$), and walking distance of 6MWT was significantly increased ($P < 0.05$) among the patients with single cane and arm sling. |
| | | Jeong et al. (26) | ($n = 57$) Stroke | Non-3D-printed | Arm sling | Using arm sling could reduce energy consumption and increase walking endurance compared with no sling ($P < 0.01$). |
| | Wrist and hand | Khallaf et al. (27) | ($n = 24$) Stroke | Non-3D-printed | Wrist-finger extension splint | Task-specific training and wrist-finger extension splint were effective in improving the results of nine holes peg test, FMA-UE, and joint range of motion ($P \leq 0.05$). |
| | | Wong et al. (28) | ($n = 30$) Stroke | Non-3D-printed | Dynamic hand orthosis | No significant difference in motor function improvement between task-oriented training combined with dynamic hand orthosis group and task-oriented training alone group. |
| | | Lannin et al. (29) | ($n = 9$) Stroke | Non-3D-printed | SaeboFlex | Although using SaeboFlex showed no significant difference on the assessment scales, the hand function had a greater improvement trend than that of the usual rehabilitation group. |
| | | Woo Y et al. (30) | ($n = 5$) Stroke | Non-3D-printed | SaeboFlex | Using SaeboFlex showed significant improvement in FMA-UE ($P < 0.05$). |
| | | Zheng et al. (31) | ($n = 40$) Stroke | 3D-printed, non-3D-printed | 3D-printed orthosis, low-temperature thermoplastic plate orthosis | 3D-printed orthoses significantly improved the modified Ashworth scale ($P = 0.02$), passive extension of wrist joint($P < 0.001$), and FMA ($P < 0.001$) compared to low-temperature thermoplastic plate orthoses. |
| | | Chen et al. (32) | ($n = 6$) Stroke | 3D-printed | 3D-printed multifunctional hand device | 3D-printed multifunctional hand device significantly improved the ARAT scores, grip force and lateral pinch force ($P < 0.05$). |
| | | Yang et al. (33) | ($n = 8$) Stroke | 3D-printed | dynamic splint | Dynamic splints could improve the hand function and decrease the spasticity ($P < 0.05$). |

*(Continued)*

TABLE 1 (Continued)

| Limbs | Joints | Reference | Participants | Type of orthoses | Applied orthoses | Major findings |
|---|---|---|---|---|---|---|
| | | Wang et al. (34) | ($n = 13$) Stroke | 3D-printed | 3D printing fingerboard | 3D printing fingerboard could improve the hand function and reduce the muscle tension. |
| | | Huang et al. (35) | ($n = 10$) Stroke | 3D-printed | 3D-DHD | 3D-DHD could significantly improve the results of BBT and the palmar pinch force test ($P < 0.05$). |
| | | Kang et al. (36) | ($n = 24$) SCI | Non-3D-printed | Wrist-driven flexor hinge orthosis | Wrist-driven flexor hinge orthosis could improve pinch force ($P < 0.001$). |
| | | Frye et al. (37) | ($n = 19$) SCI | Non-3D-printed | Prefabricated/custom-made resting hand splint | The outcomes of GRASSP had no significant difference between prefabricated and custom-made resting hand splints. |
| | | Portnova et al. (38) | ($n = 3$) SCI | 3D-printed | 3D-printed wrist-driven orthosis | 3D-printed wrist-driven orthosis could reduce assembly time and the cost of materials, and improve hand function. |
| Lower limb | Hip-knee-ankle | Yang et al. (39) | ($n = 12$) SCI | Non-3D-printed | HESWO, IRGO | HESWO could increase walking distance and speed, and reduce energy consumption compared with RGO ($P < 0.05$). |
| | | Arazpour et al. (40) | ($n = 4$) SCI | Non-3D-printed | ARGO | Compared with the standard ARGO, the ARGO with a rocker sole could significantly improve walking speed, step length, hip flexion and extension ($P < 0.05$). |
| | | Bani et al. (41) | ($n = 4$) SCI | Non-3D-printed | ARGO | ARGO with dorsiflexion assist AFO could significantly improve walking speed and stride length compared to that with SAFO ($P < 0.05$). |
| | | Arazpour et al. (42) | ($n = 5$) SCI | Non-3D-printed | ARGO | ARGO with dorsiflexion assist AFO significantly improved walking speed and endurance compared to that with SAFO ($P < 0.05$). |
| | | Samadian et al. (43) | ($n = 6$) SCI | Non-3D-printed | IRGO | Walking speed when using IRGO significantly improved after 4, 8, and 12 weeks compared to baseline ($P = 0.010$, $P = 0.003$, and $P = 0.005$). |
| | | Arazpour et al. (44) | ($n = 9$) SCI | Non-3D-printed | IRGO | IRGOs with a reciprocating link significantly improved gait speed and step length compared to IRGO without it ($P < 0.05$). |
| | | Karimi et al. (45) | ($n = 5$) SCI | Non-3D-printed | RGO, KAFO | Newly developed RGO significantly improved standing stability compared to KAFO ($P < 0.05$). |
| | | Karimi et al. (46) | ($n = 3$) SCI | Non-3D-printed | RGO, KAFO | Compared with the KAFO, energy consumption of the newly developed RGO was significantly reduced ($P < 0.05$). |
| | Knee | Portnoy et al. (47) | ($n = 31$) Stroke | Non-3D-printed | Hinged soft KO | Using KO could significantly improve the results of BBS, 6MWT, 10MWT and TUGT ($P < 0.05$). |
| | Knee-ankle | Sato et al. (48) | ($n = 112$) Stroke | Non-3D-printed | KAFO | Using KAFO early could improve FIM gain ($P = 0.032$) compared with delayed using group. |

*(Continued)*

TABLE 1 (Continued)

| Limbs | Joints | Reference | Participants | Type of orthoses | Applied orthoses | Major findings |
|---|---|---|---|---|---|---|
| | | Maeshima et al. (49) | ($n = 50$) Stroke | Non-3D-printed | APS KAFO, traditional KAFO | APS KAFO was more suitable for patients with better motor function, traditional KAFO was more suitable for patients with severe symptoms. |
| | | Talu et al. (50) | ($n = 20$) Stroke | Non-3D-printed | KIB, FLO | Among different combinations, KIB combined with FLO was the most helpful in improving the standing balance ($P < 0.05$). |
| | Ankle | Carse et al. (51) | ($n = 8$) Stroke | Non-3D-printed | SAFO | SAFO could significantly improve walking velocity, step length, and cadence of patients ($P < 0.05$). |
| | | Pongpipatpaiboon et al. (52) | ($n = 24$) Stroke | Non-3D-printed | Thermoplastic AFO, APS AFO | AFO increased toe clearance ($P = 0.038$) and limb shortening ($P < 0.0001$), and diminished hip elevation due to pelvic obliquity ($P = 0.003$). No statistical difference between different AFOs. |
| | | Tsuchiyama et al. (53) | ($n = 32$) Stroke | Non-3D-printed | Thermoplastic AFO, APS AFO | AFO could significantly improve gait stability ($P < 0.05$). However, in patients with mild ankle impairment, the results showed a worsening trend after wearing an AFO. |
| | | Lan et al. (54) | ($n = 20$) Stroke | Non-3D-pringted | Plastic AFO | AFO could significantly improve walking capacity ($P < 0.05$). |
| | | Do et al. (55) | ($n = 17$) Stroke | Non-3D-printed | Hybrid AFO, plastic AFO | Using AFO significantly increased walking speed compared to barefoot ($P < 0.05$). The hybrid and plastic AFOs showed similar effects in motor function. |
| | | Rao et al. (56) | ($n = 23$) Stroke | Non-3D-printed | Plastic AFO | With AFOs, the results of the functional reach test significantly improved compared to those without orthoses ($P < 0.05$). |
| | | Momosaki et al. (57) | ($n = 1863$) Stroke | Non-3D-printed | AFO | AFO significantly improved the FIM compared to no orthotics ($P < 0.05$). |
| | | Zollo et al. (58) | ($n = 10$) Stroke | Non-3D-printed | SAFO, dynamic AFO | No significant difference between patients with solid and dynamic AFOs. |
| | | Kim et al. (59) | ($n = 9$) Stroke | Non-3D-printed | Elastic band-type AFO, plastic AFO | The maximum dorsiflexion value of ankle joint increased significantly after using elastic band-type AFO ($P < 0.005$). |
| | | Kim et al. (60) | ($n = 10$) Stroke | Non-3D-printed | Elastic AFO, plastic AFO | Postural stability index significantly improved with AFOs compared to no orthotics ($P < 0.05$). Elastic AFO improved some aspects of postural stability more substantially than hard plastic AFO. |
| | | Farmani et al. (61) | ($n = 18$) Stroke | Non-3D-printed | Rocker bar AFO, SAFO | Rocker bar AFO significantly increased step length and gait velocity, and reduced the preswing time compared to SAFO ($P < 0.05$). |
| | | Karakkattil et al. (62) | ($n = 20$) Stroke | Non-3D-printed | Double-adjustable AFO, PLS AFO | No significant difference between using double-adjustable AFO and PLS AFO in distance of 6MWT, gait symmetry and velocity. |

*(Continued)*

TABLE 1 (Continued)

| Limbs | Joints | Reference | Participants | Type of orthoses | Applied orthoses | Major findings |
|---|---|---|---|---|---|---|
| | | Nikamp et al. (4) | ($n = 33$) Stroke | Non-3D-printed | Rigid/semi-rigid/flexible non-articulated AFO | Using AFO could significantly improve the BBS, 6MWT, functional ambulation categories and TUGT in both groups (early or delayed provision) ($P < 0.05$). Early AFO provision could significantly improve the results of BBS and the Barthel index compared with delayed provision ($P < 0.05$). |
| | | Nikamp et al. (63) | ($n = 33$) Stroke | Non-3D-printed | Rigid/semi-rigid/flexible non-articulated AFO | Early or delayed AFO provision did not show any difference on outcome measures after 26 weeks. |
| | | Nikamp et al. (64) | ($n = 26$) Stroke | Non-3D-printed | Rigid/semi-rigid/flexible non-articulated AFO | Early or delayed AFO provision showed no kinematic differences for joint angles. |
| | | Nikamp et al. (65) | ($n = 20$) Stroke | Non-3D-printed | Rigid/semi-rigid/flexible non-articulated AFO | Early or delayed AFO provision did not affect outcome measures. |
| | | Nikamp et al. (66) | ($n = 33$) Stroke | Non-3D-printed | Rigid/semi-rigid/flexible non-articulated AFO | Early AFO provision increased the incidence of falls compared with delayed provision ($P = 0.039$), but 63.6% of falls occurred while the patient was not wearing an AFO. |
| | | Pomeroy et al. (67) | ($n = 105$) Stroke | Non-3D-printed | AFO | The therapist-made AFO did not improve the effectiveness of conventional physical therapy. |
| | | Pourhoseingholi et al. (68) | ($n = 15$) Stroke | Non-3D-printed | Spring damper AFO, PLS AFO | Newly developed spring damper AFO could significantly improve the results of the BBS, TUGT and ABC compared to the PLS AFO ($P < 0.05$). |
| | | Yamamoto et al. (69) | ($n = 36$) Stroke | Non-3D-printed | AFO-OD, nonarticulated AFO | AFO-OD group showed more obvious improvement in ankle joint kinematics and kinetics than those of the nonarticulated AFO group. |
| | | Kimura et al. (70) | ($n = 8$) Stroke | Non-3D-printed | AFO-OD | AFO-OD significantly improved gait parameters compared to without orthosis ($P < 0.05$). |
| | | Yamamoto et al. (71) | ($n = 40$) Stroke | Non-3D-printed | AFO with plantar flexion stop, AFO-OD | After using orthotics, AFO-OD group had decreased thoracic tilt. But the AFO with plantar flexion stop group had increased pelvic forward tilt compared with no orthotics. |
| | | Koller et al. (72) | ($n = 10$) Stroke | Non-3D-printed | Passive-dynamic AFO, hinged AFO | With the passive-dynamic AFO, improvements in gait-related parameters were observed in some participants. |
| | | Tyson et al. (73) | ($n = 139$) Stroke | Non-3D-printed | Prefabricated PLS AFO, custom-made AFO | The user satisfaction and walking function had no significant difference between prefabricated and custom-made AFOs. |
| | | Liu et al. (74) | ($n = 12$) Stroke | 3D-printed | AFO | Compared with no AFO, gait velocity and stride length with AFO increased significantly ($P = 0.001$, $P = 0.002$). Although with no significant difference, the double limb support phase decreased with AFO. |

*(Continued)*

TABLE 1 (Continued)

| Limbs | Joints | Reference | Participants | Type of orthoses | Applied orthoses | Major findings |
|---|---|---|---|---|---|---|
| | | Hsu et al. (75) | ($n = 7$) Stroke | 3D-printed, non-3D-printed | Anterior AFO, 3D-printed ideal training AFO | Ideal training AFO increased ankle dorsiflexion during the swing phase and extended the duration of paralyzed lower limb standing phase compared with conventional AFO. |
| | | Arazpour et al. (76) | ($n = 5$) SCI | Non-3D-printed | SAFO, hinged AFO | Step length: barefoot 26.3 ± 16.37cm, SAFO: 31.3 ± 17.27cm, hinged AFO 28.5 ± 15.86cm. Only step length between SAFO and barefoot showed significant difference ($P < 0.05$). |

APS, adjustable posterior strut; 6MWT, 6-minute walk test; FMA, Fugl-Meyer assessment; FMA-UE, FMA of upper extremity; BBT, box and blocks test; FIM, functional independence measure; BBS, Berg balance scale; 10MWT, 10-m walk test; TUGT, timed up and go test; ABC, activities-specific balance confidence; ARAT, action research arm test; GRASSP, graded redefined assessment of strength, sensation and prehension; GHS, glenohumeral subluxation; SCI, spinal cord injury; ADL, activities of daily living; 3D, three-dimensional; 3D-DHD, 3D printed dynamic hand device; HESWO, hip energy storage walking orthosis; RGO, reciprocating-gait orthosis; ARGO, advanced RGO; IRGO, isocentric RGO; KAFO, knee-ankle-foot orthosis; KO, knee orthosis; KIB, knee immobilization brace; FLO, Foot Lifter Orthosis®; AFO, ankle-foot orthosis; AFO-OD, AFO with oil damper; PLS AFO, posterior leaf spring AFO; SAFO, solid AFO.

patients, showed effective improvements in finger dexterity, upper limb motor function, and range of motion of the wrist and hand joints (27). However, another study suggested that task-oriented training combined with dynamic hand orthosis did not significantly improve motor function compared to task-oriented training alone in patients with subacute stroke (28). Further studies are needed to determine the timing and circumstances of wearing orthoses, considering that not all cases using orthotic devices had beneficial effects on motor function improvement compared with no orthotics. However, sample size and other factors may have influenced the results.

Patients with cervical SCI are prone to quadriplegia, and after rehabilitation treatment, the recovery of motor function is often incomplete, and orthotic assistance is needed. The wrist-driven flexor hinge orthosis, a device designed to restore hand function by providing three-point prehension, has been used in patients with SCI and has shown a significant increase in pinch force (36). Using orthoses can improve the patient's hand function, which is helpful for ADL, such as eating. A study comparing prefabricated and custom-made resting hand splints among SCI patients showed no statistical difference (37). Although custom-made orthotic devices are generally recommended in clinical practice, sometimes their advantages are minimal, and they have the disadvantages of being time-consuming and expensive. In some cases, prefabricated orthotics can also be used. However, the custom-made orthotic devices require further improvement.

There are some special orthoses for the recovery of motor function in patients. One study showed that SaeboFlex, a spring-assisted orthosis, helped improve hand dexterity in patients with almost complete loss of hand function after stroke (29). Additionally, a study showed that SaeboFlex significantly improved upper limb motor function in patients with stroke (30). Considering that if static hand orthoses cannot effectively improve distal upper-limb motor function, it is necessary to use appropriate orthoses to improve hand function effectively.

Currently, conventional wrist and hand orthotic devices have certain disadvantages. Some of them are bulky, and their customization is time-consuming. With technological advances, numerous new orthotic devices have emerged, including custom-made three-dimensional (3D) printed orthoses. With 3D printing technology, orthoses can be accurately designed using computer graphics program, which can solve the problems of time-consuming manufacturing and difficult customization of conventional orthotic devices. The materials used for 3D printing are also readily available (80), and 3D-printed orthoses can be made of lightweight, ventilating, and biodegradable materials (81). A study compared two different types of wrist-hand orthoses, and the results showed that the therapeutic effect of 3D-printed orthoses was better than that of low-temperature thermoplastic plate orthoses. Compared with the other orthosis, 3D-printed orthosis could better reduce the spasticity of stroke patients and had an important effect on improving the motor function of the wrist joint (31). Since 3D-printed orthoses can be customized more accurately through software and are more adaptable to patients than conventional orthoses, they may provide better support. Some studies have shown that 3D-printed orthotic devices can effectively improve patients' hand function (32–34) and compared the effects of wearing time (3 weeks vs. 3 months). The results showed that the grip strength and hand function of stroke patients tended to improve with an increase in wearing time, although the difference was insignificant (34). Considering that 3D-printed orthotics can effectively improve patients' hand function, prolonging wearing time will not cause adverse reactions but will further improve the motor function of the patients. Furthermore, a 3D-printed dynamic hand device (3D-DHD) was used to supplement task-oriented training in stroke survivors. The results showed that the improvement in hand function in the 3D-DHD group was greater than that in the task-oriented training alone group (35). This suggests that 3D-printed orthoses combined with appropriate rehabilitation methods can more effectively improve the motor function of patients.

3D-printed orthoses can also be used in patients with SCI. A study has shown that using 3D printing technology to make wrist-driven orthoses could reduce hands-on assembly time and the cost of the material. In addition, hand function in patients with SCI could improve (38). Considering with 3D printing technology, we developed an orthosis that can accurately adapt to a user, and its function is not inferior to that of conventional technology. Although 3D printing technology may require more conditions, it is worth promoting and can compensate for the many defects of conventional orthoses.

### 3.2.2. Lower limb orthotic devices

Hemiplegia and SCI-induced tetraplegia/paraplegia are common causes of lower limb motor dysfunction. Lower-limb orthotic devices can support body weight, prevent and correct lower-limb deformities, effectively compensate for the function of paralyzed muscles, and limit unnecessary activities of the lower-limb joints. They can improve posture while standing and walking and help treat lower limb motor dysfunction. Moreover, lower-limb orthotic devices may help improve patients' ADL (82).

#### 3.2.2.1. Orthotic devices involving the hip joint

The hip-knee-ankle-foot orthosis (HKAFO) is the most common hip joint orthotic device according to the literature search results and is the main hip joint orthotic device reviewed in this paper. The HKAFO was used to stabilize the hip, knee, and ankle joints. It is suitable for patients with extensive lower limb muscle paralysis and assists patients in standing and walking. A reciprocating gait orthosis (RGO) is a type of HKAFO. Different types of HKAFOs have different effects on lower limb motor function. A study comparing the newly designed hip energy storage walking orthosis (HESWO) and RGO, suggested that SCI patients wearing HESWO had more significant gait improvement and lower energy consumption than those wearing RGO, considering that HESWO can provide a more energy-efficient gait (39). Arazpour et al. added a rocker sole to advanced RGO (ARGO) and found improvements in walking function compared to ARGO with a flat sole among patients with SCI (40). Two studies compared two kinds of ARGOs; and the results suggested that ARGO with dorsiflexion-assisted ankle-foot orthosis (AFO) was better than that with solid AFO in improving gait function in patients with SCI (41, 42). These studies suggest that the influence of different orthotic components on motor function improvement should be considered. Through continuous research with orthotic components, appropriate orthotic devices should be adapted according to the functional status of the patients.

One study showed that using isocentric RGO (IRGO) in patients with SCI could significantly improve walking capacity (43). Another study compared IRGO with and without the reciprocating link, and the results showed that the reciprocating link was useful in improving the walking ability of patients (44). IRGO is effective in improving walking parameters in patients with SCI. However, the sample sizes of these studies were small. To determine which orthotic devices are suitable for users, we need to increase the sample size for further studies to identify appropriate orthoses in clinical practice.

Two studies investigated whether controlling the hip joint improves motor function. They compared the standing stability between RGO and a knee-ankle-foot orthosis (KAFO) (45, 46). The results showed that compared with the KAFO group, patients with SCI wearing the newly developed RGO were more stable in standing at rest and performing tasks, especially when standing at rest (45). Meanwhile, the energy cost decreased significantly and walking style improved (46). Considering that hip joint control is helpful for standing stability, for paraplegic patients with SCI, orthotics with hip control may help improve motor function.

Although one study showed no significant difference in gait speed between powered gait orthosis and IRGO (83), orthotics with electrical/electronic components have been widely used in recent years to improve walking capacity in patients with SCI (84). However, this paper focused on orthotics without electrical/electronic components. Therefore, these orthotic devices were not reviewed in detail.

#### 3.2.2.2. Orthotic devices involving the knee and ankle joints

KAFO and AFO are the most common orthotic devices involving the knee and ankle joints. The KAFO is used in hemiplegic patients with unstable knee and ankle joints and lumbar paraplegia. It can support, stabilize, and limit the movement of the joints and is suitable for knee and ankle joints rehabilitation. Of course, there is also a knee orthosis (KO) for simple knee joint stabilization (47). AFO is widely used for foot and ankle deformities, such as strephenopodia, strephexopodia, and foot drop.

KAFO is widely used to stabilize lower limb segments during walking. However, only a few paraplegic patients discharged from the hospital continue to use KAFO. KAFO gait requires upper limb muscle strength, increases gait fatigue and may lead to upper limb musculoskeletal injury. Consequently, the KAFO is often used for standing posture or gait training rather than functional gait (85). However, some studies have shown that KAFO may positively affect patient recovery. A previous study showed that using a KAFO early could significantly improve the ADL in stroke patients (48). Another study showed that in hemiplegic patients, the adjustable posterior strut KAFO was more suitable for patients with better motor function, whereas traditional KAFO was suitable for patients with severe symptoms and difficulty obtaining practical walking ability (49). It is beneficial for patients to wear orthoses early, and different orthoses are suitable for patients with different functional statuses.

One study used three different applications: knee immobilization brace (KIB), KIB combined with Foot Lifter Orthosis® (FLO), and KIB combined with rigid taping, suggesting that KIB combined with FLO was the most helpful strategy for improving the balance of hemiplegic patients (50). Considering that simultaneous control of the knee and ankle joints is helpful for the balance of hemiplegic patients, the effect of FLO on ankle joint stabilization is better than that of rigid taping. Therefore, the KAFO, which covers both the knee and ankle joints, is most widely used for patients who need to stabilize the knee joint. However, an orthotic device that stabilizes the knee joint can also positively improve motor function. Moreover, a study using hinged soft KO among stroke patients showed that KO prevented knee hyperextension, significantly improved balance and walking distance, and reduced walking time (47). Patients can improve their walking ability by controlling the knee joint and preventing knee hyperextension.

Some studies conducted gait analysis for stroke patients with and without AFO, and the results indicated that AFO effectively improved walking ability, gait stability (51–55), balance (56), and might improve ADL (57). Furthermore, AFO reduces compensatory strategies during walking (52). However, in some patients with mild ankle impairment, the results showed a worsening trend after wearing an AFO (53). Stabilizing the ankle joint can stabilize the lower limb, effectively regulate the posture, and help improve walking capacity. However, different effects may occur depending on the severity of the patient's condition, which requires further study.

Foot drop is a common complication in hemiplegic patients. One study showed that the solid and dynamic AFO had no significant difference in controlling foot drop (58). Some studies have compared elastic AFO and hard plastic AFO with no AFO. The results showed that compared with patients without orthoses, those with orthotic devices had improved motor function (59, 60). Furthermore, elastic band-type AFO could improve foot drop better than hard plastic AFO (59), and postural stability tended to improve (60). Research has shown that plastic materials may limit the ankle joint, resulting in insufficient ankle dorsiflexion (59). Foot drop may require ankle joint stabilization; however, a stiffer material might not provide the best support. Soft materials can also provide good ankle joint stabilization and improve user comfort.

Some studies have compared the different types of AFOs. A study comparing solid AFO with hinged AFO during treadmill training in patients with SCI showed that solid AFO could improve step length compared to hinged AFO, although with no statistical difference (76). Another study suggested that a rocker bar AFO might improve walking capacity better than a solid AFO (61). Considering that different orthotic devices have different effects on patient function, further studies are needed to adapt the best orthosis under different conditions. Moreover, Do et al. showed that wearing a hybrid AFO was similar to a plastic AFO in motor function, but the hybrid AFO was lighter and more satisfactory (55). Another study compared a double-adjustable AFO with a posterior leaf spring AFO (PLS AFO) and found no significant differences in walking capacity (62). The results suggest that the selection of orthoses requires many considerations. When there is no significant difference in functional improvement, the appropriate orthosis should be selected according to factors such as wearing comfort and patient satisfaction.

Some studies have compared the duration of use of orthotic devices. A study comparing the early provision of AFOs with delayed provision showed that both groups had significant improvement in walking function after wearing AFO, and the improvement of balance was more pronounced in the early provision group (4). This suggests that using an AFO early significantly affects the recovery of lower limb motor function. However, the effectiveness of early AFO use in patients with stroke paralysis with foot drops is controversial. Some studies have shown that early or delayed AFO provision after stroke did not affect outcomes (63–65), However, providing AFO had a positive short-term effect on ankle kinematics in the early phase after stroke (65). In addition, another study showed that using an AFO early increased the risk of falls in hemiplegic patients, but it was important to note that 63.6% of falls occurred while the patient was not wearing an AFO (66). Considering that patients who have adapted to AFO gait may be more prone to falls when they do not wear orthoses, attention should be paid to the use of orthoses when motor function has not sufficiently improved. Notwithstanding, wearing an AFO is still necessary for stroke patients, and the most appropriate time to wear orthoses may require further study. A study suggested that using quick-made AFOs by therapists did not improve the effectiveness of conventional physical therapy (67). However, quick-made orthotics are an option for patients to have custom-made orthotics at an early stage of the disease (67). While the effectiveness of early or delayed wearing of orthotics remains controversial, further exploration and improvement with orthotic devices are needed.

Some AFOs have dampers. A study has shown that the newly developed AFO with spring damper is superior to the PLS AFO in improving balance (68). Studies of AFO with an oil damper (AFO-OD) have suggested that AFO-OD might significantly improve ankle joint motor function and gait parameters in stroke patients (69, 70). Another study conducted a gait analysis after rehabilitation with different AFOs. The results showed that the AFO-OD group had decreased thoracic tilt, but the AFO with plantar flexion stop group had increased pelvic forward tilt (71) after wearing orthotics. Adding dampers may optimize the function of AFO and improve motor function. Meanwhile, AFO-OD can better avoid dislocation of thorax and pelvis when walking, and can guide a more stable and natural gait.

With the development of orthotics, custom-made orthotics have become increasingly common and sophisticated. In a study that personalized the passive-dynamic AFO, improvements in parameters related to walking function were observed in some participants (72). However, another study showed that compared with prefabricated orthotics, customized orthotic devices showed no improvement in walking function and user satisfaction (73). Considering that custom-made orthoses may improve patients function from a new perspective through different components, they need further research and are actively promoted in clinical practice.

3D printing technology can also be used to fabricate lower limb orthotic devices. A study showed that after stroke patients wore 3D-printed AFO, their gait speed and stride length improved, and the double limb support phase decreased (74). Motion feedback can also be used for orthotics. A study suggested that a 3D-printed AFO with motion feedback in stroke patients improved walking function better than conventional AFO (75). This suggests that 3D-printed orthoses exhibit good performance and are comparable to conventional orthoses. 3D printing technology has potential benefits in design and production and can be actively promoted.

## 4. Conclusion

In this article, we reviewed conventional and new types of orthotic devices for stroke and SCI according to the different joints of the upper and lower limbs. Conventional orthotic devices are widely used and can effectively improve motor function. Custom-made orthoses are generally recommended; however, sometimes, there are no significant differences in efficacy or user preference between prefabricated and customized orthotic devices. In addition, custom-made conventional orthotic devices are sometimes time-consuming. Nowadays, new orthotics and various components are constantly being developed, which tend to be durable, lightweight, ventilating, and intelligent, and the kinematics of these devices are very close to the anatomy of the human limb, sometimes even in the form of human-computer interactions. However, some devices are still in development stages and cannot be widely and immediately used in clinical practice. The direction of future research on orthotic devices is to improve the functions of conventional orthotic devices and develop new types of devices. Further research is needed to make them more consistent with clinical practice, help patients improve motor function, rebuild their confidence, and enable them to return to their families and society faster.

## Author contributions

YC drafted the manuscript. SC and XC performed the literature search and extracted the articles. GX, NM, HL, and HZ assisted with drafting and revising the manuscript. ZL conceived and designed the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Epidemiological features of traumatic spinal cord injury in China: A systematic review and meta-analysis

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**Background:** Traumatic spinal cord injury (TSCI) is a highly fatal and disabling event, and its incidence rate is increasing in China. Therefore, we collated the epidemiological factors of TSCI in different regions of China to update the earlier systematic review published in 2018.

**Method:** We searched four English and three Chinese electronic databases from 1978 to October 1, 2022. From the included reports, information on sample characteristics, incidence, injury characteristics, prognostic factors, and economic burden was extracted. The selection of data was based on the PRISMA statement. The quality of the included studies was assessed by the Agency for Healthcare Research and Quality (AHRQ) tool. The results of the meta-analysis were presented in the form of pooled frequency and forest plots.

**Results:** A total of 59 reports (60 studies) from 23 provinces were included, of which 41 were in the Chinese language. The random pooled incidence of TSCI in China was estimated to be 65.15 per million (95% CI: 47.20–83.10 per million), with a range of 6.7 to 569.7 per million. The pooled male-to-female ratio was 1.95:1. The pooled mean age of the cases at the time of injury was 45.4 years. Motor vehicle accidents (MVAs) and high falls were found to be the leading causes of TSCI. Incomplete quadriplegia and AISA/Frankel grade D were the most common types of TSCI. Cervical level injury was the most prevalent. The pooled in-hospital mortality and complication rates for TSCI in China were 3% (95% CI: 2–4%) and 35% (95% CI: 23–47%). Respiratory problems were the most common complication and the leading cause of death.

**Conclusion:** Compared with previous studies, the epidemiological data on TSCI in China has changed significantly. A need to update the data over time is essential to implement appropriate preventive measures and formulate interventions according to the characteristics of the Chinese population.

KEYWORDS

**traumatic spinal cord injury, epidemiological factors, incidence, China, systematic review and meta-analysis**



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# Introduction

## Rationale

Traumatic spinal cord injury (TSCI) is one of the most devastating and catastrophic injury types, with high mortality and disability rates, causing physical and emotional hardship to patients as well as imposing a significant burden on society and families (1–3). TSCI refers to injuries that damage neural structures in the spinal canal, such as the spinal cord, nerve roots, and cauda equine, due to traumatic factors (4). TSCI is usually accompanied by sensory, motor, reflex, defecation, and other dysfunctions (5). Disability resulting from TSCI may be permanent, and medical care may not be sufficient to abrogate it (6). Over the past 40 years, China has witnessed rapid urbanization and an increase in its aging population, which led to a noticeable increase in the TSCI (7–9).

## Objectives

This study aims to update the previous research (10) published in 2018 through systematic synthesis and meta-analysis. Toward this goal, we extracted the latest epidemiological data, categorized them based on the geographical divisions of China, and the differences between the North and South regions were evaluated. Additionally, by determining the risk factors for complications or premature death, this study could also improve public awareness of preventive measures and provide a framework for health resource allocation and policy formulation.

# Methods

## Design

This systematic review and meta-analysis of the literature were performed according to the PRISMA 2020 guidelines (11).

## Search strategy

We searched the original peer-reviewed studies from the earliest record in 1978 to October 1, 2022, in the following databases: PubMed, EMBASE, Web of Science, EBSCO, China National Knowledge Infrastructure (CNKI), Wan Fang Data, and the China Science and Technology Journal Database (VIP). The search strategy we employed is described in detail in Supplementary Table 1. We searched all the fields of the database records, combining the relevant epidemiological terms and TSCI-related terms. Since there were too many irrelevant documents in PubMed and EMBASE, we added the restrictive word "human." Examples of search terms used for searching the Web of Science were: [("spinal cord injury" or "Traumatic spinal cord injury") and (epidemiology or incidence or etiology or prevalence) and China)]. We also checked the references of eligible studies, retrieved them, and identified any missing systematic reviews related to TSCI that were missing from the database search. In addition, we collected relevant summaries from the TSCI-related meeting minutes and checked the availability of the full text.

## Eligibility criteria

We used the CoCoPop model (condition, context, and population) as the inclusion structure instead of the traditional PICO approach (population, intervention, comparator, and outcome). Because it is more relevant to the issue of incidence and epidemiology (12). The inclusion and exclusion criteria are shown in Table 1.

## Data selection and collection

Two authors (YH and LL) independently screened the title and abstract of each article according to the inclusion and exclusion criteria. The full text of the selected articles was evaluated, and data was extracted. The third author (TL) rechecked the accuracy and integrity of the extracted data before analysis. Any disagreements were settled by consensus or by the third author (TL).

## Data synthesis and analysis

We used the tabular summary method to synthesize the data from the systematic review (12). The "metan" function of STATA software version 16.0 was used to develop a moment-based random model for estimating the hazard ratio, pooled effect of the incidence, percentages of in-hospital mortality, and complications (13). Forest plots were drawn to visualize the heterogeneity and the results of the meta-analysis (14). I2 values obtained by Cochrane's Q test were used to evaluate the heterogeneity. The I2 values of 25, 50, and 75% correspond to low, medium, and high heterogeneity, respectively (15). We also performed a sensitivity analysis using case-by-case exclusion to assess the impact of individual studies on the overall meta-analysis estimates. Due to the high heterogeneity between the studies, we also conducted a subgroup analysis.

## Quality assessment

Since all included studies were cross-sectional, two independent authors (YH and LL) evaluated the quality of the included studies using the Agency for Healthcare Research and Quality (AHRQ) tool (Supplementary Table 2). The AHRQ tool assessed the risk of bias in five domains: selection bias, implementation bias, follow-up bias, measurement bias, and reporting bias. Further, it consists of 11 items, with a scoring system of 1 point for "yes" and 0 points for "no" or "unclear." Based on the scores the studies were categorized as poor quality (0–3 points), medium quality (4–7 points), and good quality (8–11 points) (16). Disagreements, if any, were settled by consensus or by the third author (TL).

TABLE 1 Summary of inclusion and exclusion criteria.

| | Inclusion | Exclusion |
|---|---|---|
| Context | Any study published in any year, language or setting about TSCI in China | Reviews, animal studies, basic science studies, case reports or studies out of China |
| Population | All ages, occupations and genders | Specific ages (pediatric or geriatric), specific occupations (workers or drivers) |
| Condition | Sample characteristics (number of cases, mean age, male/female ratio, incidence), injury characteristics (etiology, severity of injury), prognostic factors (complications, in-hospital mortality, additional concurrent trauma), economic burden | Specific etiological focus (road traffic injuries, earthquake disaster), unrelated specific topics (depression, sleep disorder), specific injury level (cervical spine injury), non-traumatic spinal cord injury or singe traumatic spinal fracture |

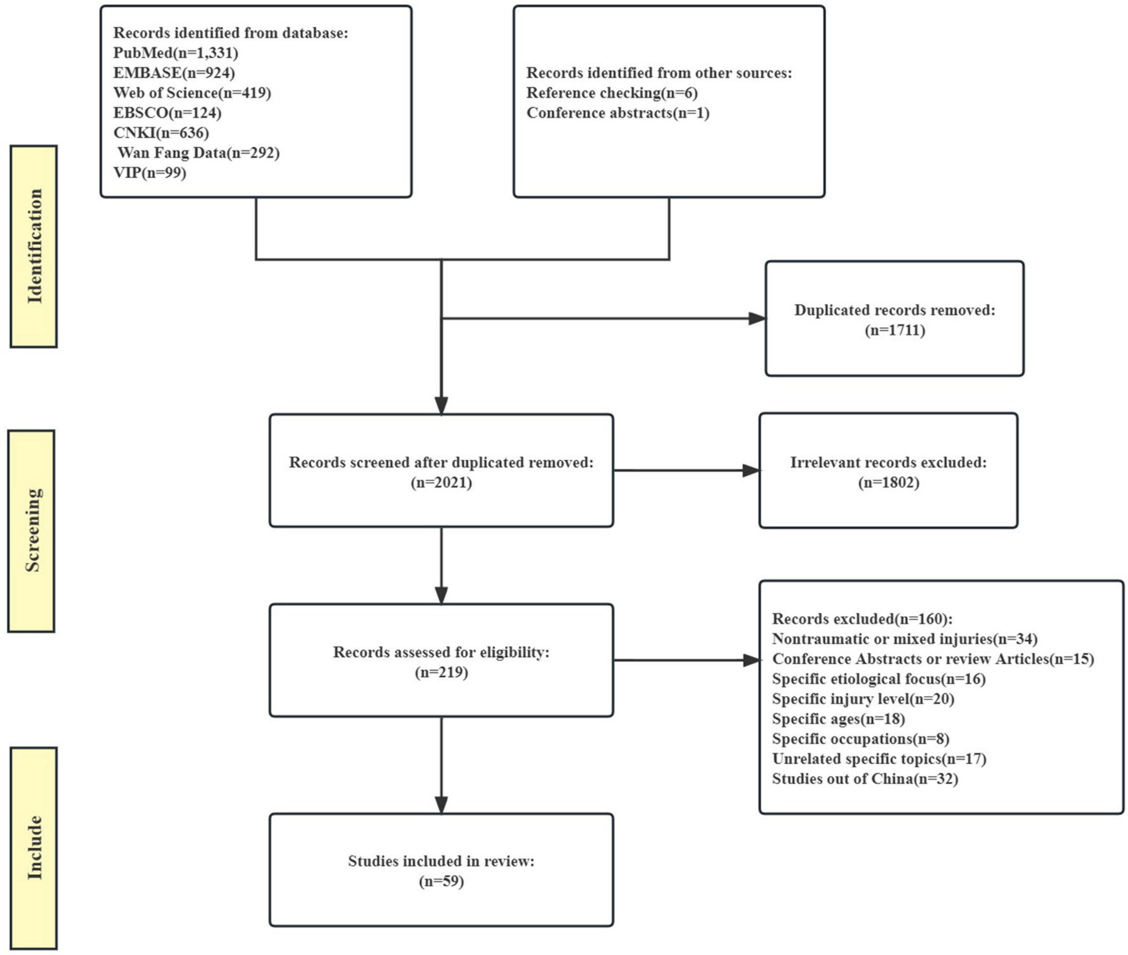


FIGURE 1
Flow diagram of each study stage.

# Results

## Study selection and characteristics

We recognized a total of 3,825 records from the initial database search and pooled them into the EndNote X9 software. The flow diagram of each study stage according to PRISMA guidelines is illustrated in Figure 1. After reviewing the abstract and the full texts, 60 relevant studies were identified (*1–*59, *52 contains two different studies, which were divided into *52A and *52B, see the Supplementary Appendix for the list of references).

TABLE 2 Sample characteristics and etiology of TSCI in China.

| | References | Region | Incidence period | Source population | Case source | Total cases | Leading causes | Second causes | Gender ratio | Mean age |
|---|---|---|---|---|---|---|---|---|---|---|
| North | Liu et al. (17) | Beijing | 2017–2019 | China rehabilitation research center | Hospitals records | 252 | MVAs | High fall | 4.1:1 | 41.2 |
| | Liu et al. (18) | Beijing | 2013–2019 | Beijing Boai Hospital | Hospitals records | 2,448 | Low fall | Assault | 3.0:1 | 39.1 ± 16.7 |
| | Cai et al. (19) | Tianjin | 2013–2017 | Three general hospitals in Tianjin city | Hospitals records | 2,471 | Low fall | High fall | 2.9:1 | 49.2 ± 14.2 |
| | Li et al. (20) | Inner Mongolia | 2012–2019 | The second affiliated hospital of Medical University | Hospitals records | 956 | High fall | MVAs | 2.3:1 | 49.9 ± 20.7 |
| | Wang et al. (21) | Beijing | 2012–2015 | PLA general hospital | Hospitals records | 625 | High fall | MVAs | 4.5:1 | 38.2 ± 12.8 |
| | Liu et al. (22) | Beijing | 2011–2019 | China rehabilitation research center | Hospitals records | 590 | High fall | MVAs | 4.7:1 | 46.3 ± 15.5 |
| | Yuan et al. (23) | Shanxi | 2011–2014 | Yuncheng central hospital | Hospitals records | 58 | MVAs | High fall | 4.0:1 | – |
| | Yang et al. (24) | Beijing | 2009–2014 | The first affiliated hospital of PLA general hospital | Hospitals records | 1,027 | MVAs | High fall | 3.6:1 | 42.5 ± 12.4 |
| | Zhou et al. (25) | Tianjin | 2009–2014 | General Hospital of Tianjin Medical University | Hospitals records | 354 | MVAs | Low fall | 2.3:1 | 50.1 ± 15.5 |
| | Xu et al. (26) | Beijing | 2008–2011 | Beijing Boai Hospital | Hospitals records | 260 | High fall | | 9.0:1 | 43.7 |
| | Wang et al. (27) | Beijing | 2005–2016 | PLA General Hospital | Hospitals records | 1,395 | MVAs | High fall | 4.1:1 | 32.1 ± 12.5 |
| | Ning et al. (28) | Tianjin | 2004–2008 | Major general hospitals in Tianjin city | Hospitals records | 869 | Low fall | MVAs | 5.6:1 | 46.0 ± 14.2 |
| | Jiang et al. (29) | Beijing | 2002–2011 | The 322nd Hospital of the PLA | Hospitals records | 423 | Struck by object | High fall | 15.3:1 | 40.0 ± 11.0 |
| | Hua et al. (30) | Beijing | 2001–2010 | General Hospital of the Chinese Armed Police Force | Hospitals records | 561 | MVAs | High fall | 4.1:1 | 34.7 ± 12.2 |
| | Li et al. (31) | Tianjin | 1999–2016 | General Hospital of Tianjin Medical University | Hospitals records | 735 | MVAs | Low fall | 2.9:1 | 49.7 ± 15.2 |
| | Feng et al. (32) | Tianjin | 1998–2009 | Tianjin Medical University General Hospital | Hospitals records | 239 | Low fall | MVAs | 4.6:1 | 45.4 ± 14.1 |
| | Hao et al. (33) | Beijing | 1992–2006 | China Rehabilitation Research Center and Beijing Boai Hospital | Hospitals records | 1,264 | MVAs | High fall | 4.0:1 | 34.9 |
| | Diao et al. (34) | Beijing | 1982–1986 | A sample of spinal cord patients in Beijing hospitals | Hospitals records | 310 | High fall | Low fall | – | – |
| | Yu et al. (35) | Tianjin | 2007 | Major general hospitals in Tianjin city | Hospitals records | 73 | Low fall | MVAs | 3.6:1 | 51.3 ± 14.6 |
| | Wei et al. (36) | Beijing | 2005 | A sample of spinal cord patients in Beijing hospitals | Hospitals records | 254 | MVAs | High fall | 2.3:1 | 41.0 ± 14.3 |
| | Li et al. (37) | Beijing | 2002 | A sample of spinal cord patients in Beijing hospitals | Hospitals records | 264 | High fall | MVAs | 3.1:1 | 41.7 |
| Northeast | Liu et al. (38) | Liaoning | 2013–2018 | Seven hospitals in Shenyang and Xi'an | Hospitals records | 2,416 | High fall | Low fall | 2.9:1 | 49.2 ± 14.4 |
| | Ru et al. (39) | Liaoning | 2010–2012 | Eight general hospitals in Dalian | Hospitals records | 1,155 | MVAs | Low fall | 2.4:1 | 50.1 ± 15.9 |

*(Continued)*

TABLE 2 (Continued)

| | References | Region | Incidence period | Source population | Case source | Total cases | Leading causes | Second causes | Gender ratio | Mean age |
|---|---|---|---|---|---|---|---|---|---|---|
| | Xu et al. (40) | Jilin | 2010–2011 | Jilin University Sino–Japanese Friendship Hospital | Hospitals records | 1,274 | Struck by object | High fall | 2.3:1 | 43.6 |
| | Chen et al. (41) | Heilongjiang | 2009–2013 | The Fourth Affiliated Hospital of Harbin Medical University | Hospitals records | 232 | MVAs | High fall | 4.0:1 | 45.4 ± 14.4 |
| Eastern | Niu et al. (42) | Jiangsu | 2015–2019 | The First Hospital of Soochow University | Hospitals records | 422 | MVAs | High fall | 3.2:1 | 51.1 ± 14.2 |
| | Tang et al. (43) | Shandong | 2014–2019 | Affiliated Hospital of Qingdao University | Hospitals records | 332 | – | – | 3.7:1 | 49.2 ± 13.7 |
| | Feng et al. (44) | Shandong | 2013–2017 | Liaocheng Peoples Hospital | Hospitals records | 338 | Low fall | MVAs | 3.1:1 | 50.1 ± 14.1 |
| | Wu et al. (45) | Jiangxi | 2012–2018 | The Affiliated Hospital of Nanchang University | Hospitals records | 1,290 | MVAs | Low fall | 7.1:1 | 53.1 ± 16.2 |
| | Niu et al. (46) | Jiangsu | 2009–2014 | Major general hospitals in Suzhou city | Hospitals records | 859 | High fall | MVAs | 2.4:1 | 47.5 ± 15.5 |
| | Wang et al. (47) | Anhui | 2007–2010 | Two general hospitals in Anhui Province | Hospitals records | 761 | High fall | MVAs | 3.4:1 | 45.0 |
| | Pan et al. (48) | Shanghai | 2005–2007 | Several hospitals in Pudong area | Hospitals records | 200 | High fall | MVAs | 3.0:1 | 44.5 |
| | Yang et al. (49) | Fujian | 2004–2013 | The 175th Hospital of the PLA | Hospitals records | 1,089 | High fall | MVAs | 3.5:1 | 44.7 |
| | Duan et al. (50) | Jiangxi | 2003–2007 | The First Affiliated Hospital of Nanchang University | Hospitals records | 650 | – | – | 2.1:1 | 46.5 |
| | Chen et al. (51) | Shandong | 2002–2007 | Affiliated Hospital of Qingdao University Medical College | Hospitals records | 251 | High fall | MVAs | 3.5:1 | 40.4 |
| | Hu et al. (52) | Shanghai | 1983–1991 | Shanghai Ruijin Hospital and Songjiang County People's Hospital | Hospitals records | 153 | High fall | MVAs | 3.3:1 | 41.3 |
| | Cheng et al. (53) | Shanghai | 1977–2007 | Shanghai Tongji University Hospital | Hospitals records | 676 | High fall | MVAs | 1.7:1 | 42.2 |
| | Sun et al. (54) | Shandong | 2011 | Affiliated Hospital of Qingdao University | Hospitals records | 35 | MVAs | High fall | 10.7:1 | 50.1 |
| | Feng et al. (55) | Jiangsu | 1991 | Six hospitals in Wuxi | Hospitals records | 35 | High fall | Struck by object | 7.8:1 | – |
| South | Zhang et al. (56) | Guangdong | 2013–2018 | Guangzhou Red Cross Hospital | Hospitals records | 62 | High fall | MVAs | 2.7:1 | 36.0 ± 14.4 |
| Central | Huang et al. (57) | Guangdong | 2012–2016 | Guangdong Work Injury Rehabilitation Hospital | Hospitals records | 397 | High fall | MVAs | 4.0:1 | 40.1 |
| | Yi et al. (58) | Hunan | 2012–2014 | Several general hospitals in Hunan | Hospitals records | 1,274 | Low fall | MVAs | 2.3:1 | 43.6 |
| | Deng et al. (59) | Hubei | 2012–2014 | Taihe Hospital Affiliated to Hubei Medical College | Hospitals records | 424 | High fall | MVAs | 1.6:1 | 46.5 |
| | Lv et al. (60) | Henan | 2008–2017 | Henan Provincial People's Hospital | Hospitals records | 692 | MVAs | High fall | 2.6:1 | 46.3 ± 15.9 |
| | Tang et al. (61) | Guangxi | 2006–2010 | Affiliated Hospital of Guangxi Medical University | Hospitals records | 221 | MVAs | High fall | 6.4:1 | 38.3 ± 12.4 |

*(Continued)*





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TABLE 2 (Continued)

| | References | Region | Incidence period | Source population | Case source | Total cases | Leading causes | Second causes | Gender ratio | Mean age |
|---|---|---|---|---|---|---|---|---|---|---|
| | Zhu et al. (62) | Hunan | 2005–2009 | Second Xiangya Hospital, Central South University | Hospitals records | 163 | MVAs | High fall | 3.8:1 | 37.0 ± 10.9 |
| | Yang et al. (63) | Guangdong | 2003–2011 | Several hospitals in Guangdong | Hospitals records | 1,340 | High fall | MVAs | 3.5:1 | 41.6 ± 14.7 |
| | Chen et al. (64) | Guangdong | 1995–2010 | Zhujiang Hospital of Southern Medical University | Hospitals records | 286 | High fall | MVAs | 7.4:1 | 36.3 ± 10.1 |
| Southwest | Ning et al. (65) | Chongqing | 2009–2013 | Chongqing Xinqiao Hospital | Hospitals records | 554 | High fall | MVAs | 4.3:1 | 45.6 ± 13.8 |
| | Mao et al. (66) | Sichuan | 1996–2002 | Huaxi Hospital of Sichuan University | Hospitals records | 132 | MVAs | High fall | 2.5:1 | 31.5 ± 7.8 |
| Northwest | Hao et al. (67) | Shaanxi | 2011–2013 | Xi'an Honghui Hospital | Hospitals records | 2,565 | Low fall | High fall | 4.7:1 | 41.5 ± 11.2 |
| | Zhang et al. (68) | Shaanxi | 2018 | Xi'an Honghui Hospital | Hospitals records | 382 | High fall | Low fall | 3.0:1 | 50.0 ± 15.2 |
| Taiwan | Yang et al. (69) | Taiwan | 2000–2003 | National Health Insurance (NHI) database | National register | 54,484 | – | – | 1.0:1 | – |
| | Wu et al. (70) | Taiwan | 1998–2008 | National Health Insurance (NHI) database | National register | 41,586 | MVAs | High fall | 1.5:1 | – |
| | Chen et al. (71) | Taiwan | 1992–1996 | Medical centers and general hospitals in Taiwan | Hospitals records | 1 586 | MVAs | High fall | 3.0:1 | 46.1 |
| | Lan et al. (72) | Taiwan | 1986–1990 | Four general hospitals in Taiwan | Hospitals records | 99 | MVAs | High fall | 4.0:1 | 44.5 |
| | Chen et al. (73) | Taiwan | 1978–1981 | Medical centers and general hospitals in Taiwan | Hospitals records | 560 | MVAs | High fall | 4.9:1 | 36.2 |
| Nationwide | Zhang et al. (68) | Whole | 2018 | National stratified whole group sampling | Hospitals records | 4,404 | High fall | Low fall | 3.0:1 | 51.6 ± 15.3 |
| | Hao et al. (74) | Whole | 2018 | National stratified whole group sampling | Hospitals records | 4,134 | MVAs | Low fall | 3.0:1 | 50.8 |
| | Jiang et al. (75) | Whole | 2013 | National stratified whole group sampling | Hospitals records | 394 | Low fall | MVAs | 1.9:1 | 43.7 ± 17.1 |





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TABLE 3 Level and severity of TSCI in China.

| References | C (%) | T (%) | L (%) | AISA A (%) | AISA B (%) | AISA C (%) | AISA D (%) | AISA E (%) | IQ (%) | IP (%) | CP (%) | CQ (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Liu et al. (17) | 47.2 | 43.3 | 9.5 | 48.0 | 15.1 | 14.3 | 22.6 | – | – | – | – | – |
| Liu et al. (18) | – | – | – | – | – | – | – | – | – | – | – | – |
| Cai et al. (19) | 63.7 | 21.1 | 15.1 | 37.9 | 9.6 | 13.4 | 39.1 | – | 37.2 | 18.9 | 25.6 | 18.3 |
| Li et al. (20) | 52.9 | 31.5 | 15.6 | 43.5 | 12.5 | 23.0 | 21.0 | – | – | – | – | – |
| Wang et al. (21) | 32.8 | 51.0 | 16.2 | 52.5 | 14.7 | 17.0 | 15.0 | 0.8 | 17.9 | 29.0 | 38.1 | 15.0 |
| Liu et al. (22) | 54.9 | 32.7 | 12.4 | 33.1 | 13.6 | 24.5 | 28.8 | – | – | – | – | – |
| Yuan et al. (23) | 55.0 | 17.0 | 28.0 | 66.0 | 14.0 | 10.0 | 10.0 | – | – | – | – | – |
| Yang et al. (24) | – | – | – | 34.6 | 7.9 | 17.7 | 16.2 | 3.3 | – | – | – | – |
| Zhou et al. (25) | 59.3 | 22.0 | 18.7 | 20.4 | 7.6 | 23.2 | 48.8 | – | – | – | – | – |
| Xu et al. (26) | 14.6 | 53.8 | 31.6 | 80.8 | 16.2 | 3.0 | 0.0 | – | 19.2# | – | 80.8# | – |
| Wang et al. (27) | – | – | – | 52.2 | 11.8 | 15.0 | 21.0 | – | – | – | – | – |
| Ning et al. (28) | 71.5 | – | – | 25.2 | 18.2 | 14.7 | 41.9 | – | – | – | – | – |
| Jiang et al. (29) | – | – | – | 45.4 | 3.1 | 17.7 | 30.0 | 3.8 | – | – | – | – |
| Hua et al. (30) | – | – | – | – | – | – | – | – | – | – | – | – |
| Li et al. (31) | – | – | – | – | – | – | – | – | 52.5 | 23.8 | 8.3 | 15.4 |
| Feng et al. (32) | 82.0 | – | – | 32.6 | 12.1 | 16.3 | 38.9 | 0.0 | 54.4 | 22.6 | 10.1 | 7.9 |
| Hao et al. (33) | 31.5 | 21.4 | 28.1 | – | – | – | – | – | 43.3# | – | 56.7# | – |
| Diao et al. (34) | – | – | – | – | – | – | – | – | – | – | – | – |
| Yu et al. (35) | 83.6 | 9.6 | 6.8 | 26.4 | 11.1 | 18.1 | 43.1 | 1.4 | – | – | – | – |
| Wei et al. (36) | 31.9 | 21.3 | 8.7 | – | – | – | – | – | 46.9# | – | 35.8# | – |
| Li et al. (37) | 4.9 | 28.0 | 66.7 | – | – | – | – | – | – | – | – | – |
| Liu et al. (38) | 55.1 | 29.9 | 14.9 | 29.8 | 5.0 | 10.9 | 54.3 | – | 39.1 | – | – | – |
| Ru et al. (39) | 57.6 | 14.7 | 27.7 | 19.6 | 2.4 | 9.6 | 68.4 | – | 52.7 | 31.5 | 8.3 | 6.3 |
| Xu et al. (40) | 32.5 | 19.5 | 52.8 | – | – | – | – | – | – | – | – | – |
| Chen et al. (41) | 76.3 | 10.3 | 13.4 | 14.2 | 15.1 | 32.8 | 37.9 | – | 63.4 | 18.5 | 5.2 | 12.9 |

*(Continued)*


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TABLE 3 (Continued)

| References | C (%) | T (%) | L (%) | AISA A (%) | AISA B (%) | AISA C (%) | AISA D (%) | AISA E (%) | IQ (%) | IP (%) | CP (%) | CQ (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Niu et al. (42) | 69.4 | 12.8 | 17.8 | – | – | 28.7 | 52.1 | – | – | – | – | – |
| Tang et al. (43) | 56.4 | 35.2 | 35.2 | 25.8 | 19.8 | 24.6 | 29.9 | – | – | – | – | – |
| Feng et al. (44) | 77.2 | – | – | 29.3 | 5.3 | 16.3 | 48.5 | 0.6 | – | – | – | – |
| Wu et al. (45) | – | – | – | 13.4 | 19.2 | 27.2 | 40.2 | – | – | – | – | – |
| Niu et al. (46) | 43.2 | 11.5 | 33.9 | 19.4 | 5.2 | 31.5 | 36.9 | 4.2 | – | – | – | – |
| Wang et al. (47) | 46.3 | 20.4 | 33.3 | 25.6 | 11.8 | 27.3 | 35.2 | – | – | – | – | – |
| Pan et al. (48) | 29.0 | 35.0 | 36.0 | 17.5 | 20.0 | 38.5 | 24.0 | – | – | – | – | – |
| Yang et al. (49) | 63.0 | 19.5 | 17.5 | 29.6 | 7.0 | 18.9 | 27.0 | 17.5 | 61.3 | 6.2 | 15.2 | 17.3 |
| Duan et al. (50) | 41.7 | 7.1 | 51.2 | – | – | – | – | – | 51.7# | – | 48.3# | – |
| Chen et al. (51) | 29.1 | 4.8 | 36.7 | 27.1 | 4.0 | 17.5 | 51.4 | – | – | – | – | – |
| Hu et al. (52) | – | – | – | – | – | – | – | – | – | 21.6 | 18.3 | – |
| Cheng et al. (53) | 17.4 | 27.0 | 55.6 | 17.6 | 4.9 | 12.0 | 38.7 | 26.8 | – | – | – | – |
| Sun et al. (54) | – | – | – | 34.3 | 20.0 | 20.0 | 25.7 | – | 65.7# | – | 34.3# | – |
| Feng et al. (55) | 31.4 | 34.3 | 34.3 | 17.1 | 42.9 | 17.1 | 22.9 | – | – | – | – | – |
| Zhang et al. (56) | 53.2 | 30.7 | 16.1 | 27.4 | 22.6 | 12.9 | 21.0 | 16.1 | – | – | – | – |
| Huang et al. (57) | 39.8 | 39.6 | 20.6 | – | – | – | – | – | 85.9# | – | 14.1# | – |
| Yi et al. (58) | 51.7 | 3.8 | 40.7 | 11.5 | 4.0 | 31.9 | 34.9 | 0.4 | 42.5 | 9.2 | 15.2 | 12.3 |
| Deng et al. (59) | 20.2 | 31.5 | 48.3 | 9.4 | 1.7 | 4.5 | 27.8 | 56.6 | – | – | – | – |
| Lv et al. (60) | 70.1 | 11.7 | 17.8 | 24.1 | 19.3 | 15.8 | 40.8 | – | 54.4 | 19.3 | 9.2 | 17.1 |
| Tang et al. (61) | 56.6 | 21.2 | 22.2 | 23.5 | 18.6 | 26.7 | 31.2 | – | – | – | – | – |
| Zhu et al. (62) | 25.2 | 36.2 | 38.7 | 25.2 | 49.1 | 21.5 | 4.3 | – | – | – | – | – |
| Yang et al. (63) | 56.7 | 20.5 | 22.8 | – | – | – | – | – | 73.6# | – | 26.4# | – |
| Chen et al. (64) | 28.7 | 46.9 | 24.4 | – | – | – | – | – | 38.8# | – | 61.2# | – |
| Ning et al. (65) | 54.0 | 30.3 | 15.7 | 39.4 | 8.7 | 21.0 | 30.8 | – | – | – | – | – |
| Mao et al. (66) | – | – | – | 42.0 | 13.0 | 29.0 | 16.0 | – | – | – | – | – |
| Hao et al. (67) | 51.8 | 14.1 | 34.1 | 27.8 | 16.2 | 11.5 | 36.7 | 7.8 | – | – | – | – |
| Zhang et al. (68) | – | – | – | 15.7 | 7.9 | 19.7 | 48.3 | 8.4 | – | – | – | – |

*(Continued)*



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TABLE 3 (Continued)

| References | C (%) | T (%) | L (%) | AISA A (%) | AISA B (%) | AISA C (%) | AISA D (%) | AISA E (%) | IQ (%) | IP (%) | CP (%) | CQ (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yang et al. (69) | – | – | – | – | – | – | – | – | – | – | – | – |
| Wu et al. (70) | – | – | – | – | – | – | – | – | – | – | – | – |
| Chen et al. (71) | 49.9 | 13.3 | 34.6 | – | – | – | – | – | – | – | – | – |
| Lan et al. (72) | – | – | – | – | – | – | – | – | – | – | – | – |
| Chen et al. (73) | 46.8 | – | | – | – | – | – | – | – | – | – | – |
| Zhang et al. (68) | 63.4 | 24.2 | 12.4 | 19.5 | 10.4 | 27.9 | 42.2 | – | 80.4# | – | 19.6# | – |
| Hao et al. (74) | 64.5 | 12.1 | 23.4 | – | – | 28.0 | 43. 66 | – | 55.2 | 26.6 | – | – |
| Jiang et al. (75) | – | – | – | – | – | – | – | – | – | – | – | – |

C, Cervical; T, Thoracic; L, Lumbosacral; IQ, Incomplete Quadriplegia; IP, Incomplete Paraplegia; CQ, Complete Quadriplegia; CP, Complete Paraplegia; # means that only complete or incomplete injuries were reported. AISA A-E; AISA/Frankel grade A-E.

## Methodological quality

We then performed a quality assessment of the included studies. The results of the quality assessment are summarized in Supplementary Table 3. Notably, almost all studies received a "yes" for questions on the sources and time of inclusion (items 1, 3). On the contrary, the questions about continuous sources (item 5) and the handling of follow-up and missing data (items 9–11) were answered "yes" less frequently. The total study score ranged from 2 to 7, with a median of 4. We assessed each study thoroughly for potential bias and did not exclude any studies.

## Sample characteristics

Table 2 displays the basic descriptive features of the 60 studies, including study authors, year of publication, region, incidence period, sample size, source population, source case, male to female ratio, and mean age. The publication period of the included studies spanned 44 years, with 40 studies published in the past 10 years (after 2012). Majority of studies were based on the review of hospital records, except for two studies (*53, *54) which were based on national registers information. The maximum sample size was 54,484 from the Taiwan National Health Insurance (NHI) database (*53), while the smallest sample size was only 35 (*38, *39). The mean age of TSCI cases at the time of injury was between 31.5 and 50.1 years, with a pooled mean age of 45.4 years. In all studies, the proportion of male patients was higher, with a highest male to female ratio of 15.3:1 (*13). And the pooled proportion of male to female ratio was 1.95:1 with a median of 4.0:1. We then extracted the top two occupations of TSCI patients from each study with largest number of TSCI patients, and found that the most vulnerable were workers, followed by farmers.

These 60 studies include data from 23 provinces, representing about 1,129.4 million people (2020 census). The remaining 11 regions (Zhejiang, Yunnan, Guizhou, Xinjiang, Hainan, Gansu, Qinghai, Tibet, Ningxia, Hong Kong, and Macau) have not published any epidemiological studies related to TSCI. For the convenience of statistics and search, we categorized the studies into the following groups according to their geographical division: North (*1–*21), Northeast (*22–*25), East (*26–*39), South Central (*40–*48), Southwest (*49–*50), Northwest (*51–*52A), Taiwan (*53–*57), and Nationwide (*52B, *58–*59).

## Injury characteristics

Following these preliminary analyses, we looked at the characteristics of the TSCI cases. We found that the most frequent causes of TSCI were motor vehicle accidents (MVAs), which accounted for 40.7% of all the cases, followed by high falls (39.8%). The detailed causes of TSCI are summarized in Table 2. The level of injury was reported in forty-four studies, which showed the majority of injuries occurred at the cervical level, followed by the lumbosacral level (Table 3). Of note, 41 studies used the AISA/Frankel grade in describing injury severity, while 21 studies measured the extent of the

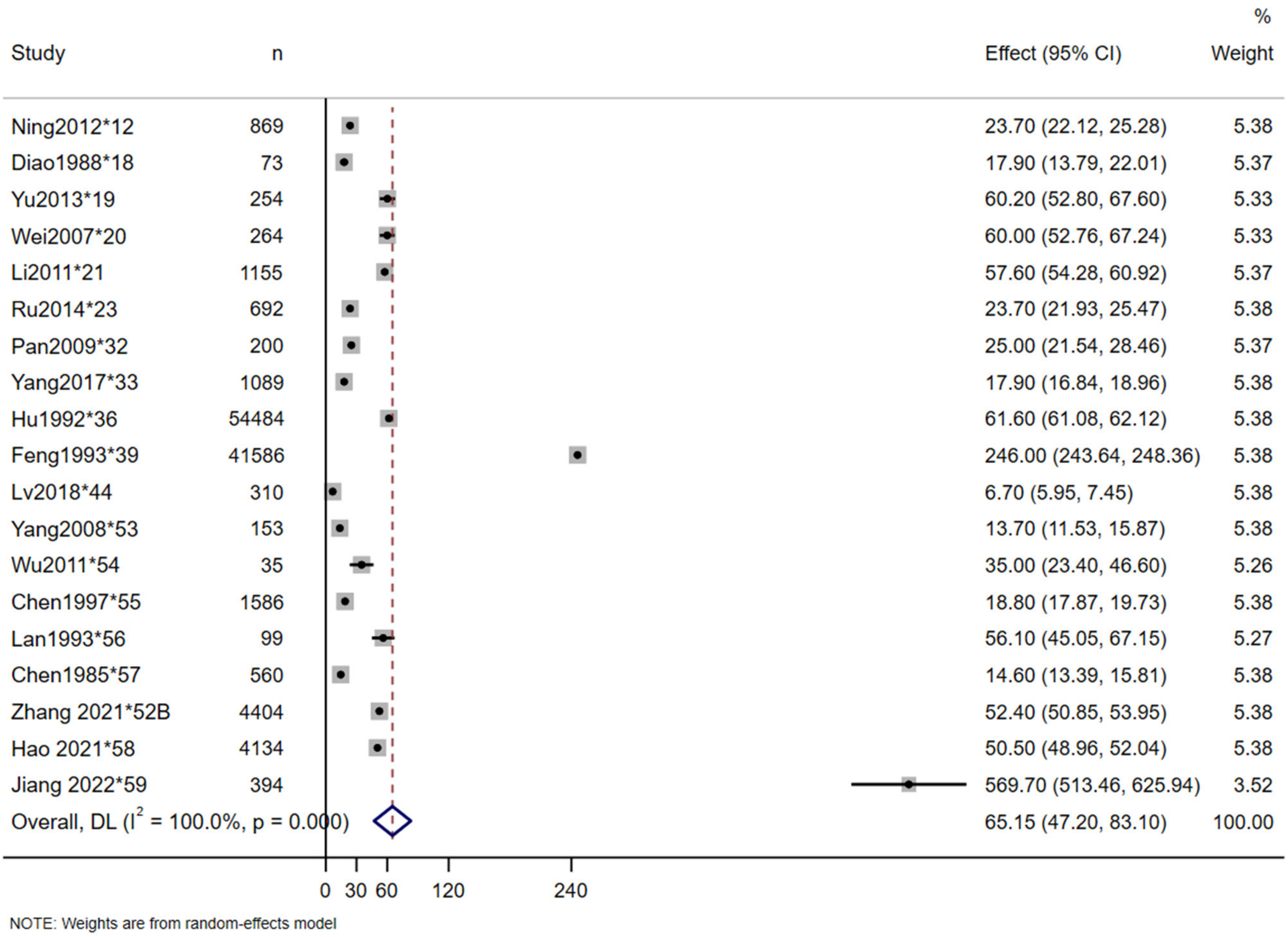


FIGURE 2
Incidence of TSCI meta-analysis in nationwide.

injury (complete or incomplete) and the neurological level of the injury (tetraplegia or paraplegia). Eleven studies did not report the severity of injuries. According to 24 studies, AISA D was the most common grade with a highest proportion of 68.4% (*23), followed by grade A, as reported by 13 studies. Further, incomplete injuries were more prevalent than complete injuries, with incomplete quadriplegia being the most common.

## Incidence

The incidence rates in this study were calculated by dividing the number of new-onset TSCI cases in a given area during a given period of time by the total at-risk population during the same period. A total of 19 studies reported the incidence of TSCI, which ranged from 6.7 per million in 1988 (*18) to 569.7 per million in 2022 (*59). The estimated incidence rate of TSCI in China was 65.15 per million (95% CI: 47.20–83.10 per million, heterogeneity test: I2 = 100%, $p$-value = 0) (Figure 2). Owing to the high heterogeneity between the studies, we also conducted a North-South subgroup analysis to explore the causes. In the subgroup analysis, a total of 7 and 9 studies were included in the North and South subgroups, respectively, and 3 studies that were conducted nationwide were excluded. The subgroup analyses showed that the incidence of TSCI in the North was 34.10 per million (95% CI: 23.22–50.06 per million, heterogeneity test: I2 = 99.2%, $p$-value = 0), and in the South was 28.75 per million (95% CI: 14.39–57.42 per million, heterogeneity test: I2 = 100%, $p$-value = 0) (Figure 3). The hazard ratio's pooled effect was used to estimate the incidence rate. Heterogeneity test between groups: $p$-value = 0.672. We also performed a sensitivity analysis using case-by-case exclusion, and no study was excluded (Supplementary Figure 1).

## Prognostic factors

Twenty-three studies reported the in-hospital mortality of TSCI, and 20 studies reported the major causes of death. The pooled estimate for the in-hospital mortality of TSCI in China was 3% (95% CI: 3–4%, heterogeneity test: I2 = 93.5%,

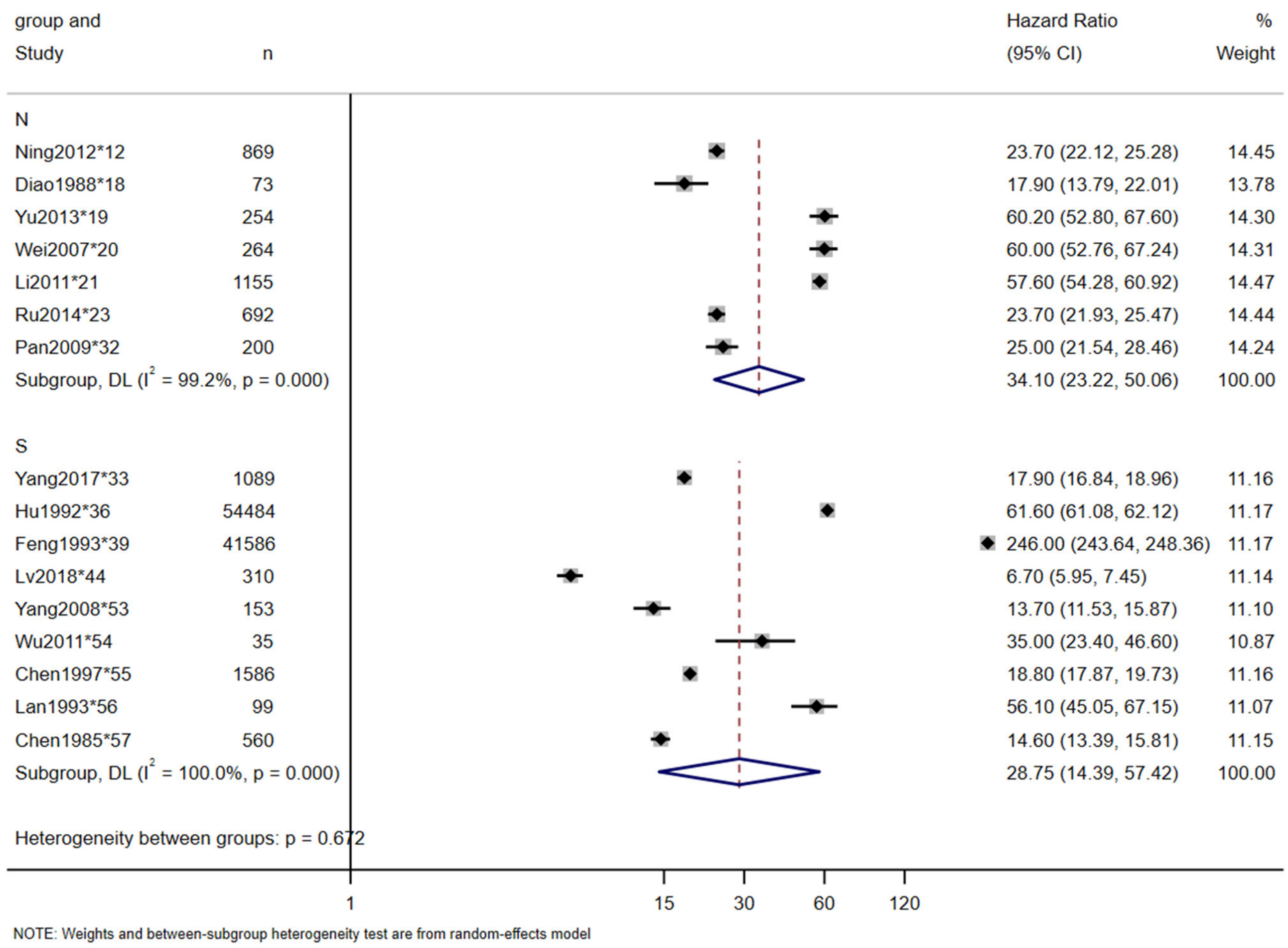


FIGURE 3
Incidence of TSCI meta-analysis in North-South subgroup.

*p*-value = 0) (Figure 4). In the subgroup analysis, the estimation of TSCI in-hospital mortality in the North was 3% (95% CI: 2–4%, heterogeneity test: I2 = 89.7%, *p*-value = 0), and in the South was 5% (95% CI: 3–10%, heterogeneity test: I2 = 96.5%, *p*-value = 0). Heterogeneity test between groups: *p*-value = 0.094 (Figure 5). The most frequent cause of death from TSCI was respiratory failure, as reported by 15 studies. A total of 11 studies mentioned the incidence of additional concurrent trauma, ranging from 51.0% (*15) to 94.6% (*51), the pooled estimate for the proportion of additional concurrent trauma in China was 71% (95% CI: 60–81%, heterogeneity test: I2 = 99.6%, *p*-value = 0) (Supplementary Figure 2). The main additional concurrent trauma was spinal fracture. Thirty studies mentioned complications from TSCI, among which respiratory diseases and urinary diseases were the most common. Further, 21 studies reported the complication rate of TSCI, ranging from 6.2% (*9) to 96.5% (*48). Our analysis shows that the pooled estimate for the proportion of in-hospital mortality in China was 35% (95% CI: 23–47%, heterogeneity test: I2 = 99.7%, *p*-value = 0) (Figure 6). Our subgroup analysis in Figure 7, shows that the in-hospital mortality in the North was 20% (95% CI: 16–25%, heterogeneity test: I2 = 96.1%, *p*-value = 0) and in the South was 44% (95% CI: 33–59%, heterogeneity test: I2 = 99.6%, *p*-value = 0). Heterogeneity test between groups: *p*-value = 0. No study was excluded due to sensitivity analysis (Supplementary Figures 3, 4).

## Economic burden

Twelve studies mentioned the economic burden of TSCI, 10 of which mentioned the average hospitalization costs, ranging from 4.1 thousand RMB in 1988 (*18) to 252.3 thousand RMB in 2020 (*1). The pooled estimate for the economic burden of TSCI was 48.5 thousand RMB.

# Discussion

In this study, we conducted the first meta-analysis of the epidemiological data on TSCI in China and updated the previous study published in 2018 (10). We searched 7 databases and identified 59 papers (60 studies), representing 23 provinces and about 1,129.4 million people. Three studies reported

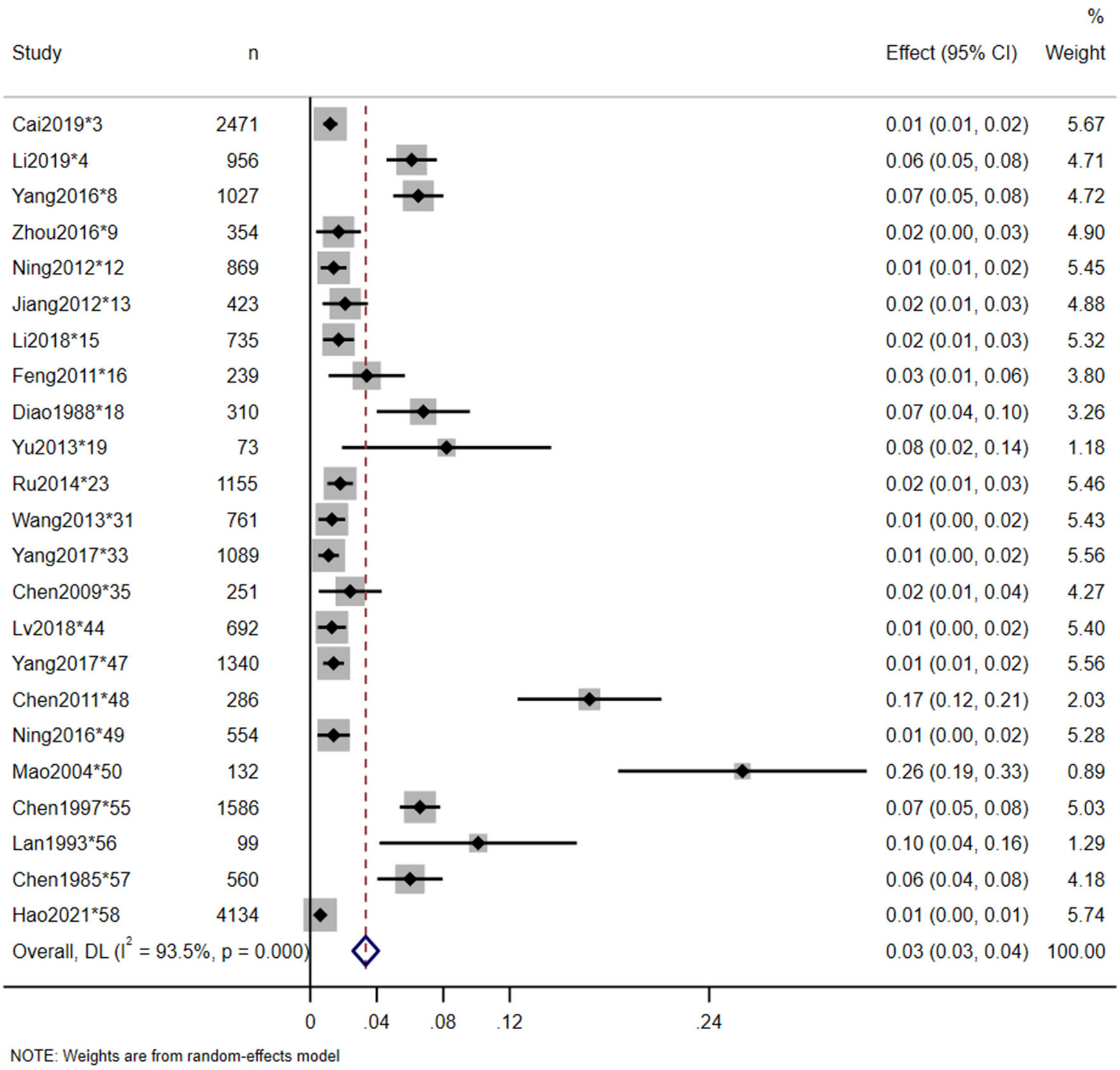


FIGURE 4
In-hospital mortality of TSCI meta-analysis in nationwide.

epidemiological data through stratified sampling nationwide. While 11 provinces have no reports of TSCI epidemiology, 15 provinces (65.2%) have only 1–2 studies. Among all the reports, 19 studies, all from Beijing and Tianjin, accounted for 31.7% of the total. The imbalance in the number of publications in different provinces has significantly affected the analysis of the national epidemiological data. Taking this disparity into account, along with the difference in economic levels in different regions of China, we conducted a North-South region-wise subgroup analysis to explore the sources of heterogeneity in the meta-analysis. Based on the region, we included thirty-three studies in the northern group and 24 in the southern group. The demarcation between north and south China is often considered to be the Qinling mountain range and the Huaihe river. The economic levels of the North and South had an obvious disparity revealed by the gross domestic product (GDP) of the South, which accounted for about 62% of the national total in 2018. Moreover, the industrial landscape is quite different between these regions. The northern region was biased toward heavy industry, while the southern region vigorously developed the economy through software and internet services industry. However, the net inflow of population in large cities in the southern region is on the rise, presenting a pattern of population flow from north to south, accompanied by a significantly faster urbanization rate compared to the northern region.

Our data points out that the annual incidence of TSCI ranged from 6.7 to 569.7 per million in China, and the random pooled incidence was estimated to be 65.15 per million. The annual incidence of TSCI in China reported in 2018 ranged from 13 to 60 per million (10), while the incidence of TSCI in Asia reported in 2012 ranged from 12.06 to 61.6 per million (76). Furthermore, the global TSCI incidence in 2011 was estimated to be 23 per million (77). Compared with other studies, the incidence of TSCI in China is higher than that in Asia and the rest of the world and still exhibiting an increasing trend. In the subgroup analysis, the estimated incidence of 28.75 per million in the south is lower than that of 34.10 per million in the north and much lower than the national average. This reduction is explained by the exclusion of three nationwide studies, especially the 569.7 per million reported

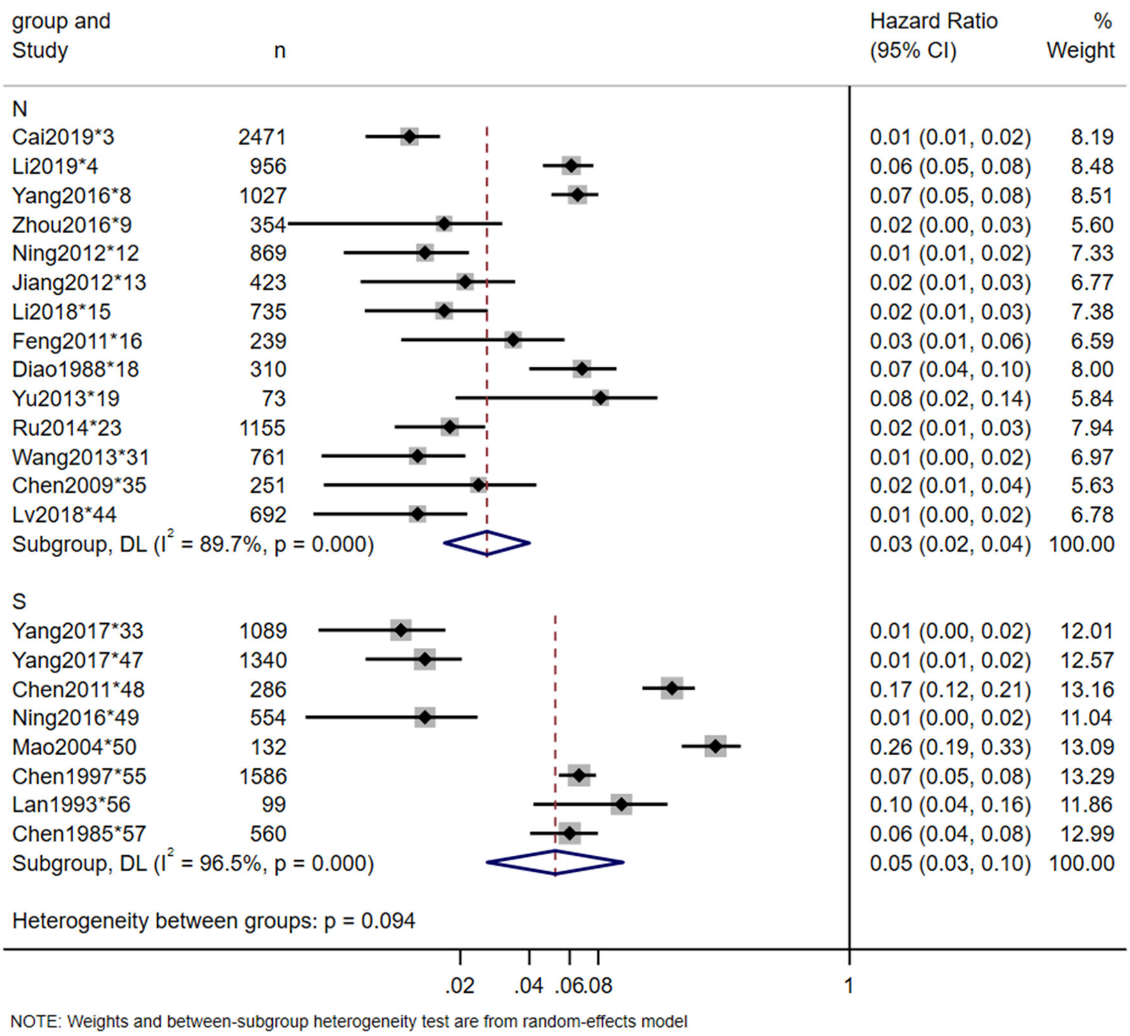


FIGURE 5
In-hospital mortality of TSCI meta-analysis North-South subgroup.

in 2013(*52B). Of note, the industrial structure in the north is biased toward heavy industry, which exposes workers to high-risk environments and could explain the increased incidence of TSCI in the north compared to the south. Coal miners, for example, were the most common occupation for those with TSCI in Tianjin (*13). Comparing the incidence rate of TSCI at different time points in the same province, for example, the incidence rate of Beijing was 6.7 per million (* 18) in 1988 to 60.2 per million (* 20) in 2007, we can find an increasing TSCI incidence over time.

We found that the mean age at the time of injury reported worldwide was 33 years, down from 45.4 years in this study. We also noticed a correlation between increasing age and TSCI when comparing studies conducted in the same province at different time points. This may be related to China's transition toward an aging society, where a higher proportion of people over the age of 35 are engaging in high-risk occupations (78). Moreover, we found that there was a significant gender difference in TSCI incidence. The proportion of male TSCI patients was higher in almost all studies, with the highest male-to-female ratio of 15.3:1 (*13) and the pooled estimate for the male-to-female ratio was 1.95:1. This could be due to male workers engaging in high-risk work, such as truck driving and high-altitude construction work, more than their female counterparts. In addition, male drivers are more likely to engage in risky behaviors. For example, Chen et al. reported violence and alcoholism as potential causes for TSCI (*57).

In our analysis, motor vehicle accidents and high falls were the most common etiologies of TSCI, which was consistent with the 2018 study (10). This is related to the increase in the usage of private cars, urbanization, and the rapid economic growth after a change in China's economic policies. In the severity assessment of TSCI, the AISA/Frankel grade is the most commonly used method for classification. Most patients were classified as grade A in Asia (76) and in previous study (10). On the contrary, we found that grade D was the most prevalent, followed by grade A. This is also consistent with our finding that the most common neurological injury associated with TSCI was incomplete quadriplegia. This could be because of the increase in the aging population in China and their associated lifestyle of staying alone resulting in an increased chance of low falls. In this study, low fall was found to be the third most common cause of TSCI.

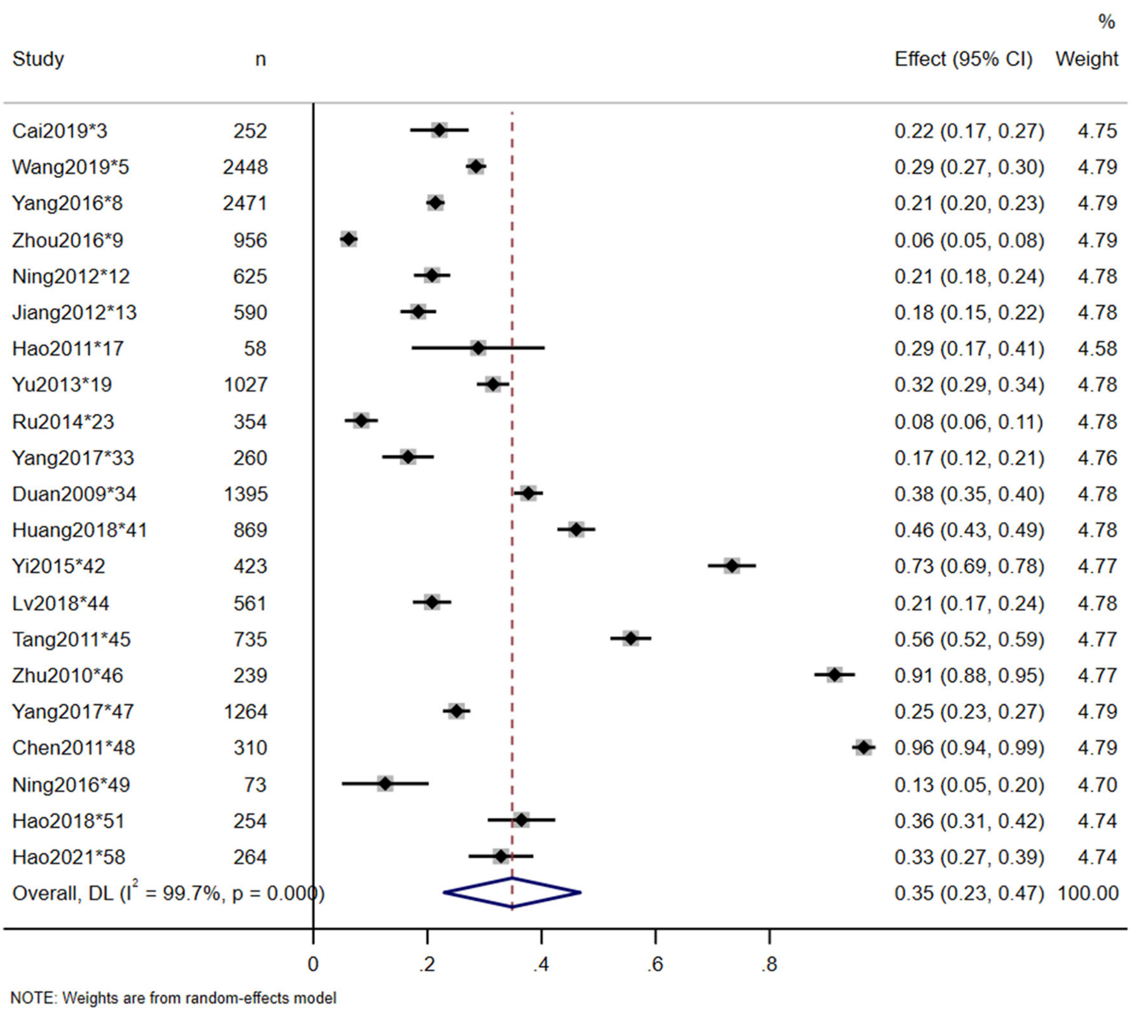


FIGURE 6
Complication rate of TSCI meta-analysis in nationwide.

The report on in-hospital mortality and complications can help us understand the risks of TSCI, guide treatment to reduce and avoid complications, and ultimately achieve the goal of reducing mortality. The pooled in-hospital mortality rate in this study was estimated at 3%, and the main cause of death was respiratory failure. Some studies mentioned the death of respiratory failure due to cervical spinal cord compression in the acute stage, and the death of pulmonary infection after tracheotomy due to respiratory system related complications in the subacute stage. But this may be an underestimate, as up to 46% of injury deaths on death certificates between 2006 and 2016 did not have an S or T code (N code) for the nature of the injury (79). Besides, the number of TSCI patients who may have died at the scene or en route to the hospital is undetermined and the tradition in some regions of China is to take seriously ill patients home to spend the last time with their families or give up treatment due to financial burden. The high disability rate of TSCI is not only reflected in nervous system damage, but also in the increased complications. The complication rate of TSCI in China was estimated at 35%, and the major secondary complications were respiratory and urinary diseases. However, after comparing the results with the developing countries (80), the results showed that pressure ulcers and urinary tract infections were the most common. In the subgroup analysis, the in-hospital mortality and complication rates in the south were higher than those in the north. Since the main complications and causes of death were respiratory related diseases, the difference between the south and north may be related to the difference in climate or medical factors.

Our study has several limitations, as follows: (1) Most of the reports we included were retrospective studies of hospital records in individual provinces, with very limited community-based studies, and hence may suffer from publication bias. (2) The diagnostic criteria of these studies were inconsistent and lacked objective indicators such as MRI rates. Most studies only used AISA/Frankel grade to evaluate, so it was difficult to conduct a meta-analysis in such instances. (3) This study focused on TSCI survivors, which excluded those who died before reaching the hospital or who returned home due to tradition or economic burden, and there were few studies describing the additional concurrent trauma at admission, which may have an impact on the outcome of the study. (4) It is unclear whether the hospitals that conducted the study are representative of the region or whether there are other hospitals

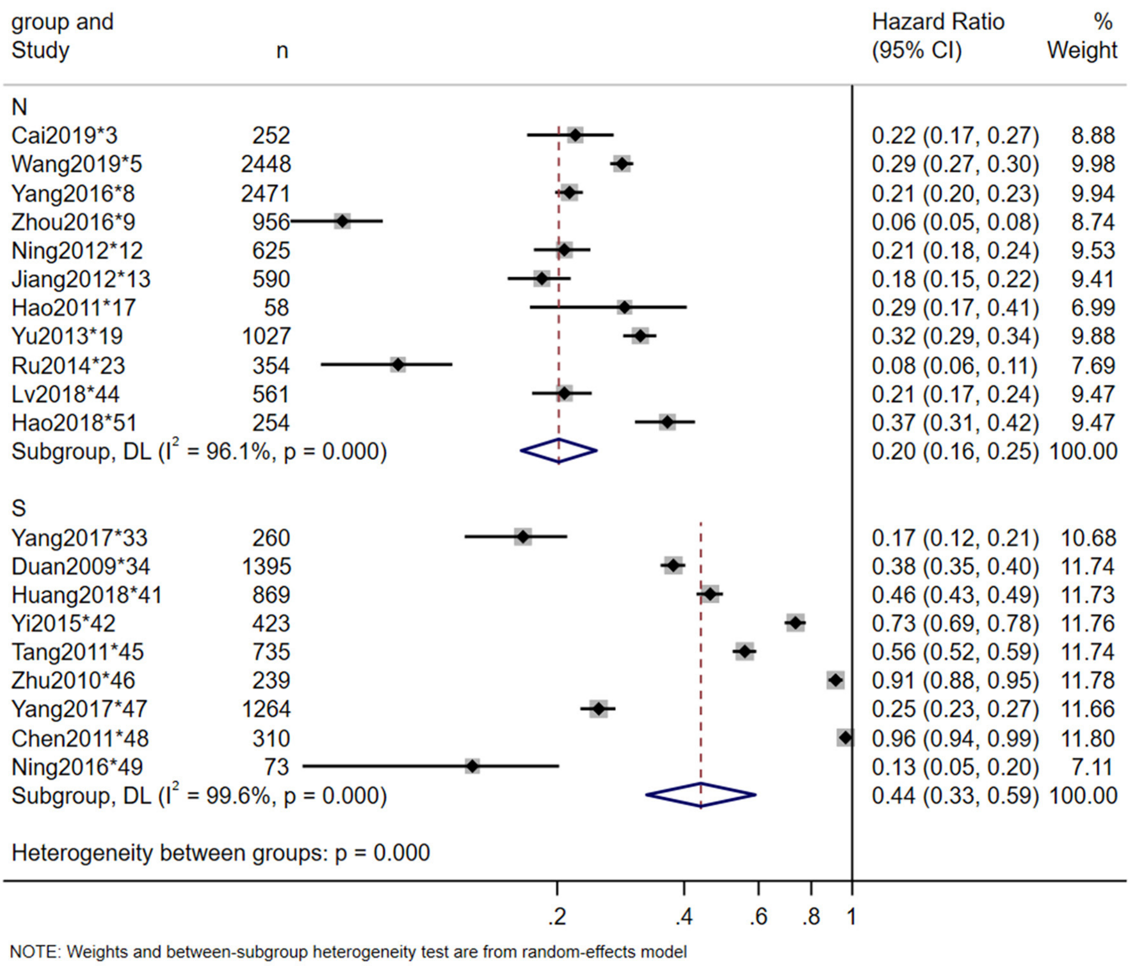


FIGURE 7
Complication rate of TSCI meta-analysis in North-South subgroup.

in the region that also treat TSCI, leaving a possibility that the epidemiological data may be inaccurate. (5) There were few large-scale national epidemiological surveys on TSCI, and these studies were mainly concentrated in the provinces with better resources. Due to the aforementioned limitations, accurate epidemiological data on TSCI are difficult to obtain in China.

## Conclusion

Traumatic spinal cord injury can usually be reduced by early prevention, and the government should issue appropriate policies based on epidemiological survey data and the different regions in the north and south. The increasing incidence of TSCI in China suggests that an urgent emphasis on prevention of the occurrence of TSCI in high-risk occupations and prevention of treatment complications is required. It is proposed that the standardization of TSCI epidemiological reports should be established in the future. Future research that are prospective, nationwide, and multicenter are required for establishing the epidemiology and TSCI. Finally, we hope that this review can provide guidance for traumatic spinal cord injury prevention, treatment, and rehabilitation in China.

## Author contributions

YH and LL conceived the idea and performed data collection and extraction. TL and CF contributed to data inspection and synthesis. YH, YX, FY, and BH analyzed the data and wrote the manuscript. JZ and YW completed the critical review of manuscript. YY and XF supervised the project. All authors discussed the results and and approved the final version for publication.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1131791/full#supplementary-material

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# Incidence and prevalence of traumatic spinal cord injury in Canada using health administrative data

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**Introduction:** Incidence and prevalence data are needed for the planning, funding, delivery and evaluation of injury prevention and health care programs. The objective of this study was to estimate the Canadian traumatic spinal cord injury (TSCI) incidence, prevalence and trends over time using national-level health administrative data.

**Methods:** ICD-10 CA codes were used to identify the cases for the hospital admission and discharge incidence rates of TSCI in Canada from 2005 to 2016. Provincial estimates were calculated using the location of the admitting facility. Age and sex-specific incidence rates were set to the 2015/2016 rates for the 2017 to 2019 estimates. Annual incidence rates were used as input for the prevalence model that applied annual survivorship rates derived from life expectancy data.

**Results:** For 2019, it was estimated that there were 1,199 cases (32.0 per million) of TSCI admitted to hospitals, with 123 (10% of admissions) in-hospital deaths and 1,076 people with TSCI (28.7 per million) were discharged in Canada. The estimated number of people living with TSCI was 30,239 (804/million); 15,533 (52%) with paraplegia and 14,706 (48%) with tetraplegia. Trends included an increase in the number of people injured each year from 874 to 1,199 incident cases (37%), an older average age at injury rising from 46.6 years to 54.3 years and a larger proportion over the age of 65 changing from 22 to 38%, during the 15-year time frame.

**Conclusion:** This study provides a standard method for calculating the incidence and prevalence of TSCI in Canada using national-level health administrative data. The estimates are conservative based on the limitations of the data but represent a large Canadian sample over 15 years, which highlight national trends. An increasing number of TSCI cases among the elderly population due to falls reported in this study can inform health care planning, prevention strategies, and future research.

KEYWORDS
**spinal cord injury, epidemiology, incidence, prevalence, routinely collected health data**

## Introduction

Spinal cord injury (SCI) is a relatively uncommon injury compared to other health conditions, however, its occurrence has profound long-lasting personal, social and financial impacts on individuals, families, the health care system and society. Estimates of incidence and prevalence are needed for the planning, funding, delivery and evaluation of injury prevention and health care programs.

Incidence and prevalence rates vary based on data sources used and the way data are collected and validated. Data collected for administrative or billing purposes in a health care system are referred to as health administrative data (1). In Canada, a record is created for every hospital visit upon discharge and contains demographic, administrative and some clinical data (2). Diagnoses and procedures are coded using the International Statistical Classification of Diseases and Related Health Problems (ICD) codes and these data are managed nationally by the Canadian Institute of Health Information (CIHI). While health administrative data can describe a population, they lack detailed clinical and neurological data. Acknowledging its limitations, health administrative data have been utilized to estimate the incidence of traumatic spinal cord injury (TSCI) in several countries (3–6).

Health administrative data have previously been used to estimate the incidence of TSCI within specific regions or single provinces of Canada, such as Ontario reporting 21 to 49/million (7–9), Alberta reporting 52/million (10), British Columbia reporting 36/million (11), and Manitoba reporting 17 to 26/million (12). We previously estimated the Canadian TSCI incidence to be 41/million and the prevalence as 1,300/million by applying health administrative data from a single province (Alberta) to the Canadian population in 2010 (13). There are subtle differences in case ascertainment among these studies (e.g., age restrictions, inclusion or exclusion of those who do not survive initial hospital stay, different TSCI classification). A standard method for estimating TSCI incidence described in our methods may advance the field and enable accurate comparisons among regions and over time. We therefore wanted to update these estimates with national-level health administrative data, provide provincial estimates and examine trends over time.

The objective of this study was to estimate the Canadian TSCI incidence, prevalence and trends over time using national-level health administrative data from January 2005 to December 2016 and estimate to 2019. The results were compared to previous estimates and other countries that have published TSCI incidence rates using administrative data.

# Materials and methods

## Data specification

Data were requested from CIHI (14), for the National Trauma Registry (NTR) (15) from April 1, 2004 to March 31, 2011 and for the Discharge Abstract Database (DAD) (2) from April 1, 2011 to March 31, 2017 (for a schematic, see Supplementary Figure 1). The time periods reflect when the required data were available and coded with ICD-10 CA (Tenth Revision, Canada). The NTR ended in 2011 and the DAD included the data variables from NTR's minimal data set. These data sources include all provinces and territories in Canada, except Québec and are collected in the same manner. Cases of TSCI were selected on the criteria of an ICD-10 CA TSCI code (see codes and descriptions in Table 1), an external cause of injury code and an acute facility code.

The NTR excluded external causes of injury resulting from complications, misadventures, adverse incidents/reactions from surgical care (for associated ICD-10 CA codes see Supplementary Table 1), therefore these cases were excluded from the DAD extract and all subsequent estimates based on this data. To ensure confidentiality, cells were suppressed when values were less than 5 observations. Years were combined into pairs for the 2005 to 2016 period to avoid a large number of suppressed cells for tabulations of five-year age groups by sex.

**TABLE 1** ICD-10 CA codes used to identify traumatic spinal cord injury cases.

| ICD-10 code | Code description |
|---|---|
| S14.0 | Concussion and oedema of cervical spinal cord |
| S14.10 | Complete lesion of cervical spinal cord |
| S14.11 | Central cord lesion of cervical spinal cord |
| S14.12 | Anterior cord syndrome of cervical spinal cord |
| S14.13 | Posterior cord syndrome of cervical spinal cord |
| S14.18 | Other injuries of cervical spinal cord |
| S14.19 | Unspecified lesion of cervical spinal cord |
| S24.0 | Concussion and oedema of thoracic spinal cord |
| S24.10 | Complete lesion of thoracic spinal cord |
| S24.11 | Central cord lesion of thoracic spinal cord |
| S24.12 | Anterior cord syndrome of thoracic spinal cord |
| S24.13 | Posterior cord syndrome of thoracic spinal cord |
| S24.18 | Other injuries of thoracic spinal cord |
| S24.19 | Unspecified lesion of thoracic spinal cord |
| S34.0 | Concussion and oedema of lumbar spinal cord |
| S34.10 | Complete lesion of lumbar spinal cord |
| S34.11 | Central cord lesion of lumbar spinal cord |
| S34.12 | Anterior cord syndrome of lumbar spinal cord |
| S34.13 | Posterior cord syndrome of lumbar spinal cord |
| S34.18 | Other injuries of lumbar spinal cord |
| S34.19 | Unspecified lesion of lumbar spinal cord |
| S34.30 | Laceration of cauda equina |
| S34.38 | Other and unspecified injury of cauda equina |
| T06.0 | Injuries of brain and cranial nerves with injuries of nerves and spinal cord at neck level |
| T06.1 | Injuries of nerves and spinal cord involving other multiple body regions |

## Procedure for estimating TSCI incidence

Data were tabulated by unique identifiers and indexed by date to count all unique individuals by age and sex that had an ICD-10 code from Table 1 in the diagnosis variable (for the aggregated data see Supplementary Table 2). The discharge incidence represents the unique individuals that survived the initial hospital stay and were discharged from an acute facility. Survival and mortality were defined by the discharge disposition data variable. The methodology developed to calculate the admission and discharge incidences of TSCI is shown in Figure 1. The discharge rates for Canada, except Québec, were calculated by subtracting the number of in-hospital deaths from the number of TSCI admission cases and dividing by the corresponding population, from Statistics Canada's annual population estimates. The provincial admission incidence estimates were based on the location of the admitting facility and the corresponding provincial population from Statistics Canada (16).

To derive national rates that included an estimation for Québec, we accessed Injury and Trauma Emergency Department and Hospitalization Statistics reports that contained data on all injury and trauma visits to the emergency department and hospitalizations in acute care hospitals in Canadian provinces, including Québec, from 2014 to 2018 (17). Provincial hospitalizations and external cause of injury data were used as an indication of how rates of TSCI compare among provinces in Canada. Specifically, provincial variances were applied to Québec's population to estimate Québec's provincial TSCI incidence rates. These rates were incorporated into the rates that excluded Québec to estimate the national rates for the period 2005 to 2016. To calculate the rates for 2017 to 2019, it was assumed that the 2015 to 2016 period rates were stable for these 3 years.

The national annual rates were then multiplied by the Canadian population (16) for each year to estimate annual discharge TSCI incidence case numbers by age group and sex. Using these annual case numbers, in-hospital mortality relative to discharge ratios were calculated from the health administrative data, which were then used to estimate national annual admission case numbers.

## Procedure for estimating TSCI prevalence

The methodology for calculating the prevalence of TSCI in Canada is shown in Figure 2. The age- and sex-specific TSCI discharge incidence rates predicted back to 1926 are required as input data for the prevalence model (see Supplementary Figure 2). The annual discharge case estimates by age were grouped into people with tetraplegia and paraplegia using ICD-10 codes (for estimated percentages see Supplementary Table 3). The annual incidence population for tetraplegia and paraplegia was added to the survivors from previous years in a cohort survival population model (Figure 2). Cohort survivors were calculated by applying annual survivorship rates for tetraplegia and paraplegia derived from data on relative life expectancy (for life expectancy see

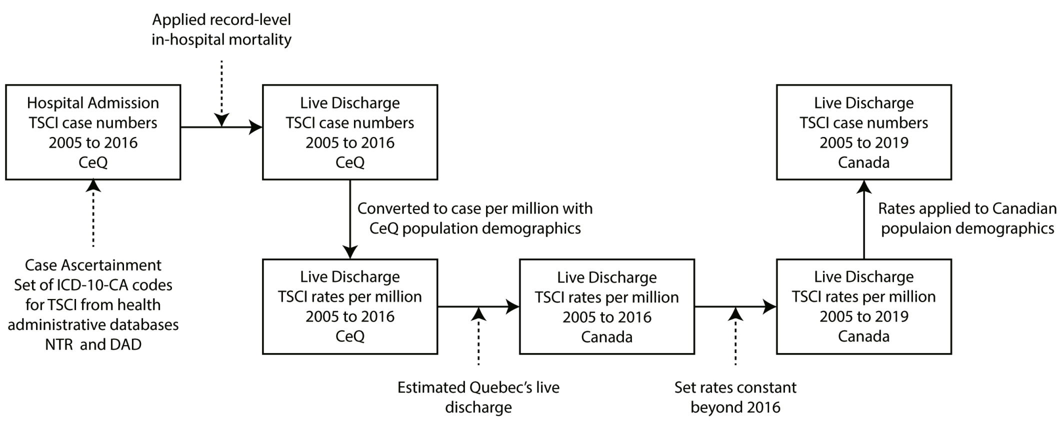


FIGURE 1
Process map of traumatic spinal cord injury (TSCI) incidence estimation methodology. All TSCI case numbers and rates were calculated by five-year age- and sex-specific groups. ICD-10-CA, International Classification of Disease, Version 10, Canadian revision; TSCI, traumatic spinal cord injury; CeQ, Canada excluding Québec; DAD, Discharge Abstract Database; NTR, National Trauma Registry.

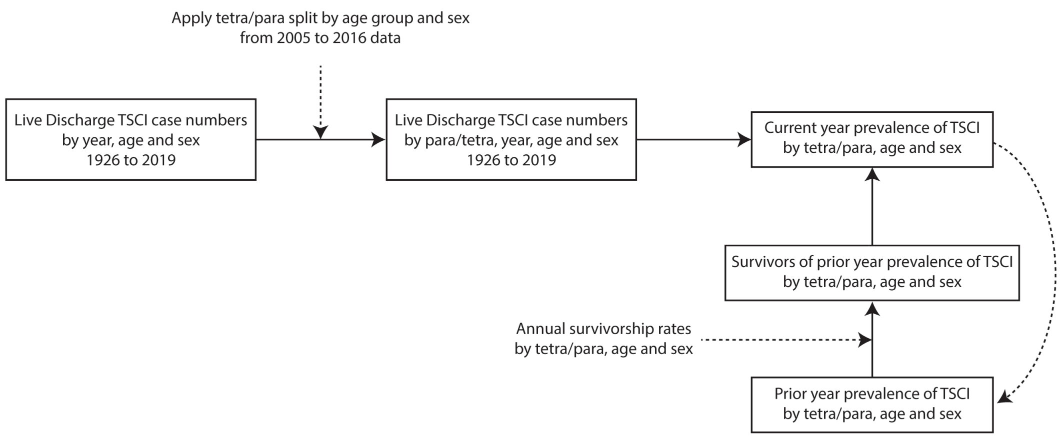


FIGURE 2
Process map of TSCI prevalence estimation methodology. All TSCI case numbers and rates are calculated by five-year age groups. TSCI, traumatic spinal cord injury; tetra/para, tetraplegia and paraplegia.

TABLE 2 Provincial traumatic spinal cord injury admission incidence rates per million population, ranked by population size.

| Province | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ontario | 21.71 | 20.69 | 23.11 | 20.10 | 18.62 | 22.46 | 24.28 | 23.71 | 21.98 | 23.83 | 24.80 | 26.62 | 22.71 |
| British Columbia | 34.56 | 39.37 | 37.52 | 38.40 | 37.18 | 30.00 | 32.67 | 35.85 | 34.20 | 42.83 | 37.49 | 36.99 | 36.43 |
| Alberta | 30.71 | 37.70 | 41.26 | 39.77 | 38.60 | 33.49 | 32.72 | 33.50 | 32.02 | 31.16 | 27.53 | 31.16 | 33.95 |
| Manitoba | 33.10 | 38.87 | 36.99 | 30.89 | 29.79 | 35.22 | 36.47 | 39.99 | 27.66 | 24.98 | 33.97 | 37.93 | 33.80 |
| Saskatchewan | 35.23 | 34.26 | 46.90 | 47.18 | 44.45 | 39.95 | 40.32 | 38.67 | 38.92 | 47.29 | 45.97 | 35.70 | 41.26 |
| Nova Scotia | 21.32 | 25.59 | 27.81 | 24.58 | 26.65 | 31.84 | 25.41 | 28.57 | 34.99 | 29.72 | 24.43 | 31.62 | 27.72 |
| New Brunswick | 32.08 | 29.51 | 25.49 | 24.10 | 34.67 | 29.21 | 30.44 | 34.36 | 37.05 | 35.78 | 26.53 | 38.29 | 31.48 |
| Newfoundland and Labrador | NR | NR | 23.57 | 29.32 | 27.09 | 19.16 | 28.57 | 28.49 | 36.03 | 45.42 | 35.93 | 30.17 | 25.44 |

Data in this table were derived from the CIHI data request without estimates on Quebec. NR, not reported due to low number of incident cases.

Supplementary Table 4) (18) to estimate prevalence for the year. All data analysis was performed using SAS version 9.2. The study protocol was approved by the university ethics board.

# Results

## Provincial TSCI incidence rates

Provincial incidence rates based on hospital admission from 2005 to 2016 are shown in Table 2. The province of Ontario had the lowest admission incidence rate (22.7 per million) and Saskatchewan had the highest admission incidence rate (41.3 per million) over the 12-year data range from the health administrative data.

## National Incidence and prevalence rates

For 2019, it was estimated that there were 1,199 cases of TSCI admitted to hospital (32.0 per million), with 123 in-hospital deaths (10% of admissions) and 1,076 cases of TSCI discharged (28.7 per million). The discharges were projected to include 728 cases of tetraplegia (68% of the cases) and 348 cases of paraplegia (32%). The estimated number of people living with TSCI was 30,239 (804/million); 15,533 with paraplegia (52%) and 14,706 with tetraplegia (48%).

Over 15 years, the estimated admission incidence of TSCI in Canada increased by 37% when compared to 2005 when there were 874 cases, with an incidence of 27.1 per million. There was a 134% increase in the number of admissions within the 65+ age group over the 15 year study period, compared to a 9% increase in the <65 age group for the same period. The discharge incidence increased by 41% from 814 cases (25.2 per million) in 2005, with the 65+ age group admissions increasing by 130%, compared to the <65 age group which increased by 9%. The prevalence declined by 5%, from 31,727 cases (984 per million) in 2005. Individuals with tetraplegia were more prevalent (from 64 to 68% of discharge incidence) and had a reduced life expectancy compared to individuals with paraplegia reported in the literature (18). This was incorporated into the prevalence model (see Supplementary Table 4). Additionally, the age at injury increased, thereby impacting survival and prevalence.

Estimated age-specific TSCI incidence case numbers are shown in Figure 3A and the resultant age-specific TSCI incidence rates (cases per million) estimated for 2019 are shown in Figure 3B, alongside the age distribution of the Canadian population. Further exploration of estimated 2019 national discharge rates by age- and sex-specific groups are shown in Table 3. The discharge rates are higher for males in almost all of the age groups, except the 0 to 4-year age group. The age-specific prevalence estimates are shown in Figure 4 and the prevalence details on age and injury level are in Table 4. Additional years of admission, discharge and prevalence data going back to 2005 (by five-year age groups and sex) are available upon request.

## Demographics over time

Of the estimated incident cases, 76 and 73% were male in 2005 and 2019, respectively. With an increased average age from 46.6 years in 2005 to 54.3 years in 2019; 22% were 65 years or older in 2005 and 38% were 65 years or older in 2019 based on admission incident cases. Data for 15-year age groups are in Figure 5. There are differences in age- and sex-specific discharge incidence rates. In 2005, 52% of the TSCI incidence cases were in individuals under the age of 45, and 48% were 45+; by 2019, the overall incidence rate proportions reversed, with the 45+ group accounting for 66% and the under 45 age group for 34%.

The external cause of injury for the CIHI data (excluding Québec) is shown in Figure 6. Falls were the most common cause of injury over the 12-year range accounting for 42% followed by motor vehicle collisions (MVC) at 27%. The most common cause varied by age, with sports being the most common for the 0 to 14-year age group (38%), MVC for the 15–29 (42%) and 30–44 age groups (35%), and falls for all other age groups (45–59 age group, 44%; 60–74 age group, 63%; and 75+ age group, 73%). Further breakdown by cause of injury is provided in Supplementary Table 5.

# Discussion

Results of this study estimated that in 2019, there were 1,199 cases of TSCI admitted to acute care hospitals (32.0 per million) and 1,076 cases discharged to the community (28.7 per million) in Canada. The estimated prevalence of TSCI in 2019 was 30, 239

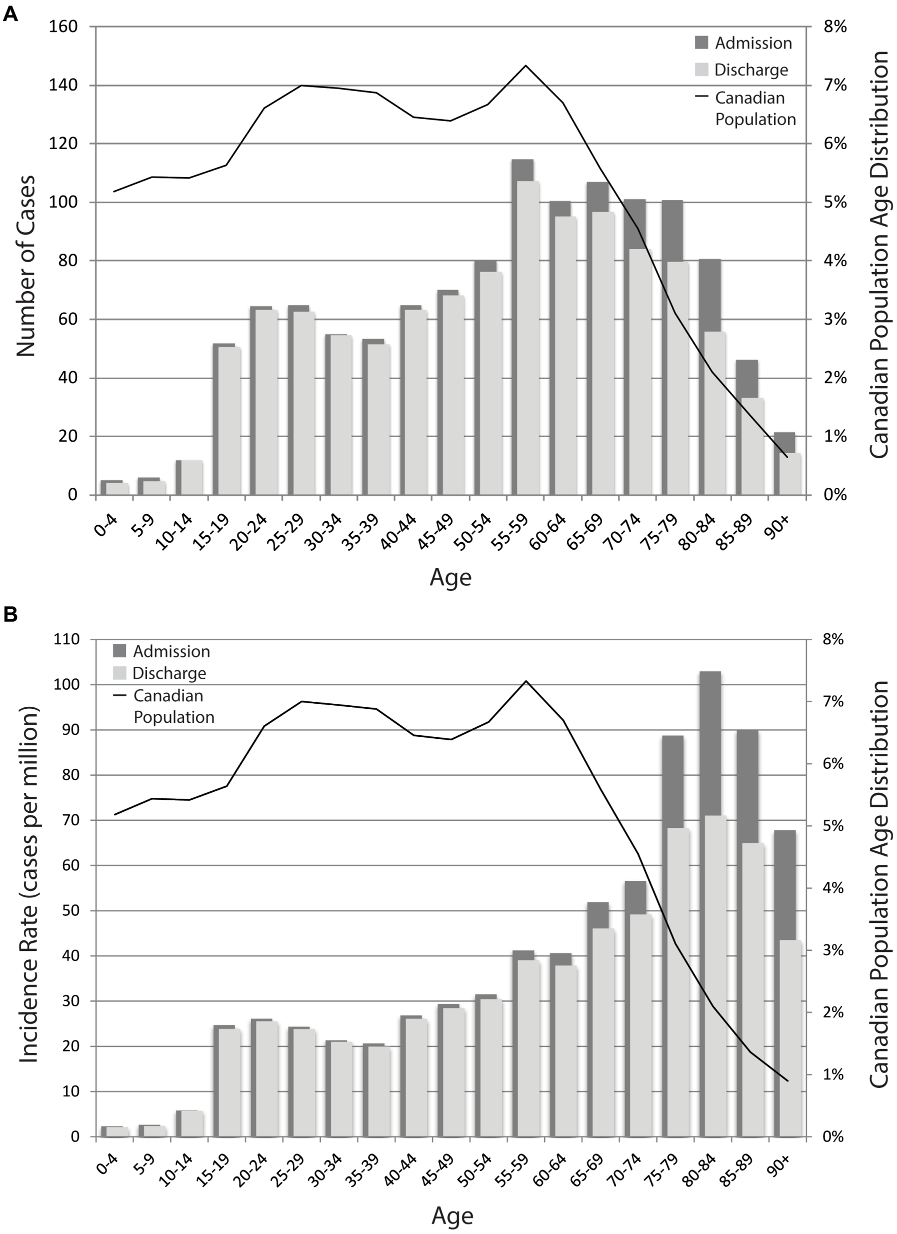


FIGURE 3
**(A)** Estimated 2019 national TSCI incidence case numbers. Age-specific incidence in 2019, as shown by the number of cases. **(B)** Estimated 2019 national TSCI incidence rates. Age-specific incidence in 2019 as shown by the cases per million per population. Rates are estimated using the case number and the age-specific Canadian population. The bars correspond to the y-axis on the left and the black line corresponds to the y-axis on the right.

(804/million). Using data from 2005 to 2016 and projecting to 2019 revealed trends including, an increased overall number of people injured each year from 874 to 1,199 incident cases, an older average age at injury rising from 46.6 years to 54.3 years and a larger proportion over the age of 65 changing from 22 to 38% during the 15-year time frame. This work contributes to the literature by using a previously published prevalence model with national-level data and establishing a standard way to report on incidence using health administrative data. Clinicians, health care programs and community partners, must anticipate an increasing number of cases of TSCI, particularly involving an older population. In addition, prevention programs should focus on the elderly and the soon-to-be elderly, in an attempt to reduce the incidence of TSCI in these populations.

Differences in the results between our 2010 estimates and the current estimates can be summarized by three factors: the data sources, case identification and time periods the data cover. First, when assessing the data sources, the geographic coverage, cohort size, in-hospital mortality and life expectancy data should be considered. The current 2019 estimates used data from nine of 10 provinces plus all territories, and a cohort of more than 8,000 cases. Estimated rates were applied to the population of a single province (Québec) since the

**TABLE 3** National age- and sex-specific live discharge incidence rates of TSCI in Canada for 2019.

| Age, years | Male | Female | Total |
|---|---|---|---|
| 0–4 | 2.0 | 2.3 | 2.2 |
| 5–9 | 3.9 | 0.7 | 2.4 |
| 10–14 | 6.6 | 4.9 | 5.7 |
| 15–19 | 33.5 | 13.8 | 23.9 |
| 20–24 | 38.1 | 11.8 | 25.5 |
| 25–29 | 37.9 | 8.8 | 23.8 |
| 30–34 | 33.6 | 8.1 | 21.0 |
| 35–39 | 32.0 | 7.9 | 19.9 |
| 40–44 | 40.5 | 12.0 | 26.1 |
| 45–49 | 47.8 | 9.3 | 28.4 |
| 50–54 | 46.4 | 14.6 | 30.4 |
| 55–59 | 61.6 | 16.8 | 39.1 |
| 60–64 | 58.9 | 17.6 | 37.9 |
| 65–69 | 68.8 | 24.6 | 46.1 |
| 70–74 | 71.8 | 28.3 | 49.2 |
| 75–79 | 82.3 | 56.0 | 68.3 |
| 80–84 | 88.4 | 57.2 | 71.0 |
| 85–89 | 97.3 | 43.4 | 65.0 |
| 90+ | 67.7 | 32.8 | 43.5 |
| Total | 42.1 | 15.3 | 28.6 |

Incidence rates are shown as cases per million per population.

**TABLE 4** Estimated age and severity-specific prevalence of TSCI in Canada for 2019.

| Age, years | Paraplegia | Tetraplegia | Total |
|---|---|---|---|
| 0–4 | 4 | 9 | 12 |
| 5–9 | 11 | 18 | 29 |
| 10–14 | 25 | 40 | 65 |
| 15–19 | 113 | 141 | 254 |
| 20–24 | 287 | 316 | 603 |
| 25–29 | 528 | 535 | 1,062 |
| 30–34 | 685 | 685 | 1,370 |
| 35–39 | 845 | 868 | 1,712 |
| 40–44 | 1,030 | 1,097 | 2,127 |
| 45–49 | 1,301 | 1,385 | 2,686 |
| 50–54 | 1,689 | 1,776 | 3,465 |
| 55–59 | 2,204 | 2,274 | 4,478 |
| 60–64 | 2,152 | 2,069 | 4,221 |
| 65–69 | 1,805 | 1,565 | 3,370 |
| 70–74 | 1,337 | 1,032 | 2,370 |
| 75–79 | 787 | 533 | 1,321 |
| 80–84 | 446 | 265 | 711 |
| 85–89 | 214 | 87 | 301 |
| 90+ | 71 | 11 | 82 |
| Total | 15,533 | 14,706 | 30,239 |

Numbers may not sum to age group total due to rounding.

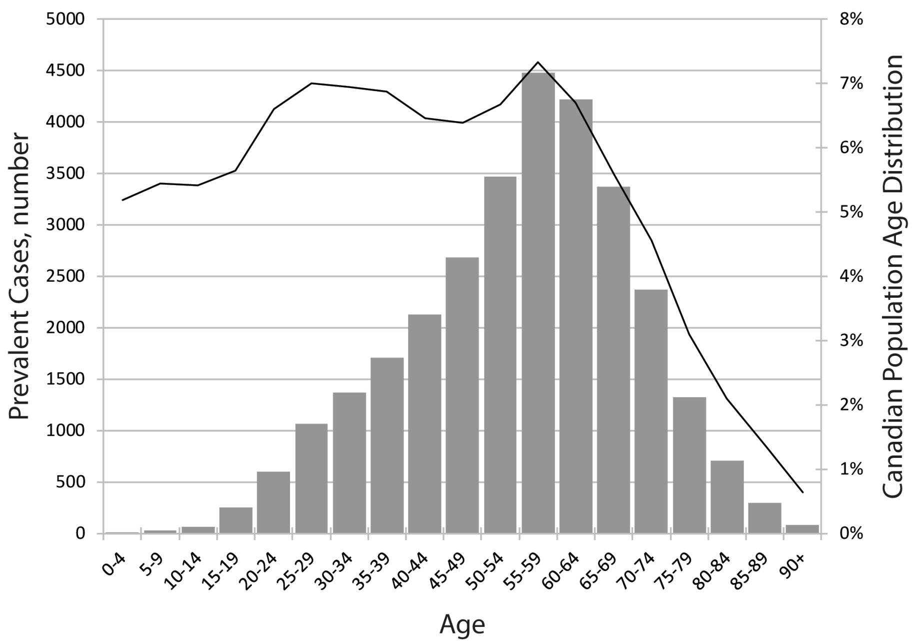


FIGURE 4
Estimated 2019 national TSCI prevalence numbers. Age-specific prevalence as shown by the number of people. The bars correspond to the y-axis on the left and the black line corresponds to the y-axis on the right.

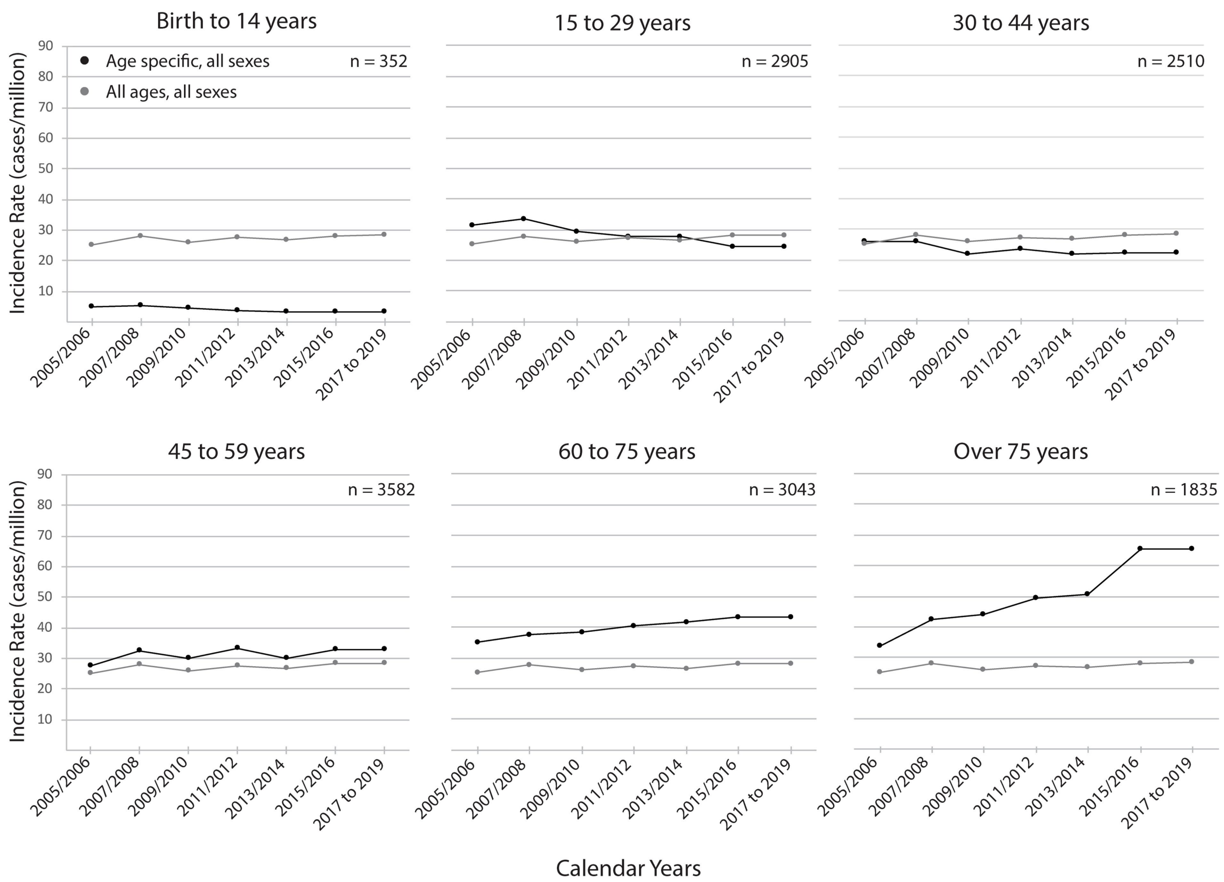


FIGURE 5
Estimated national TSCI discharge incidence rates, by age group and year. Age-specific discharge incidence rates are shown by cases per million of the age-specific population. The black line represents each age group-specific incidence rates and the gray line represents the incidence rates for all ages as a reference. The 2017 to 2019 age-specific rates were set to 2015 to 2016 rates since that was the most recent year of health administrative data available. The estimated case numbers corresponding to the incidence rates are shown in each panel to provide a context of the estimated case load volume over the 15 calendar years.

data were not available. Additionally, age-specific in-hospital mortality and updated life expectancy data were incorporated into the current prevalence model. In 2010, data from the province of Alberta was used as it provided the population estimate, which included a cohort of 450 cases (10). Assumptions were made when a single province's age- and sex-specific incidence rates were applied to the population of Canada and used a single mortality rate for all ages for the 2010 estimates (13).

Second, while both estimates used ICD coding to identify cases of TSCI, there are several differences in case ascertainment relating to the coding version and timing of data collection. The current estimates used ICD-10 codes, in contrast, the 2010 estimates were based on a set of ICD-9 codes. Third, the time periods differ. The current estimates used data collected over 12 years, from 2005 to 2016 with the age- and sex-specific incidence rates from 2015/2016 held constant to estimate rates for 2017 to 2019. The 2010 estimates used data collected over 3 years from 1997 to 1999 (10) and the average incidence rates from the late 1990s were applied to the 2010 Canadian population (13) assuming that the age- and sex-specific incidence rates remained constant for a decade.

Advantages of the 2019 estimates include using recent record-level data, with more accurate coding, covering a greater geographical area with larger sample size, age-specific in-hospital mortality and updated life expectancy data. The drawback to using national-level health administrative data in the 2019 estimates was the lack of medical record verification; data used in the 2010 study were validated. In this study, we were not able to validate with medical records since the national data request was de-identified.

Few studies have been published on the incidence and prevalence of TSCI in Canada over the past decade. A literature review of the incidence of TSCI summarized the Canadian studies, with our previous work representing the only national estimate (13), and regional estimates ranging from 3.6 to 52.5/million (19). The adult incidence rate in the province of Ontario was reported to be 24/million (9) from 2005 to 2011, which aligns with the previous studies from 2003 to 2006 with a range of 23.1 to 24.2/million (7). These published estimates for Ontario are lower than our national estimate of 32/million but are similar to the provincial rates for Ontario from the national health administrative data (from 2005 to 2016 at 18.6 to 26.6/million), although our data includes pediatric TSCI. The idea that provinces have varying incidences has been suggested and this is the first study to show results by province from a single study using the same time period and data collection methods.

Our updated prevalence of 30,239 (804/million) falls in the global range of 236 to 4,187/million (20). The global map for TSCI, an

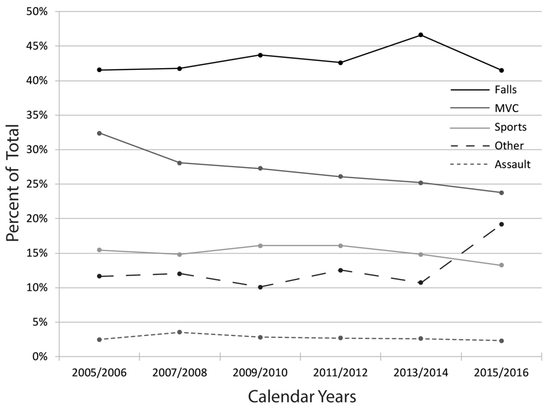


FIGURE 6
External cause of traumatic spinal cord injury in Canada (excluding Québec), by year. Data are based on the administrative data request and external cause of injury codes. External cause of injury can be viewed by age groups in the Supplementary Table 5.

initiative of the International Spinal Cord Society Prevention Committee, reports estimates worldwide (20) and the current results will provide updated estimates on the incidence, prevalence and data on the etiology of TSCI. The Global Burden of Disease study, the only other source of national-level data, reported a 2016 Canadian incidence of 9,654 (2,500/million) and a prevalence of 324,689 (75,200/million) (21), which is 10 times higher than our 2019 estimates. The discrepancy could be explained by differences in the TSCI definition using ICD codes. The Global Burden of Disease study (21) included additional ICD-10 codes that are not included in our case identification, for example, codes for nerves injuries (for a code comparison see Supplementary Table 6). The large differences between these estimates emphasize the importance of an agreed-upon standard set of codes that define TSCI to share data nationally and internationally.

How trauma is defined also contributes to the coding of SCI. The International Classification of External Causes of Injury considers injuries resulting from iatrogenic causes as traumatic (22), but iatrogenic SCI has not been investigated in Canada. Three different studies have reported a 5–18% frequency of iatrogenic SCI with most resulting from spinal surgery (23–25). In the SCI field, the International SCI Data Set Committee considers iatrogenic causes of SCI as traumatic and acknowledged challenges with this classification (26). Despite the decisions of these groups, the CIHI National Trauma Registry does not include iatrogenic causes of injury and many data holdings do not address this discrepancy.

In terms of the age-specific data and external causes of these injuries, the incidence of TSCI increased in the older age groups and decreased in the younger age groups over the 12 years. While the discharge incidence rate for the 15 to 29 age group fell from 31.5/million in 2005 to 24.4/million by 2019. Over the same period, the rate for the 75+ population almost doubled from 33.9/million to 65.4/million, the highest rate for all age groups. The decrease in MVC injuries and fatalities which is a common cause of TSCI in younger populations (see Supplementary Figure 3) (27), an increase in falls recorded in trauma emergency room admissions (17) as well as the increasing proportion of the Canadian population over the age of 65, may explain some of these trends. An increase in TSCI among older individuals due to falls has been observed in data from a Canadian SCI registry (Rick Hansen Spinal Cord Injury Registry) (28) as well as in other countries, including Ireland, the Netherlands, Norway, Switzerland, Czech Republic, Italy, Spain and Korea (23, 29–35). Furthermore, the New Zealand Ministry of Transport reported a decrease in morbidity and mortality (41, 50%) resulting from MVC over 23 years (1993 to 2016) (36). A Canadian pediatric study reported that hospitalization rates from transport-related causes significantly decreased from 2006 to 2012 and suggested provincial prevention policies and legislation targeting drivers, passengers, cyclists and pedestrians may have been responsible (37). Finally, Spain and the US have reported a decreasing incidence in pediatric TSCI and also suggest a decrease in injuries involving vehicles are a contributing factor (38, 39).

The results from this study involving national TSCI data will be helpful to forecast health care resources. Trends toward an increased age of injury, and possibly different causes of injury, will impact planning, funding, delivery and evaluation of injury prevention and health care. Prevention outreach and research should continue to include all ages but there should be an increased awareness of SCI and its causes among clinicians who treat elderly patients and in assistive-living and long-term care settings. With an aging population, there will be a need to examine issues such as end of life decision making and rehabilitation goals, as well as a need to include gerontology experts on clinical teams.

The challenges of using health administrative data are well documented and result in limitations (40, 41). TSCI is a clinical diagnosis that requires training to classify the level and severity of the neurological injury. The varying types of injuries and resultant loss of function comprise a heterogeneous population with sub-categories that are not always captured by ICD-10 coding. Our group conducted previous work on the validity of ICD-10 coding in TSCI, where a clinical diagnosis was compared with ICD-10 codes that found approximately 11% (42) of confirmed TSCI cases did not have a corresponding ICD-10 code for TSCI (Table 1) and therefore would not be included in the data used for this study. Researchers in Ontario reported that these ICD-10-CA codes have high specificity (true negative rate) and moderate sensitivity (true positive rate), also suggesting persons with TSCI could be missed with ICD coding (43). A validation study in Norway found that ICD-9 coding for TSCI can lead to overestimation (44). Using a combination of seven ICD-10 codes (which corresponds to all except two codes in our list) this group reported that approximately 16% of TSCI patients were missed (44). Based on the published ICD-10 coding validity work, the estimated 1,199 cases admitted to Canadian hospitals in 2019 are conservative and the true number could be approximately 10% higher.

Future work should try and capture SCI cases missed with ICD-10-CA coding by validating records using clinical registries and include SCI cases from iatrogenic causes. Improvements in coding practices and advances in the ICD coding with the introduction of ICD-11 will also assist in capturing more cases of TSCI in health administrative data. Finally, adding data from Québec rather than estimating the incidence, will further enhance the accuracy of these results.

In conclusion, this study reported an updated conservative estimate for the incidence and prevalence of TSCI in Canada using national health administrative data and compared to previous estimates. In Canada, because trends and regional differences in TSCI incidence exist, estimates should be continually updated. To further improve these estimates, work is needed to include incident cases of TSCI not captured by current coding methods in health administrative data. These results have implications for planning health care resources, informing prevention strategies, and establishing research priorities in the elderly who are susceptible to TSCI caused by falls.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical review and approval of this study was completed by the University of British Columbia Research Ethics Board (H15-00471). Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## Author contributions

NT and VN designed the work and involved with acquisition of the data. NT and XC were responsible for data analysis. NT drafted the work. VN, XC, NF, SH, ND, BK, and MD critically reviewed and revised the work. All authors were involved with reviewing and interpreting the data and approved the final version of the work.

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## Conflict of interest

NT, VN, XC, NF, and SH were employed by Praxis Spinal Cord Institute.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1201025/full#supplementary-material

SUPPLEMENTARY TABLE 1

External Cause of Injury Codes for Iatrogenic Causes.

SUPPLEMENTARY TABLE 2

Aggregated data from CIHI data request (National Trauma Registry & Discharge Abstract Database) for Canada (except Quebec) of Admission and Discharge Case Number, by Year.

SUPPLEMENTARY TABLE 3

TSCI by Tetraplegia, Paraplegia, Age Group and Sex for 2005 to 2016, CIHI data (excluding Quebec).

SUPPLEMENTARY TABLE 4

Estimated Life Expectancy for Persons Living with TSCI as a Percent of that for their Peers in the General Population.

SUPPLEMENTARY TABLE 5

External Cause of Injury by Age, 2005 to 2016, percent of total.

SUPPLEMENTARY TABLE 6

Comparison of ICD-10 Codes for TSCI.

SUPPLEMENTARY FIGURE 1

CIHI data schematic.

SUPPLEMENTARY FIGURE 2

Detailed process flow (incidence and prevalence).

SUPPLEMENTARY FIGURE 3

MVC injury and fatality crude rates, Canada 1984–2017.

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# Dual diagnosis of TBI and SCI: an epidemiological study in the pediatric population

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**Introduction:** Dual diagnosis (DD) with traumatic brain injury (TBI) and spinal cord injury (SCI) poses clinical and rehabilitation challenges. While comorbid TBI is common among adults with SCI, little is known about the epidemiology in the pediatric population. The primary objective of this study was to evaluate the prevalence of TBI among children in the United States hospitalized with SCI. Secondary objectives were to compare children hospitalized with DD with those with isolated SCI with regards to age, gender, race, hospital length of stay, and hospital charges.

**Methods:** A retrospective analysis of hospital discharges among children aged 0–18 years occurring between 2016–2018 from U.S. hospitals participating in the Kids' Inpatient Database. ICD-10 codes were used to identify cases of SCI, which were then categorized by the presence or absence of comorbid TBI.

**Results:** 38.8% of children hospitalized with SCI had a co-occurring TBI. While DD disproportionately occurred among male children (67% of cases), when compared with children with isolated SCI, those with DD were not significantly more likely to be male. They were more likely to be Caucasian. The mean age of children with DD (13.2 ± 5.6 years) was significantly less than that of children with isolated SCI (14.4 ± 4.3 years). DD was associated with longer average lengths of stay (6 versus 4 days) and increased mean total hospital charges ($124,198 versus $98,089) when compared to isolated SCI.

**Conclusion:** Comorbid TBI is prevalent among U.S. children hospitalized with SCI. Future research is needed to better delineate the impact of DD on mortality, quality of life, and functional outcomes.

KEYWORDS
**dual diagnosis, Pediatrics, traumatic brain injury, spinal cord injury, epidemiology**

## Introduction

Neurological insults are a significant pediatric health issue, both nationally and internationally (1). While traumatic brain injuries (TBIs) are relatively common, traumatic spinal cord injuries (SCIs) are an uncommon cause of morbidity and mortality in children. However, when they occur, they represent a different challenge than SCI in adults (2, 3). Co-morbid traumatic brain injury (TBI) with spinal cord injury (SCI) may greatly impact patients' rehabilitation courses and functional outcomes (4). Unfortunately, there remains a dearth of literature addressing the implications of these dual diagnoses (DD) in pediatric patients.

Prior retrospective reviews using large datasets, including the Kids' Inpatient Database (KID), have elucidated demographic information regarding children who have sustained (isolated) TBIs and spinal injuries and have provided information regarding in-hospital mortality rates. Using the KID, Lu et.al identified 220,771 pediatric cases of TBI between 2006 and 2012, 66% of which occurred among boys. They reported a mean hospital length of stay of 5 days and an in-hospital mortality rate of 4% (5). Piatt used the KID to determine that the incidence of hospital admission for SCI among individuals aged 21 or younger was 24 per 1 million in 2009. That year, there were 2,139 cases of SCI identified in the dataset. 2.8% of those cases reportedly resulted in death during the hospitalization (6).

Prior research has also yielded information about the epidemiology of DD, though this has been better studied in adult populations. It is well-recognized that adults with SCI commonly have comorbid TBIs. The incidence of SCI in comatose patients is higher than the general trauma population (7). While there has been considerable variability in the estimated prevalence of DD, studies suggest a prevalence of TBI as high as 60 percent among adults with SCI (8, 9). In a single-center study, 31.6% of children with SCI had a concomitant brain injury (10). Other retrospective studies evaluating DD among patients with SCI who received inpatient rehabilitation excluded individuals under the age of 18 (8, 11, 12).

Co-occurring TBI and SCI can have considerable implications for a patient's rehabilitation progress, speed of recovery, and prognosis (13). For example, it may impact one's adjustment to disability, ability to learn new skills, motivation, tolerance of potentially sedating medications, and risk for complications. Moreover, the presence of DD may affect the speed of and the degree to which one recovers function after injury (4). Prior studies have demonstrated that adults with DD are more likely to require transfer from acute inpatient rehabilitation facilities to acute care facilities, more likely to suffer severe medical complications, and less likely to be discharged home as compared to those with SCI alone (11, 13). When compared to those with isolated TBI, adults with comorbid SCI demonstrate lower gains in cognitive domains during their courses of inpatient rehabilitation, particularly with problem solving and comprehension (12). When compared to adults with SCI without co-morbid TBI, those with DD are discharged from inpatient rehabilitation with greater cognitive impairment and having achieved less improvement in their motor Functional Independence Measure (FIM™) scores (14).

Anatomical factors contribute to the risk of DD in the pediatric population (15). Childrens' heads are often disproportionately large and heavy relative to their bodies and are poorly supported by weak muscles and ligaments as well as unfused epiphyses (10). They also have increased water content within their intervertebral discs and shallow facet joints. All of these aspects contribute to a more malleable spine, increasing the risk of neurological injury even without bony injuries. Studies have shown that most spinal injuries in children occur at a higher location in the cervical spine, particularly at the C0-C2 level (16). These high cervical SCI levels are more likely to be associated with brain injury (17, 18).

Children's skulls are thin and pliable in early development, providing less protection to the underlying brain (19, 20). As such, brain injuries can occur with or without an actual bony fracture; however, it has been suggested that the presence of skull fractures increases the possibility of underlying intracranial injury (21). Additionally, and uniquely to the pediatric population, as children's heads grow, existing fractures subsequently grow and can result in delayed neurological deficits.

Key physiological differences exist between children and adults that may also have important implications for their risk for and recovery from DD. Blood volume is small by comparison, and cerebral blood flow varies with age. It is usually lowest at birth, peaks between ages 3 and 7, and progressively decreases to adult levels. Cerebral metabolism also changes with age. It starts at around 60% of adult values at birth and then it rapidly increases to values significantly greater than adult values by age 5. It subsequently slowly decreases to adult levels through adolescence. This is important for progressive myelination and synaptogenesis (22).

Pediatric DD also poses challenges due to the ongoing brain development that occurs in childhood. Cognitive impairments in children with brain injury may not be immediately evident after the injury, and may only become apparent as the child gets older (23). It may be particularly difficult to recognize mild TBI in younger children, though formal comprehensive testing may facilitate earlier detection of impairments in the cognitive domains (24).

This study was undertaken to better understand the epidemiology of DD in children in the United States. The primary aim was to establish the prevalence of DD with SCI and TBI in the pediatric population with secondary outcomes evaluating demographic data, length of stay, total hospital charges, and insurance status. Such analyses are critical to help better understand the needs of children with these injuries.

# Materials and methods

## Database

This study analyzed data from the KID Database, which consists of a compilation of de-identified discharge data from a sample of all hospital discharges of patients younger than 21 years of age, from 4,000 community, non-rehabilitation hospitals in the United States. It currently includes sites from 48 states and the District of Columbia. It is prepared every 3 years by the Healthcare Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (25). It is used to identify, track, and analyze national trends in healthcare utilization, access, charges, quality, and outcomes. KID data elements include primary and secondary diagnoses and procedures, discharge status, patient demographics, hospital characteristics, expected payment source, total charges (Tot charge), length of stay (LOS), as well as severity and comorbidity measures (25). This study used de-identified data and was exempt from the University of Miami IRB review.

## Study design

A descriptive, retrospective, cross-sectional study was performed to assess the period prevalence (2016–2018) and epidemiology of SCI and combined SCI with TBI in pediatric groups. Age limit was set from 0 to 18 years. The International Classification of Diseases Version 10 (ICD-10) codes for SCI and TBI were included (see Appendix).

## Inclusion/exclusion criteria

All individuals in the database aged 0–18 years with a diagnosis of SCI made between 2016–2018 were included. Those with comorbid TBI were considered separately from those with isolated SCI.

## Statistical analysis

Normally distributed continuous variables (age) were compared with mean and standard deviation using independent sample *t*-tests. Initially, the LOS and Tot charge data sets were analyzed as normally distributed continuous variables, however, variances demonstrated that these sets were, in fact, not normally distributed (skewness values of 3.8 and 10.4, respectively). Thus, these non-normally distributed continuous variables (LOS, Tot charge) were compared with median and interquartile range using Wilcoxon signed-rank sum tests. Descriptive statistics for demographics and insurance status were generated. Categorical variables (race, gender, and insurance) were described with numbers and percentages and assessed using $\chi 2$ test.

Chi-Square test and *t*-test were conducted to examine differences in demographic characteristics by injury types to identify possible confounders. The Wilcoxon rank sums test was used to report the associations between specific injury and LOS or the respective total charge using a 2 tailed t approximation approach. Tot charges data were analyzed using a linear regression, adjusting for age, gender, race, and insurance status, to evaluate for the potential association of different types of injuries (SCI vs. DD). Data analysis was performed using Statistical Analysis System (SAS) version 9.4 and an $\alpha \leq 0.05$ was considered statistically significant.

# Results

## Prevalence

The database contained data on 1,286 children hospitalized with SCI during the time period of interest: 2016–2018. Utilizing the aforementioned ICD-10 codes for SCI and TBI, we identified 787 individuals with isolated SCI and 499 individuals with both SCI and TBI (Table 1). Thus, the prevalence of DD among children with SCI was 38.8% (95% CI 36.14,41.46%).

## Age

In the isolated SCI group, 75% of individuals were aged 13–17 (half of those were ages 16–17) and 25% between 0–13. In the DD group, 75% were 6–17 (half of those were ages 15–17) and 25% between the ages of 0–6. While the DD group demonstrated greater variability in the spread of ages, as indicated by an interquartile spread of 10 years (age 6–16) compared to 4 years (age 13–17) in the SCI group, both groups demonstrated a median age (16 and 15, respectively) in the upper quartile. This showed a clustering in the older teenage years (≥15) in both groups. The DD group also showed a clustering in the younger ages (<6 years), which was not observed in the isolated SCI group. As seen in Figure, those with SCI alone had a higher average age than DD and that difference was statistically significant (see Figure 1).

**TABLE 1** Characteristics of pediatric patients with spinal cord injury alone and dual diagnosis.

| | SCI alone (*n* = 787) | DD (*N* = 499) | *p*-value |
|---|---|---|---|
| Age (mean ± SD) | 14.4 ± 4.3 | 13.2 ± 5.6 | <0.0001 |
| Gender (female; *n*, %) | 288 (36.56) | 166 (33.37) | 0.22 |
| Race, (*n*, %) | | | <0.0001 |
| White | 397 (50.44) | 290 (58.12) | |
| Black | 204 (25.92) | 75 (15.03) | |
| Hispanic | 125 (15.88) | 87 (17.43) | |
| Other | 61 (7.75) | 47 (9.42) | |
| Insurance, (*n*, %) | | | 0.44 |
| Medicare/medicaid | 359 (45.62) | 212 (42.48) | |
| Private | 350 (44.47) | 240 (48.10) | |
| Other | 78 (9.91) | 47 (9.42) | |
| LOS (day), median (IQR) | 4 (9) | 6 (13) | 0.0002 |
| Total charges ($), Median (IQR) | $98.089 (186,215) | $124,198 (262,014) | 0.0012 |

SCI, spinal cord injury; DD, dual diagnosis; LOS, length of stay; IQR, interquartile range.

## Gender

In both groups, males comprised the largest demographic group, representing 64% and 67% of SCI and DD, respectively. The gender distribution between the two groups was not statistically significant (Table 1).

## Race

White people comprised the largest demographic population in both groups, representing 50% of the SCI and 58% of the DD group. This was followed by Black people and Hispanic people representing 26% and 16% of the SCI and 15% and 17% of the DD group, respectively. The race distribution between the two groups was statistically significant (Figure 2).

## Insurance

In the SCI group, 46% had Medicaid, 44% had private insurance, and 10% were listed as "other." In the DD group, 42% had Medicaid, 48% had private insurance, and 10% were listed as "other." We did not find any statistically significant differences in the type of insurance between the SCI alone group and DD group (Table 1).

## Length of stay and total charges

The average hospital LOS in the SCI group was 4 days, compared to 6 days in the DD group. The average total charge in the SCI group was $98,089 compared to the $124, 198 in the DD group. Two extra days of stay and approximately $25,000 extra charges per child in the DD group, compared to the SCI alone group, were statistically significant (Figures 3, 4). The same association and difference in extra charge persisted in the adjusted model.

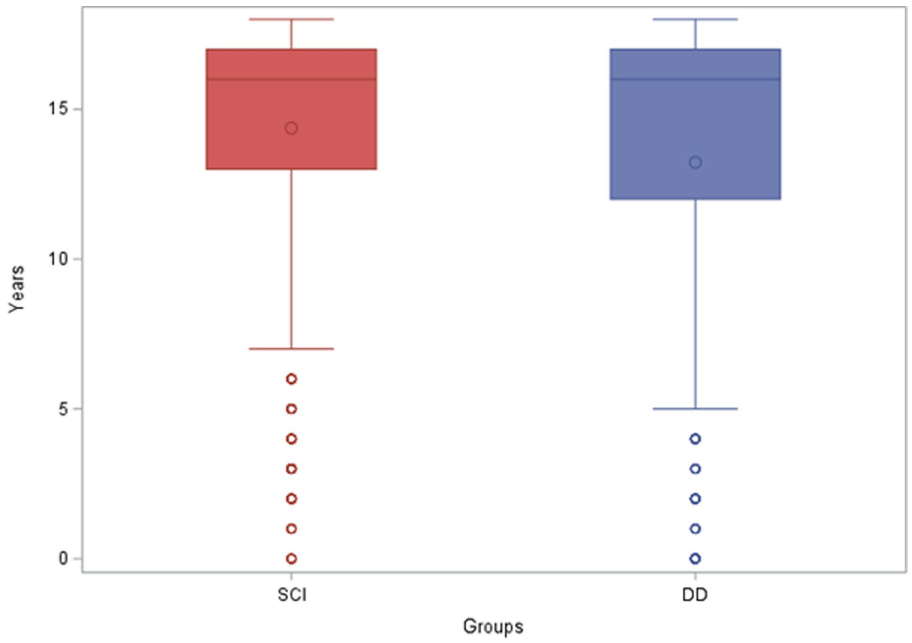


FIGURE 1
Age of pediatric patients with spinal cord injury alone and dual diagnosis. SCI, spinal cord injury; DD, dual diagnosis.

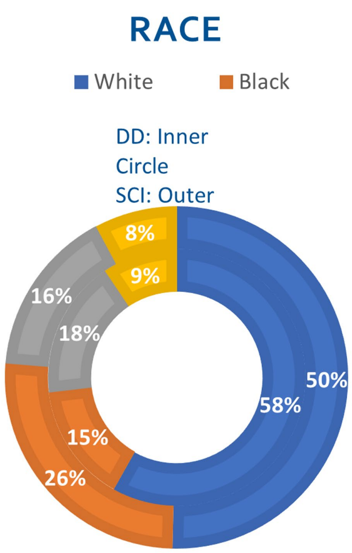


FIGURE 2
Race of pediatric patients with spinal cord injury alone and dual diagnosis. SCI, spinal cord injury; DD, dual diagnosis.

## Discussion

While prior studies have highlighted the burden of traumatic SCI among US children and adolescents (26), published data on the prevalence of dual diagnosis in this population was previously limited to a single-center study (10).

To the best of our knowledge, this report represents the first epidemiological study comparing the two groups, SCI alone versus DD (i.e., SCI and TBI), in the pediatric population using a large representative national database. This study confirms the key finding of Vova et al. of a high prevalence of comorbid TBI among children with SCI. Accordingly, there is good reason to adopt practice guidelines that include assessment for TBI among all children hospitalized with SCI.

Another interesting finding of this study pertains to the distribution of age among children with SCI, both with and without comorbid TBI. Both groups demonstrated a clustering in the older teenage years. However, the DD group also showed greater variability in the younger ages and a small cluster in ages 6 and younger which was not seen in the isolated SCI group. SCI is relatively rare in children 15 years of age and younger; in fact, of the almost 2.4 million children identified through the KID Database in a 3-year span, SCI accounted for only 0.02% of the national data number. In contrast to the rare nature of SCI in the pediatric population, the 2015 Center for Disease Control (CDC) Report to Congress on TBI identified children aged 0–4 and adolescents aged 15–19 as a high-risk group for TBI (27). Our study also demonstrates that a younger population group is affected by concomitant TBI, in addition to the teenage population.

Race differences were observed in our study, with Caucasians comprising the largest demographic group and a greater percentage of the DD group than the isolated SCI group. This is similar to other pediatric studies which demonstrate that from 0–15 years of age, White people are more commonly found to have these injuries than Non-White people, with all modes of injury, except firearms (6). However, this differs from adult studies, which suggest that Non-White people make up the majority of SCI cases, due in large part to the elevated incidence among African-Americans.

Males represented a higher percentage than females (approximately 3:1 ratio) in both the isolated SCI and DD groups. However, amongst those with SCI, neither gender was statistically more likely to have comorbid TBI. According to the 2011 National Spinal Cord Injury Statistical Center, Birmingham, Alabama data, the ratio of males to females in the SCI population alone is approximately 4:1 (28). There is limited data on the ratio of males to females in the

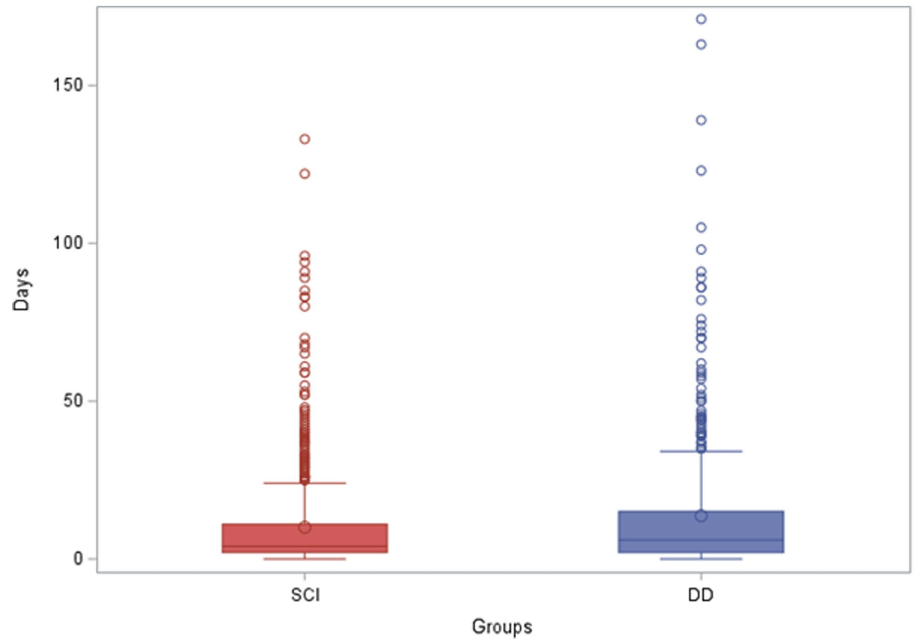


FIGURE 3
Length of stay of pediatric patients with spinal cord injury alone and dual diagnosis. LOS, length of stay; SCI, spinal cord injury; DD, dual diagnosis.

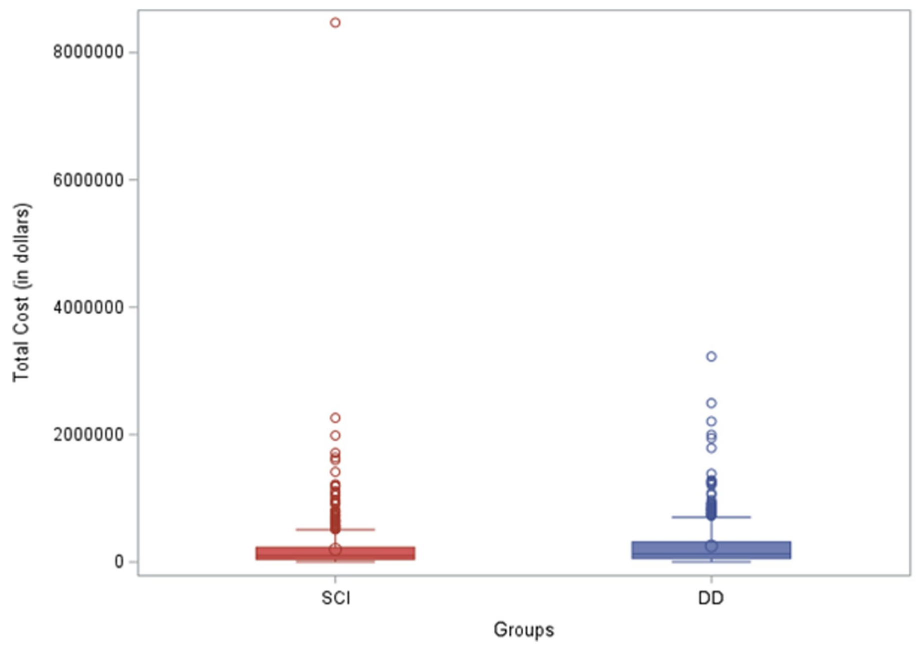


FIGURE 4
Total charges of pediatric patients with spinal cord injury alone and dual diagnosis. SCI, spinal cord injury; DD, dual diagnosis.

DD population, with one study finding approximately a 1.8:1 M:F ratio (12). While males comprise the majority in both the adult and pediatric SCI and DD population, in the pediatric population, the gap between the genders is narrowed.

This study also revealed that pediatric DD is associated with longer hospital lengths of stay and higher health expenditures when compared to the same population with isolated SCI. According to Zonfrillo et al., children hospitalized with severe TBI and SCI did not demonstrate a difference in standardized hospital costs relative to their home zip code level median annual household income (29). In this study, the type of insurance was similar between the SCI alone group and DD group. In both groups, there were a relatively equal percentage of those with Medicaid and those with private insurance. However, we observed that the length of stay and total hospital cost in the DD group was longer and costlier than in the SCI alone group. Consequently, having a DD places a higher burden on the healthcare system. Identifying these increased healthcare costs helps to suggest improvement in allocation of resources.

Among the limitations of this study is the potential for information bias. Similar to what Sikka et al. observed in 2019, in attempting to determine prevalence of TBI from acute care records, documentation variability exists among physicians and advanced practitioners (30). Additionally, the analysis relies on administrative billing data for the identification of cases where the accuracy of the codes may be unreliable. This likely results in under-representation of cases, suggesting that the percentage of dual diagnosis is probably higher than found. Moreover, ICD-10 codes do not reflect or capture the degree of brain injury severity. Also, only data pertaining to the acute hospitalization was available, and there was no information on rehabilitation nor any outcomes after hospital discharge. Additionally, because the data excluded deaths prior to admission, we could not evaluate the prevalence of DD among those with injuries resulting in death at the scene.

A final limitation concerns its generalizability to a global pediatric population. While some demographic data (e.g., gender and age) is likely widely generalizable, we do not believe one can appropriately extrapolate U.S. data regarding insurance status, race, hospital charges, or hospital lengths of stay to draw conclusions about these variables among injured children in other countries.

## Conclusion

This study has demonstrated that more than a third of U.S. children hospitalized with SCI have comorbid TBI. DD among children contributes to longer hospital lengths of stay and greater health care expenditures when compared to SCI alone. Greater awareness of DD in children is needed to ensure appropriate screening for TBI in pediatric patients with SCI.

To better identify the true prevalence of dual diagnosis in children, it would be beneficial to prospectively collect data in those with SCI that includes comprehensive evaluation for TBI. Such evaluations would need to include neurological imaging reports, Glasgow Coma Scale scores, the presence and/or duration of loss of consciousness and post-traumatic amnesia, and the results of neuropsychological testing. Further research is also necessary to identify the impact of DD on the functional outcomes and quality of life of affected children, as well as their risks for mortality and long-term complications.

## Data availability statement

The data analyzed in this study was obtained from the Agency of Healthcare Research and Quality (AHRQ), Healthcare Cost and Utilization Project (HCUP), Kid's Inpatient Database (KID; https://hcup-us.ahrq.gov/kidoverview.jsp), the following licenses/restrictions apply: all HCUP data users, including data purchasers and collaborators, must complete the online HCUP Data Use Agreement Training Tool, and must read and sign the Data Use Agreement for Nationwide Databases before HCUP data can be accessed. Requests to access these datasets should be directed to HCUP, hcup@ahrq.gov.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## Author contributions

JG made substantial contributions to the conception and design of the work, the acquisition, analysis, and interpretation of the data, drafted the work and substantively revised it, and has approved the submitted version. LS made substantial contributions to the design of the work, the acquisition, analysis, and interpretation of the data, substantively revised the work, and has approved the submitted version. ET made substantial contributions to the interpretation of the data and has approved the submitted version. NR made substantial contributions to the acquisition, analysis, and interpretation of the data and has approved the submitted version. CB made substantial contributions to the acquisition, analysis, and interpretation of the data and has approved the submitted version. KL made substantial contributions to the conception and design of the work, the acquisition, analysis, and interpretation of the data, and has approved the submitted version. AV made substantial contributions to the conception and design of the work, the acquisition, analysis, and interpretation of the data, drafted the work and substantively revised it, and has approved the submitted version. All agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1241550/full#supplementary-material

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# A data-driven approach to categorize patients with traumatic spinal cord injury: cluster analysis of a multicentre database

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**Background:** Conducting clinical trials for traumatic spinal cord injury (tSCI) presents challenges due to patient heterogeneity. Identifying clinically similar subgroups using patient demographics and baseline injury characteristics could lead to better patient-centered care and integrated care delivery.

**Purpose:** We sought to (1) apply an unsupervised machine learning approach of cluster analysis to identify subgroups of tSCI patients using patient demographics and injury characteristics at baseline, (2) to find clinical similarity within subgroups using etiological variables and outcome variables, and (3) to create multi-dimensional labels for categorizing patients.

**Study design:** Retrospective analysis using prospectively collected data from a large national multicenter SCI registry.

**Methods:** A method of spectral clustering was used to identify patient subgroups based on the following baseline variables collected since admission until rehabilitation: location of the injury, severity of the injury, Functional Independence Measure (FIM) motor, and demographic data (age, and body mass index). The FIM motor score, the FIM motor score change, and the total length of stay were assessed on the subgroups as outcome variables at discharge to establish the clinical similarity of the patients within derived subgroups. Furthermore, we discussed the relevance of the identified subgroups based on the etiological variables (energy and mechanism of injury) and compared them with the literature. Our study also employed a qualitative approach to systematically describe the identified subgroups, crafting multi-dimensional labels to highlight distinguishing factors and patient-focused insights.

**Results:** Data on 334 tSCI patients from the Rick Hansen Spinal Cord Injury Registry was analyzed. Five significantly different subgroups were identified ($p$-value $\leq 0.05$) based on baseline variables. Outcome variables at discharge superimposed on these subgroups had statistically different values between them

($p$-value ≤0.05) and supported the notion of clinical similarity of patients within each subgroup.

**Conclusion:** Utilizing cluster analysis, we identified five clinically similar subgroups of tSCI patients at baseline, yielding statistically significant inter-group differences in clinical outcomes. These subgroups offer a novel, data-driven categorization of tSCI patients which aligns with their demographics and injury characteristics. As it also correlates with traditional tSCI classifications, this categorization could lead to improved personalized patient-centered care.

KEYWORDS

**traumatic spinal cord injury, patient-centric approach, patient categorization, data-driven method, cluster analysis**

## 1. Introduction

Traumatic spinal cord injury (tSCI) has significant physical, social, and vocational consequences for patients and their families (1). The loss of independence, increased lifelong mortality rates, and high costs for care place a great burden on the individuals and the healthcare system (1–3), making the appropriate treatment of this devastating disorder crucially important. The management of tSCI requires significant health care resource utilization (4), owing to a possible need for short-term intensive acute care and appropriate management of long-term secondary complications (3). Better specialization for managing tSCI is needed to address the unique needs of patients and to better allocate healthcare resources (5). The implementation of targeted care and effective treatment options could produce substantial benefits for both the patient and the healthcare system.

Early research suggests that specialized care, as opposed to general care, can help produce positive outcomes, including decreased length of stay (LOS) and decreased incidence of secondary complications (6–8). However, the optimal model of healthcare delivery for patients with tSCI has not yet been defined (5); despite current advances, the considerable heterogeneity within the tSCI patient population remains a prominent challenge (9). The variety of pathologies, levels of neurological impairment, and different potentials for recovery within tSCI patients (10, 11) makes it difficult to determine the efficacy of management strategies when novel therapies and standards of care are applied to a group with mixed needs and outcome trajectories. The identification of tSCI patient subgroups with clinically similar characteristics should facilitate better communication between patients and providers, guide optimal management, and inform the development of targeted therapies and models of care.

The categorization and management of tSCI have traditionally been guided by established classifications. Most tSCI studies rely on the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) to classify patients into groups, which is considered the gold standard for neurological assessment (12, 13). Based on the ISNCSCI, the American Spinal Injury Association Impairment Scale (AIS) is a measure of the neurological severity of injury, and is the most important predictor of recovery in tSCI patients (14). However, classification based on AIS grade alone does not adequately address the heterogeneity observed in the tSCI population; there is considerable variation in spontaneous recovery within each AIS grade (range: A–D), leading to differences in recovery trajectories between patients with presumedly similar initial clinical impairment (11). In other words, knowledge about individual prognostic variables for tSCI provides limited information about complex interactions between other variables and how they may influence prognosis. While the AIS grade itself might be the most important indicator for the prediction of recovery, other clinical factors such as age, injury characteristics, and functional measures have also been reported as significant prognostic variables (15).

As a first step towards understanding the heterogeneity inherent in tSCI, Dvorak and colleagues (9) proposed a classification scheme based on the joint use of baseline neurological level of injury (NLI) and severity of neurological impairment (i.e., AIS grade) – two of the predominant predictors of neurological outcome (13, 15). This approach was deemed the "Canadian Classification" and serves to guide tSCI researchers on how to better classify patients for clinical trials, and how to avoid unrecognized heterogeneity (or imbalances) between treatment groups. Dvorak's work made several important contributions, including a demonstration that classifying based on the joint distribution of the two baseline characteristics (level and severity of injury), beyond simple univariable classification, can reveal meaningful differences in the recovery potential of patients (9).

The digital age has produced a wealth of healthcare data, providing new opportunities to apply data analytics for improved decision-making by facilitating predictive modeling, treatment pattern identification, and detection of subtle correlations that may be overlooked in traditional methods (16, 17).

Through the lens of data analytics, we aim to build upon previous research by using unsupervised machine learning and specifically spectral clustering (SC), to examine the simultaneous interactions within multiple variables and identify previously unrecognized associations in a data-driven manner. In this approach, the analysis is based on the data itself rather than being influenced by preconceived notions or assumptions about the data (17, 18). Our study therefore represents a data-driven approach to understanding and categorizing tSCI that could potentially guide management of these complex injuries. Notably, such a methodology has previously been applied to research on adult spinal deformity (19).

We hypothesize that a data-driven approach can identify subgroups with clinical similarity within a heterogeneous population of tSCI patients and provide a clinically relevant categorization. To this end, the objectives of this study are to (1) apply an unsupervised machine learning approach, specifically cluster analysis, to identify subgroups of tSCI patients using patient demographics and injury characteristics at baseline, (2) to find clinical similarity within subgroups using etiological variables and outcome variables at discharge, and (3) to categorize patients with clinically similar characteristics by creating multi-dimensional labels.

## 2. Methods

This was a retrospective study using prospectively collected data from a large national, multicenter SCI registry. It included variables from different time points (e.g., admission, inpatient rehabilitation, and discharge), and was conducted in two phases.

During the first phase, SC was performed on a subset of variables at baseline to identify subgroups of tSCI patients. Clinical similarities were then identified between each subgroup by superimposing the outcome variables at discharge and etiological variables. The rationale behind exclusively forming subgroups based on baseline variables, and then superimposing outcome variables, is to assess the distinction among patient categories, with respect to selected outcomes. This choice protocol results in a subgrouping independent of outcome variables. As such, the identified subgroups can later be studied against a range of outcomes.

During the second phase, the results were interpreted from a point of view of statistical significance between each group. Thereafter, exemplars were used to describe (or "label") patient's subgroups qualitatively and systematically to reveal any patient-centred insights that can be drawn from the identified clinically similar subgroups.

### 2.1. Rick Hansen Spinal Cord Injury Registry

The analyzed data set consisted of patients enrolled in the Rick Hansen Spinal Cord Injury Registry (RHSCIR): a Canada-wide, prospectively collected multicenter database (20). RHSCIR collects data on individuals who have sustained an acute tSCI and received care at one of the participating 18 acute or 12 rehabilitation sites. All sites obtained Institutional Research Ethics Board (REB) approval to enroll patients and enter their data into the registry. A wide variety of data was collected from the pre-hospital, surgical, acute, and in-patient rehabilitation phases of the enrolled patients' care, including but not limited to: socio-demographic factors, medical history, injury details, diagnoses and interventions, neurologic impairment, complications, and patient-reported outcomes. Upon discharge, a survey was conducted at 1, 2, 5, and 10-year intervals (from the date of injury) to obtain patient-reported outcome measures. The registry was created to support research and facilitate the implementation and optimization of best clinical practices (20).

### 2.2. Study population

The data for this study was collected from RHSCIR, which enrolled 8,273 patients with acute tSCI between 2004 and 2017. Data were extracted from RHSCIR for all eligible patients with an acute tSCI between the year 2004 to 2017. Patients were included in this study according to the following inclusion criteria:

- The potential participant was at least 18 years old at the time of injury.
- They had complete data for the variables of interest collected at the acute (0–15 days) time stamp.
- They had complete data for the variables of interest collected at discharge.
- They provided explicit consent for specific data collection, including patient-reported outcomes, across all study time points.

Of the original data, 334 patients met the inclusion criteria for the study. The specific numbers of patients adhering to these criteria at each stage of the study are shown in the flowchart in Figure 1.

While the tSCI patient population is the focus of the present study, we note that all spine trauma patients with injuries from the C1 to L5 vertebrae were considered. The spinal cord terminates at the conus medullaris, most commonly at the L1 vertebral body or L1-2 disk interspace level in adults (21). Injuries to the lumbar vertebral bodies may involve the lumbosacral nerve roots and cause cauda equina syndrome (CES), which is not strictly a type of SCI. We chose to include patients with injuries to all levels of the spine and observe the patterns that emerge from the data. Thus, our population of interest includes all patients with impairment of the spinal cord or cauda equina function resulting from trauma.

### 2.3. Variable selection

Variables related to patient demographic, injury, outcome characteristics, and etiology of tSCI were selected based on supporting clinical literature (1, 3, 15, 22–28), expert opinion, and availability in RHSCIR database. The list of variables selected from the dataset are presented in Table 1. Note that the neurological assessments included in the dataset were conducted within a time frame of less than 15 days following the injury.

#### 2.3.1. Outcome variables selection

Both patients and the healthcare system stand to benefit from more specialized tSCI care (5, 29). While the optimal method of healthcare delivery for this patient population has yet to be fully elucidated, there is emerging evidence that specialized care for tSCI patients is associated with reduced LOS and decreased overall mortality (5). The clustering used in this study, driven by baseline patient- and injury-related characteristics, should itself be able to produce clinically similar subgroups with distinct healthcare needs. In this case, patient needs were evaluated using the total Functional Independence Measure (FIM) motor score at discharge (a prognostic factor for long-term outcomes and economic burden) (30), FIM motor score change (measured as the difference between discharge and admission FIM motor scores), and the total LOS (a surrogate measure for healthcare resource utilization).

#### 2.3.2. Etiological variables

In this study, "etiological variables" refers to factors contributing to the cause or origin of the traumatic spinal cord injuries. Our analysis incorporated these variables with the aim of capturing crucial aspects of the injury's cause and initial impact. These aspects can influence the severity of the injury and the patient's subsequent recovery.

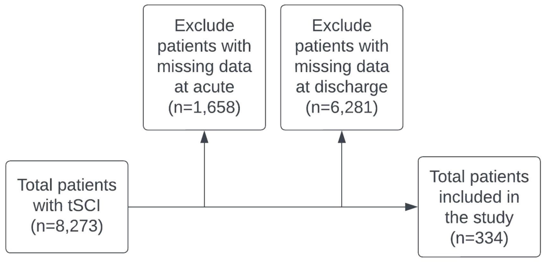


FIGURE 1
Study population flowchart. Noted that 4,164 patient cases labeled as 'missing data' resulted from the absence of explicit consent across all study time points.

Two etiological variables were included in our study: "Mechanism of Injury," and "Energy." "Mechanism of Injury" describes the initial mechanical force that caused the SCI, such as a fall, a motor vehicle accident, and other types of incidents. "Energy" refers to the intensity of the initial mechanical force that led to a patient's injury (15, 22).

## 2.4. Cluster analysis and interpretation methods

Cluster analysis (CA) is an unsupervised learning method used for revealing hidden structures in data. Cluster analysis group objects with similar traits into subgroups while minimizing intragroup heterogeneity (16, 18, 31). To find the subgroups of tSCI patients based on baseline variables in the present study (Table 1), multiple clustering algorithms were assessed, and SC was chosen to explore patterns in our data. SC varies from the most commonly used partitioning-based clustering algorithm, K-means clustering (32, 33) as it is not dependent on distance from a centroid and it also does not require clusters to be spherical. Rather, the distance metric used for SC ensures that cluster members are near to one another. As a result, patients in the same subgroups tend to have similar values based on selected characteristics. Unlike K-means, which identifies subgroups with linear borders, SC is capable of forming subgroups with nonlinear boundaries (34).

To identify the optimal number of subgroups, the performance of SC using different numbers of subgroups was evaluated using the Silhouette Coefficient, the Davies-Bouldin index, and the elbow method (35–37).

## 2.5. Interpretation methods

Statistically significant differences and exemplars were used to interpret key findings of the analysis.

### 2.5.1. Statistically significant difference

After subgroups were created using SC, continuous variables were analyzed using a Kruskal-Wallis test (not meeting the normality assumption) (38) to identify whether there were statistically significant intergroup differences across all subgroups (considered as $p \leq 0.05$). Although the *p*-value is not traditionally a focal point in cluster analysis, its application here provided deeper insights by enabling us to identify distinguishing factors among subgroups. Variables found to statistically differ were then explored in a pairwise manner between subgroups using Mann–Whitney U tests (39), further enhancing our understanding of the patient subgroups. Continuous variables were presented with means and standard deviations, whereas categorical variables were presented with frequency of occurrence and percentages.

### 2.5.2. Exemplars

The concept of exemplars is used in this study to provide a tangible illustration of the characteristics of each identified cluster. Exemplar terms are used to represent each subgroup, and are also defined as the medoid of each cluster. Medoids are known as "actual objects" in the data (i.e., a typical patient); the object within a cluster that has the minimum sum of distances to all other objects in the cluster. Therefore, typical patient cases from each subgroup have been provided as a method of interpretation of SC analysis. Using this method, significant findings from statistically significant tests can be demonstrated for each subgroup.

### 2.5.3. Subgroup labelling

Once patient subgroups were identified using SC analysis, they were then qualitatively described (i.e., "labelled") to elucidate patient-centred insights that could be learned from the data-driven groupings of patients. Three types of multi-dimensional labels were created to demonstrate the clinical similarity of the following characteristics: (1) patient at presentation, (2) spine injury, and (3) patient at discharge. These multi-dimensional labels served to highlight the distinguishing factors that emerged in each patient subgroup with similar characteristics and to explore whether the "label" (i.e., the pattern of values of distinguishing variables in each subgroup) provided clinically intuitive and plausible characterization in the context of tSCI. Labelling was approached systematically; for each subgroup, only those variables that were determined to have values statistically different from other subgroups were considered as "distinguishing" and thus were used as labels. In addition, we discussed the relevance of the identified subgroups based on the etiological variables and compared them with the literature.

# 3. Results

The 334 patients that met the inclusion criteria for the study and were divided into 5 subgroups using SC. These subgroups were verified as clinically relevant through consultation with field experts and literature review. Table 2 shows the variables at baseline that were found to have statistically significant differences ($p < 0.05$) between the subgroups. Tables 3, 4 present the outcome variables and additional variables related to the mechanism of injury superimposed on each subgroup.

## 3.1. Subgroup labels and exemplars

Multi-dimensional labels were created to describe patient demographic and injury characteristics with distinguishing variables

TABLE 1 The list of baseline, outcome, and etiological variables selected in our study.

| Variable name | Description | Variable type | Values |
|---|---|---|---|
| **a. Baseline variables** | | | |
| Age | At the time of injury | Numerical | Age (years) |
| Body Mass Index (BMI) | BMI is measured in kg/m$^2$. Dichotomized to obese (BMI ≥ 30) or not obese (BMI < 30). | Categorical | Obese, not_obese |
| Baseline AIS class | The severity of neurological impairment collected at admission. Range: a (severe, motor and sensory complete injury) to D (motor and sensory incomplete injury). AIS E is normal. | Categorical | AIS acute A, AIS acute B, AIS acute C, AIS acute D |
| Primary Location of Injury (PLI) | The vertebral level in the spinal column where the trauma occurred. Range: C1-L5 | Categorical | C1,C2,C3,C4,C5,C6,C7, T1,T2,T3,T4,T5,T6,T7, T8,T9,T10,T11,T12,L1, L2,L3,L4,L5 |
| Baseline FIM motor score | An examination of global motor function collected at admission to rehabilitation. | Numerical | FIMMotorScore_adm [13–91] |
| **b. Outcome variables** | | | |
| FIM motor score at discharge | An examination of global motor function collected at discharge from rehabilitation. | Numerical | FIMMotorScore_disch [13–91] |
| FIM motor score change | The difference between discharge and admission FIM motor scores | Numerical | Fim Motor Difference |
| Length of stay | The total length of stay in days, from the time of admission at the hospital to community discharge | Numerical | LOSTotal (days) |
| **c. Etiological variables** | | | |
| Energy | The energy of the mechanism of the injury | Categorical | Energy_High, Energy Low |
| Mechanism of injury | The initial mechanical force delivery to the spinal cord and cause the injury | Categorical | Injury_Transport, Injury_Assault – blunt, Injury_Assault – penetrating, Injury_Fall, Injury_Other traumatic cause, Injury_Sports |

at baseline and discharge. Where applicable, specifiers were used to describe variables on a spectrum of severity (i.e., “mild,” “moderate,” “severe” or “extreme”) relative to other subgroups (Table 5). Additionally, a phenotype anatomical figure was constructed to visually highlight the anatomical order of the subgroups, providing a perspective on patient demographics and injury traits (Figure 2). Lastly, exemplars (typical patient case representative of each subgroup) were described.

### 3.1.1. Exemplar for subgroup 1

60-year-old non-obese individual presenting with a motor incomplete injury (AIS D) to the C3-C4 vertebrae, an NLI at C4, and a FIM motor score of 35 at admission. Patient 1’s total length of stay was 102 days before being discharged with a FIM motor score of 87.

### 3.1.2. Exemplar for subgroup 2

37-year-old non-obese individual presenting with a motor and sensory complete injury to the C6-C7 vertebrae, an NLI of C5, and a FIM motor score of 24 at admission. Patient 2’s total length of stay was 212 days before being discharged with a FIM motor score of 75.

### 3.1.3. Exemplar for subgroup 3

36-year-old non-obese individual presenting with a motor and sensory complete injury to the T4-T5 vertebrae, an NLI at T2, and a FIM motor score of 30 at admission. Patient 3’s total length of stay was 112 days before being discharged with a FIM motor score of 73.

### 3.1.4. Exemplar for subgroup 4

47-year-old obese individual presenting with a motor and sensory complete injury to the T11-T12 vertebrae, and NLI at L2, and a FIM motor score of 49 at admission. Patient 4’s total length of stay was 101 days before being discharged with a FIM motor score of 84.

### 3.1.5. Exemplar for subgroup 5

26-year-old non-obese individual presenting with a motor incomplete (AIS D) to the L1 vertebra, an NLI at L2, and a FIM motor score of 50 at admission. Patient 5’s total length of stay was 105 days before being discharged with a FIM motor score of 88.

## 4. Discussion

In the present study, an unsupervised machine learning approach of cluster analysis utilizing SC was deployed to categorize tSCI patients into clinically similar subgroups based on patient demographics and injury characteristics at baseline. Clustering based on baseline data enabled an exploration for latent relationships between patient demographic and injury characteristics without depending on selected outcomes that might not be comprehensive measures of the condition’ behaviour.

TABLE 2 Baseline variables.

| Variable | *P*-value (among all subgroups) | Subgroup 1 | Subgroup 2 | Subgroup 3 | Subgroup 4 | Subgroup 5 |
|---|---|---|---|---|---|---|
| | | | *N* (%) | | | |
| PLI | | | | | | |
| C1 | <0.001 | 2 (1.77) | 1 (1.39) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| C2 | <0.001 | 9 (7.96)*b | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| C3 | <0.001 | 48 (42.48)*a | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| C4 | <0.001 | 66 (58.41)*a | 1 (1.39) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| C5 | <0.001 | 68 (60.18)*a | 22 (30.56)*a | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| C6 | <0.001 | 52 (46.02)*b | 39 (54.17)*b | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| C7 | <0.001 | 29 (25.66)*a | 30 (41.67)*a | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| T1 | <0.001 | 1 (0.88) | 3 (4.17) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| T2 | <0.001 | 1 (0.88) | 0 (0.0) | 4 (10.0)*a | 0 (0.0) | 0 (0.0) |
| T3 | <0.001 | 0 (0.0) | 0 (0.0) | 10 (25.0)*a | 0 (0.0) | 0 (0.0) |
| T4 | <0.001 | 0 (0.0) | 0 (0.0) | 19 (47.5)*a | 0 (0.0) | 0 (0.0) |
| T5 | <0.001 | 0 (0.0) | 0 (0.0) | 17 (42.5)*a | 0 (0.0) | 0 (0.0) |
| T6 | <0.001 | 0 (0.0) | 0 (0.0) | 15 (37.5)*a | 0 (0.0) | 0 (0.0) |
| T7 | <0.001 | 0 (0.0) | 4 (5.56)*b | 8 (20.0)*a | 0 (0.0) | 0 (0.0) |
| T8 | <0.001 | 0 (0.0) | 9 (12.5)*a | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| T9 | <0.001 | 0 (0.0) | 11 (15.28)*b | 0 (0.0)*c | 4 (16.0)*b | 0 (0.0) |
| T10 | <0.001 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 10 (40.0)*a | 0 (0.0) |
| T11 | <0.001 | 0 (0.0) | 0 (0.0) | 1 (2.5)*c | 21 (84.0)*a | 0 (0.0) |
| T12 | <0.001 | 0 (0.0) | 0 (0.0) | 1 (2.5)*b | 12 (48.0)*b | 28 (33.33)*b |
| L1 | <0.001 | 0 (0.0) | 0 (0.0) | 1 (2.5)*c | 0 (0.0) | 48 (57.14)*a |
| L2 | <0.001 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 12 (14.29)*a |
| L3 | <0.001 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 11 (13.1)*a |
| L4 | <0.001 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (4.76)*c |
| L5 | <0.001 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (4.76)*c |
| AIS acute D | 3.04E-16 | 65 (57.52)*a | 2 (2.78)*c | 2 (5.0)*c | 2 (8.0)*c | 28 (33.33)*a |
| AIS acute C | 0.00021 | 35 (30.97)*b | 5 (6.94)*c | 2 (5.0)*c | 4 (16.0) | 16 (19.05)*b |
| AIS acute B | 1.02E-05 | 4 (3.54)*b | 22 (30.56)*b | 4 (10.0) | 4 (16.0) | 14 (16.67)*c |
| AIS acute A | 8.14E-18 | 9 (7.96)*a | 43 (59.72)*b | 32 (80.0)*a | 15 (60.0)*b | 26 (30.95)*a |
| Obese patients | 0.002 | 49 (43.36)*c | 29 (40.28)*c | 29 (72.5)*b | 18 (72.0)*b | 39 (46.43)*c |
| Mean (standard deviation) | | | | | | |
| Age | 1.02E-11 | 54.15 (16.27)*a | 40.22 (15.94) | 38.12 (15.31) | 43.0 (16.14)*c | 36.7 (16.13)*c |
| FIMMotorScore_adm | 4.47E-19 | 29.07 (20.49)*b | 21.6 (9.46)*b | 31.55 (12.53)*a | 35.0 (12.05)*a | 44.71 (15.24)*a |
| Number of patients | NA | 113 | 72 | 40 | 25 | 84 |

*a: significantly different from all 4 other subgroups; *b: significantly different from 3 other subgroups; *c: significantly different from 2 other subgroups. All variables are significantly different across subgroups at $p < 0.00$ significance level using Kruskal-Wallis.

The five patient subgroups with clinical similarities were defined with a data-driven approach that did not rely on *a priori* assumptions or outcome variables, and subgroups were distinguished based on age, BMI, baseline injury severity (AIS grade), PLI, and baseline FIM motor score. The three outcome variables used in the study (FIM motor score at discharge, FIM motor score change, and total LOS) were superimposed on these subgroups to evaluate the distinction of patient subgroups and to explore their clinical relevance. FIM motor

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TABLE 3 Outcome variables superimposed on identified subgroups.

| Variable | *p*-value (among all subgroups) | Subgroup 1 | Subgroup 2 | Subgroup 3 | Subgroup 4 | Subgroup 5 |
|---|---|---|---|---|---|---|
| Mean (standard deviation) | | | | | | |
| LOSTotal | 9.99E-13 | 117.94 (58.4)*c | 182.01 (85.31)*a | 132.2 (61.57)*b | 99.44 (43.69)*c | 92.77 (43.75)*b |
| FIMMotorScore_disch | 4.70E-12 | 63.45 (25.67)*c | 50.29 (24.12)*a | 64.3 (17.27)*b | 74.12 (15.13)*b | 79.21 (7.58)*a |
| Fim motor difference | 0.09 | 34.38 (21.01) | 28.69 (20.29) | 32.75 (16.45) | 39.12 (14.18) | 34.5 (14.98) |

*a: significantly different from all 4 other subgroups; *b: significantly different from 3 other subgroups; *c: significantly different from 2 other subgroups. All variables are significantly different across subgroups at $p < 0.00$ significance level using Kruskal-Wallis.

TABLE 4 Etiological variables superimposed on identified subgroups.

| Etiological variables | Subgroup 1 | Subgroup 2 | Subgroup 3 | Subgroup 4 | Subgroup 5 |
|---|---|---|---|---|---|
| Energy_High (%) | 21 (18.58) | 38 (52.78) | 34 (85.0) | 12 (48.0) | 49 (58.33) |
| Energy_Low (%) | 86 (76.11) | 34 (47.22) | 5 (12.5) | 13 (52.0) | 30 (35.71) |
| Number of Injury_Transport (%) | 22 (19.47) | 26 (36.11) | 17 (42.5) | 9 (36.0) | 31 (36.9) |
| Number of Injury_Assault – blunt (%) | 3 (2.65) | 1 (1.39) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Number of Injury_Assault – penetrating (%) | 2 (1.77) | 2 (2.78) | 2 (5.0) | 0 (0.0) | 3 (3.57) |
| Number of Injury_Fall (%) | 64 (56.64) | 24 (33.33) | 11 (27.5) | 12 (48.0) | 30 (35.71) |
| Number of Injury_Other traumatic cause (%) | 7 (6.19) | 6 (8.33) | 3 (7.5) | 2 (8.0) | 8 (9.52) |
| Number of Injury_Sports (%) | 15 (13.27) | 13 (18.06) | 7 (17.5) | 2 (8.0) | 12 (14.29) |

score at discharge and total LOS resulted in statistically significant differences across all patient subgroups (Table 3).

The choice of input variables in cluster analysis is a crucial factor that can influence the quality of the analysis and, by extension, the robustness of the conclusions drawn from the study. As part of our research, we carefully selected baseline variables based on their relevance, clinical significance, and prior evidence of impact on patient outcomes (Table 1). This choice ensured that our cluster analysis was grounded in a strong theoretical and empirical basis. Several studies have demonstrated the importance of these variables in patient outcomes. For instance, age plays a significant role in recovery and functional outcomes following tSCI (1, 3). Similarly, the AIS classification at baseline has shown to be a strong predictor of neurological recovery and rehabilitation outcomes (25). The baseline FIM motor score has been identified as a valuable predictor for functional outcomes and discharge planning in tSCI patients (27). While both AIS scores and the total FIM motor score provide insights into a patient's neurological and functional statuses, their combined use in our research presents a holistic, patient-centered approach. The AIS details specific neurological information, while the total FIM motor score measures patient-reported motor functionality. Together, they furnish a comprehensive understanding of the patient's condition and experience. Lastly, the primary location of injury (PLI) has been linked to variations in functional outcomes and recovery potential (26).

Though obesity is not a prognostic variable commonly considered in the tSCI patient population (15), it was included in the present study based on several sources of supporting evidence. A study of note by Stenson and colleagues examined the relationship between obesity and inpatient rehabilitation outcomes for patients with tSCI; it found that obese patients had longer hospital stays and less improvement in motor function when compared to non-obese patients (40). Furthermore, this same study concludes that obese patients were less likely to be discharged home and more likely to be discharged to another healthcare facility (40). Additionally, other studies found that obesity not only affects a patient's recovery process, but also affects the required healthcare resources and rehabilitation needs of these patients (41, 42). By incorporating obesity as a baseline variable in our study, we were able to distinguish between patient groups when evaluating their hospital or rehabilitation facility LOS. Our result is consistent with previous studies reporting a relationship between obesity and prolonged LOS in patients with tSCI (40, 41).

Our sample included tSCI patients with trauma to any vertebral level from C1 to L5 and resultant impairment to the spinal cord or cauda equina (43). In the interest of finding naturally-emerging patterns in the patient sample, we did not prespecify groups based on the anatomical location of their injury. Based on our results, the PLI was among the primary factors that distinguished patient subgroups. Furthermore, when observed from an inter-group perspective, this classification characterized patients into a purely cervical spine trauma (subgroup 1), a mixed lower cervical or/and thoracic spine trauma (subgroup 2), a purely thoracic spine trauma (subgroup 3), a lower thoracic spine trauma (subgroup 4), and a lumbar spine trauma (subgroup 5).

The choice inclusion of SC in our method identified subgroups of patients with a pattern of PLI that was clinically informative; these subgroups separated traumatic injury to the spinal cord (subgroups 1, 2, 3, and 4) from trauma below the spinal cord (subgroup 5), which is more likely to produce cauda equina injury. Our findings extend on previous work examining the factors associated with traumatic cauda

TABLE 5 Multi-dimensional labels with distinguishing variables for identified subgroups.

| Subgroup/ label | Patient at presentation | Spine injury | Patient at discharge |
|---|---|---|---|
| Subgroup 1 | Older non-obese patient with moderate functional impairment | Motor incomplete cervical injury from low energy fall | Moderate: third highest mean LOS, second lowest mean FIM motor score at discharge |
| Subgroup 2 | Non-obese patient with severe functional impairment | Motor complete cervical or/and thoracic injury from diverse mechanisms | Poor: highest mean LOS, lowest mean FIM motor score at discharge |
| Subgroup 3 | Obese patient with moderate functional impairment | Complete (severe) thoracic injury from high energy motor vehicle accident | Moderate: second highest mean LOS, third highest mean FIM motor score at discharge |
| Subgroup 4 | Obese, older patient with mild functional impairment | Complete (severe) lower thoracic injury from diverse mechanisms | Moderate: second lowest mean LOS, second highest mean FIM motor score at discharge |
| Subgroup 5 | Young patient with mild functional impairment | Bimodal (severe and non-severe) lumbar injury from diverse mechanisms | Favourable: lowest mean LOS, highest mean FIM motor score at discharge |

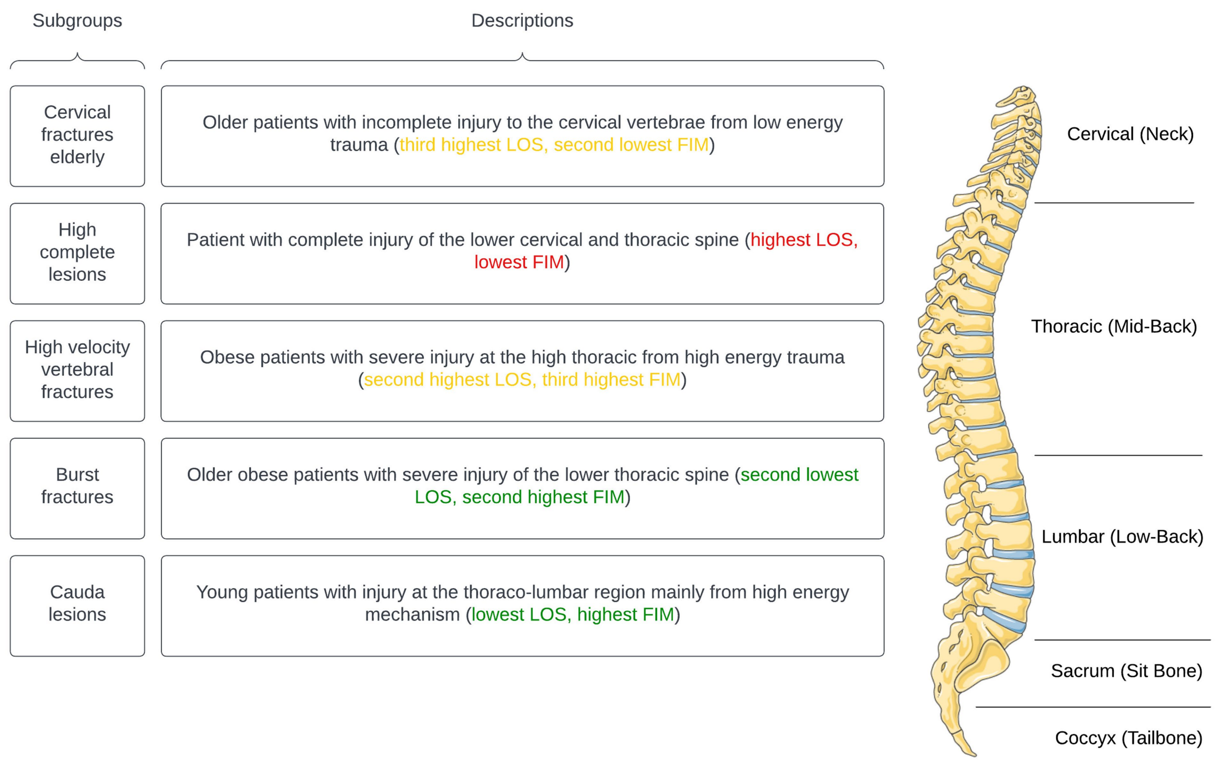


FIGURE 2
Subgroups with clinically significant phenotypes (parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License).

equina injury (tCEI), an understudied condition (44). SC identified a patient subgroup with comparable characteristics to those reported by Attabib and colleagues (44), including a similar mean age and a bimodal distribution in initial injury severity (i.e., peaks at AIS A and D). Notably, patients in subgroup 5 demonstrated the most favourable outcome across all patient subgroups, supporting the notion that these patients have a considerable chance of functional recovery after injury (44). However, it is important to note that Attabib and colleagues used the NLI as determined by the ISNCSCI to classify patients as having tCEI, whereas we opted to use PLI as the only anatomical data in this study.

Potential subjectivity in evaluating NLI may impact the accuracy of tSCI patient classification methods such as the groundwork laid by Dvorak and colleagues (45, 46). Our data-driven approach alleviates this reliance on NLI assessment and improves the Canadian Classification method in two primary ways.

First, reliability of assessment of NLI might impact the consistency of data collected for classifying tSCI patients. The Canadian classification's singular reliance upon the neurological examination to collect baseline characteristics – NLI and injury severity based on AIS grade – have some practical drawbacks. For instance, conducting baseline examinations in an acute setting is challenging, and results can be confounded by patient-specific factors such as intoxication, sedation, or concurrent brain injuries (46–48). This represents real-world clinical challenges that contribute to the complexity of tSCI patients. To address these issues, our analysis incorporated cluster analysis using context-relevant data to explore inherent patterns within our study population and identify clinically relevant patient subgroups. Furthermore, the PLI was found to be a significant factor; a surrogate for the skeletal level of injury referring to the vertebral column level on the radiograph where trauma has taken place. This demonstrates PLI's potential as an alternative anatomical classification of SCI that is more accurate and reliable than the ISNCSCI neurological assessment, which is susceptible to poor reliability (49).

Second, the Canadian Classification system uses *a priori* to classify patients (9). This may affect the generalizability in different clinical settings, where data inaccuracies triggered by patient-specific factors can introduce bias. This may in turn influence the applicability of the data, particularly when translating novel therapeutics from animal models to clinical practice (1). In contrast, our study sought to explore the clinical insights obtainable when context-relevant data alone drives the analysis without depending on outcome variables. We discovered patterns linking variables to outcomes that naturally incorporated data applicability. By applying SC to a set of baseline variables, we were able to uncover key interactions among demographic, anthropometric, and clinical variables such as age, body mass index, and injury mechanism/etiology.

Total LOS had high standard deviations in all subgroups comparing to other variables. This high variation within each cluster supports the finding of Craven and colleagues (24), who developed a prediction model for patients' rehabilitation LOS in Canada. Their findings report that the prediction of rehabilitation LOS is beyond impairment characteristics (e.g., administration, resource allocation etc.). As our subgroups were created based on demographics and injury characteristics, the high variability in LOS is therefore understandable.

Although the rate of change among the subgroups from inpatient rehabilitation to discharge in FIM motor score ("FIM Motor Difference") was not significantly different, each one showed improved scores. Subgroups 1, 3, 4, and 5 had similar mean FIM motor score changes, while subgroup 2, which had the longest LOS and the smallest FIM motor score at discharge, had the lowest mean FIM Motor Difference. This trend generates several hypotheses: first, considering the variation in different locations of injury in subgroup 2 and the lowest FIM Motor Difference, it is possible that patients in this subgroup may have suffered from multiple traumas as the majority of cases included in this group report high energy injuries. Second, while the FIM Motor Difference was not statistically different among subgroups, the similar mean value across subgroups 1, 3, 4, and 5, demonstrates their similar potential of motor gain for independence. In comparison, the complete injury in subgroup 2, which had a lower mean FIM Motor Difference, seemed to lead to limited independence gain, and therefore results in a longer hospital stay. Further investigation is required to validate these data-driven insights of FIM motor score change.

When additional injury-related variables (i.e., mechanism and energy of injury) were superimposed on the patient subgroups, they exhibited patterns of traumatic injury that were distinct and clinically intuitive (Table 4). For example, subgroup 1 – which counts comparatively more elderly patients – had the highest proportion of injuries attributed to low-energy mechanisms (76.11%), and of injuries specifically caused by falls (56.64%). In contrast, subgroups 2 to 5 had a higher proportion of high-energy mechanisms attributed to transportation, and patients in these subgroups were comparatively younger. This corresponds with the literature on the etiology of tSCI, which reports high-energy impacts (e.g., traffic accidents and sport-related injuries) as more common in younger individuals, and low-energy impacts (e.g., falls) as a more frequent occurence in older adults, who commonly have degenerative changes leading to central cord syndrome or osteoporotic fractures of the cervical spine (50, 51).

To further understand the characteristics and clinical significance of the identified subgroups, we analyzed the data from Tables 4, 5 and compared them to relevant clinical literature. Subgroup 2 predominantly consists of patients with complete spinal cord injuries (tetra/paraplegia) resulting from motor vehicle accidents (52–54). Subgroup 5 includes patients with cauda equina injury or sacral dysraphism following a spinal cord injury (44, 53, 55). Subgroup 4 comprises injuries in the thoraco-lumbar region, often burst fractures (53, 56, 57). Subgroup 3 counts more chance fractures or seat belt fractures resulting in a spinal cord injury (40, 53, 55). Finally, subgroup 1 represents low energy falls in the elderly that result in a spinal cord injury (22, 55, 58, 59).

In our study, a distinctive pattern emerged within subgroup 1, revealing an overlap of injuries across both the upper and lower cervical regions. This observation is particularly prevalent among the elderly participants whose predominant mechanism of injury was falls. This pattern accentuates the vulnerabilities of the elderly demographic to spinal injuries, consistent with established clinical findings (60). While the clinical literature broadly categorizes cervical injuries into distinct upper and lower zones, our data-driven examination highlights the nuances of injury patterns, suggesting that such traditional delineations may manifest differently within specific patient demographics.

Our findings also provide insight into the prognosis of these different patient profiles (Table 5). Older age has a negative impact on neurological and functional recovery (61). However, our analysis shows that older patients with tSCI caused by the prototypical geriatric fall (subgroup 1) have a relatively moderate prognosis when compared to younger patients in other subgroups. This suggests that age should be considered in the context of other factors, such as the energy and location of injury, and ensuing neurological deficit (15) when predicting motor impairment and LOS.

In order to assist clinicians providing care for tSCI patients and allow personalized approaches to treatment, classifications to evaluate patients need to take the heterogeneity of SCIs into consideration (9). Our analysis identified five subgroups of patients that could be described in a simple yet intuitive manner, producing patient and injury-related labels at presentation and discharge (Table 5). Furthermore, our analysis allowed an exemplar case to be drawn from each patient subgroup. We were able to illustrate that baseline clinical factors commonly available in the acute setting (age, BMI, injury-related information) can contribute to a better understanding of individual patient needs, potentially enabling more tailored care. A national survey of Canadian SCI centers revealed that insufficient SCI-specific knowledge, poor recognition of the condition in the acute setting, and communication between clinicians were all major challenges to providing specialized SCI care (29). The identification of clinically similar subgroups of tSCI patients and presenting their clinical characteristics is a step towards addressing these challenges by equipping clinicians with a way to better recognize and communicate this condition. By applying advanced machine learning algorithms to sift through greater combinations of clinical variables without *a priori* assumptions, it becomes possible to reveal previously unrecognized patterns within the analyzed data or consolidate known associations within the variables. These results could provide clinically relevant insights for clinicians managing patients with tSCI, especially as large multicenter SCI registries accumulate more data.

In the realm of healthcare, the vast potential of AI is undeniable. Similarly, the need for rigorous oversight in AI-driven research is evident (62, 63). Recognizing both the promise and the challenges, in our study, we prioritized clinical relevancy by basing our data selection on clinically accepted practices. We applied unsupervised learning to the data to unveil inherent patterns without making prior assumptions, which resulted in classifications tied to the specific attributes of the cohort. The clinical relevancy of the identified subgroups was examined through a rigorous process involving an extensive review of clinical literature and consultations with medical experts. Thus, our methodology offers a refined perspective on data-driven patient categorization, underscoring the significance of clinical relevancy in the application of AI in healthcare. This insight could promote a more tailored, patient-centric approach to care and treatment strategies.

## 5. Limitations

Our research utilized data drawn from a Canada-wide, prospectively collected registry with a limited number of patients, which may restrict generalizability. Although the variables used in the cluster analysis may differ if replicated elsewhere, the derived patient labels presented are clinically intuitive and might be generalizable across care systems.

While cluster analysis can be a useful tool in new research, it has some limitations that should be considered. Different clustering methods may identify different subgroups, which may be sensitive to dropped cases. In addition, there are limited ways to validate these obtained subgroups. In the case of this study, we used cluster analysis to demonstrate the potential of a data-driven approach to autonomously separate patient populations that are clinically distinct. However, it should be noted that the clustering method does not currently offer a straightforward way to assign a patient into a specific group as it does not use cut-off values, but rather groups patients based on their averaged similarities across the input variables.

In our pursuit to demonstrate the utility of a data-driven methodology as a supplementary approach for patient categorization, we must acknowledge the study's findings are bound by the dataset's scope and completeness of the respective data in our study cohort. This accentuates the need for comprehensive data to facilitate nuanced analyses in subsequent research.

## 6. Future work

Future research on tSCI can focus on improving and expanding the use of cluster analysis in databases, as well as building on its results to develop prediction models for patterns of patient recovery. Future studies could also involve focusing on specific domains of interest, such as patient outcomes, motor and sensory functioning, and could consider additional patient characteristics such as interventions and socio-demographics in the acute clinical evaluation. In addition, incorporating advanced neuroimaging and molecular biomarkers, which are more sensitive to disease processes (64), may provide insight into how these data could contribute to predicting and customizing the individual trajectories of recovery and unique needs of each patient.

## 7. Conclusion

We deployed spectral clustering method and identified five subgroups of traumatic spinal cord injury patients with clinical intra-group similarities and statistically significant inter-group differences for baseline demographic and injury characteristics collected at admission and outcome variables at discharge. This data-driven approach resulted in clinically relevant and plausible insights without depending on *a priori* decisions, a step toward better understanding of the heterogeneity inherent in tSCI. We demonstrated that cluster analysis can be used to further define the patterns or groups of other patient characteristics that exist in the tSCI population, thus contributing to categorizing the tSCI population into subgroups with distinct needs. This data-driven patient categorization holds the potential to support the delivery of more specialized, patient-centered care.

## Data availability statement

The data analyzed in this study was obtained from the Rick Hansen Spinal Cord Injury Registry (RHSCIR), managed by the Praxis Spinal Cord Institute (https://praxisinstitute.org/research-care/key-initiatives/national-sci-registry/), the following licenses/restrictions apply: access to these datasets is subject to adherence to RHSCIR Data Use and Disclosure Policy. Requests to access these datasets should be directed to the Praxis Spinal Cord Institute, dataservices@praxisinstitute.org.

## Ethics statement

The studies involving humans were approved by ethics approval was obtained from each contributing site's Research Ethics Boards (see the acknowledgement section of the manuscript for site details). The studies were conducted in accordance with the local legislation and institutional requirements. Participants either provided written informed consent for participation in this study or had a minimal chart review dataset collected under a consent waiver.

## Author contributions

SB: Investigation, Software, Visualization, Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing, Formal analysis. RH: Validation, Methodology, Resources, Writing – review & editing. NB: Resources, Supervision, Writing – review & editing, Funding acquisition. WM: Resources, Validation, Supervision, Writing – review & editing, Conceptualization, Funding acquisition, Methodology. HV: Validation, Resources, Supervision, Writing – review & editing. EW: Validation, Resources, Writing – review & editing. AS: Validation, Resources, Writing – review & editing. SK: Validation, Resources, Writing – review & editing. J-MM-T: Validation, Resources, Writing – review & editing. ET: Validation, Resources, Writing – review & editing. ZW: Validation, Writing – review & editing. PP: Methodology, Project administration, Validation, Conceptualization, Investigation, Funding acquisition, Supervision, Writing – review & editing.

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## Conflict of interest

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## Publisher's note



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# Nationwide emergency department visits for pediatric traumatic spinal cord injury in the United States, 2016–2020

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**Introduction:** Traumatic spinal cord injury (tSCI) is a debilitating neurological condition resulting in lifelong disability for many individuals. The primary objectives of our study were to describe national trends in incident emergency department (ED) visits for tSCI among children (less than 21 years) in the United States, and to determine the proportion of visits that resulted in immediate hospitalization each year, including stratified by age and sex. Secondary objectives were to examine associations between select characteristics and hospitalization following tSCI, as well as to assess sports-related tSCIs over time, including by individual sport and geographic region.

**Methods:** We used the Healthcare Cost and Utilization Project Nationwide Emergency Department Sample to identify ED visits among children between January 2016 and December 2020 for incident tSCI. Diagnosis codes were used to identify tSCI and sports-related injury etiologies. Census Bureau data were used to approximate annual rates of pediatric ED visits for tSCI per 100,000 children. Unconditional logistic regression modeling assessed whether select factors were associated with hospital admission.

**Results:** We found that the annual ED visit rate for tSCI remained relatively stable between 2016 and 2020, with approximately 2,200 new all-cause pediatric ED visits for tSCI annually. Roughly 70% of ED visits for tSCI resulted in hospitalization; most ED visits for tSCI were by older children (15–20 years) and males, who were also more often admitted to the hospital. Notable secondary findings included: (a) compared with older children (15–20 years), younger children (10–14 years) were less likely to be hospitalized immediately following an ED visit for tSCI; (b) patient sex and race were not associated with hospital admission; and (c) American tackle football was the leading cause of sports-related ED visits for tSCI among children. Our findings also suggest that the proportion of sports-related tSCI ED visits may have increased in recent years.

**Discussion:** Future research should further examine trends in the underlying etiologies of pediatric tSCI, while assessing the effectiveness of new and existing interventions aimed at tSCI prevention.

KEYWORDS

spinal cord injury, epidemiology, pediatric, emergency department, sports

## Introduction

Traumatic spinal cord injury (tSCI) is a debilitating neurological condition that results in lifelong disability and impairment for many individuals and imposes substantial economic stress on healthcare systems worldwide (1, 2). Individuals with tSCI often have complex healthcare needs, which may be associated with multimorbidity and lower quality of life (3, 4).

Although the incidence of pediatric tSCI in the United States has declined in recent years, there remain limited published data on pediatric emergency department (ED) visits for tSCI and the underlying etiology of these injuries (5–7). One national study from the United States found an average of 1,308 annual ED visits with a principal diagnosis of tSCI for individuals less than 18 years of age between 2007 and 2010 (7). Over 60% of ED visits led to hospitalization; however, 20.1% of children were discharged home (7). A more recent national study from the United States observed that there were over 1,200 tSCI hospitalizations for individuals less than 21 years of age in 2016 (8).

Furthermore, despite the considerable contribution that sports play in the etiology in tSCI, few recent studies have explored the epidemiology of sports-related tSCI in children (less than 21 years of age) (9–11). One study found that while motor vehicle crashes were the most common documented external cause of injury code, sports-related pediatric tSCI were more common among older children (9). Given the impact of sports on tSCI, it may also be important to understand the relationship between tSCI incidence and the reported reduction in physical activity globally during the COVID-19 pandemic (12, 13). Addressing these knowledge gaps is key in injury prevention, as sport-related SCIs are a potential target area for public health education and interventions to improve knowledge and awareness of sports safety.

Therefore, the primary objectives of our study were to describe national trends in incident ED visits for tSCI among children (less than 21 years) between 2016 and 2020 in the United States and to determine the proportion of ED visits that resulted in immediate hospitalization each year, including stratified by age and sex. Our secondary objectives were to examine associations between select characteristics (such as age, sex, and race) and hospitalization following tSCI, as well as to assess sports-related tSCIs over time, including by individual sport and geographic region.

## Materials and methods

### Ethics and reporting

This study was exempt from ethics board review by the Office of Research Ethics at the University of British Columbia. Informed consent was not required from study participants since the data provider deidentified all health records. Furthermore, this research was conducted according to the terms outlined in the United States Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) Data Use Agreement. This included suppressing small cell counts less than or equal to 10. Our study complies with the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) statement (Supplementary Table 1) (14).

### Data source and study design

Multiple years (2016–2020) of the HCUP Nationwide Emergency Department Sample (NEDS) were used. The NEDS is the largest annual ED database with data for all payers in the United States; it is a stratified probability sample of community, non-rehabilitation, hospital-owned EDs. Approximately 20% of the universe of EDs were sampled within each stratum, with sample weights being computed by HCUP for individual ED discharges and hospitals, respectively (15). Due to its rigorous sampling and weighting strategy, the NEDS is a valuable database that may be used to compute nationally representative estimates of ED visits in the United States. In 2020, the NEDS contains data for more than 28 million distinct ED visits, which, when weighted, are representative of more than 120 million unique ED encounters. Detailed clinical and nonclinical data is recorded in the NEDS for each ED visit and corresponding admission, including but not limited to: International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS; beginning 1 October 2015) diagnosis, procedure, and external cause of morbidity codes; patient demographic details (such as age, sex, race, and quartile of median household income); hospital characteristics (such as region, teaching status, trauma center designation, and ownership); and information about healthcare charges (ED charges and, where applicable, inpatient charges) and the payer (such as Medicare, private insurance, or no charge).

### Emergency department visits

Eligible ED visits examined in our study included those where a primary or secondary ICD-10-CM diagnosis of initial traumatic spinal cord injury (tSCI) was recorded among children (less than 21 years).

Study visits were identified using HCUP's clinical classifications software refined (CCSR, v2022.1) category for "SCI, initial encounter" (INJ009) (16). The CCSR aggregates individual ICD-10-CM codes into more than 530 clinically meaningful categories across 22 body systems. Clinical experts and epidemiologists from our team reviewed ICD-10-CM codes in CCSR category INJ009 to confirm that all available incident tSCI diagnostic codes were included in our algorithm to identify eligible ED visits (8, 17). All diagnostic codes used in our study are provided in Supplementary Tables 2, 3.

### Trend analyses

The annual number of nationwide ED visits for incident tSCI among children between 2016 and 2020 was our primary study outcome, whereas immediate hospital admission, which included admissions to the same hospital and transfers to other short-term hospitals, was our secondary study outcome. Transfers to other short-term hospitals were classified as hospital admissions based on the presumption that the majority of such transfers would result in an inpatient stay. Using HCUP ED discharge weights, we estimated the total national number of pediatric ED visits for tSCI in each calendar year from 2016 to 2020, as well as the total number of visits for tSCI in each year by age (0–4, 5–9, 10–14, and 15–20 years) and sex. We then used yearly US Census Bureau data provided by HCUP to approximate overall annual rates of pediatric ED visits for tSCI per 100,000 children and tSCI visit rates stratified by age and sex.

The number of ED visits for tSCI resulting in immediate hospital admission were examined in each year and reported as a percentage of total ED visits for tSCI. Annual hospital admission percentages were also stratified by age and sex.

## Hospital admissions

Hospital admission analyses were limited to years 2019 and 2020, the last calendar year prior to the COVID-19 pandemic and the first year of the COVID-19 pandemic, respectively. At the time of our study, NEDS data after 2020 was not available. For these analyses, we excluded ED visits where patient payer status, zip income quartile, or race were missing and ED visits where the hospital trauma level designation was unknown.

Descriptive statistics were used to summarize sociodemographic, clinical, and hospital characteristics. Chi-square tests were used to determine whether distributions across examined ED sociodemographic, clinical, and hospital categories differed between children admitted and not admitted to hospital, respectively.

Unconditional logistic regression modeling was used to assess whether select sociodemographic and clinical factors were associated with immediate hospital admission. The same multivariable model was developed for each calendar year. Model covariates were selected *a priori* if they were presumed to be associated with hospital admission and included: age, sex, race, primary payer, and hospital trauma level designation. Models accounted for the complex NEDS survey design by including the strata and clustering of patients and hospitals to compute precise variance estimates for adjusted odds ratios. The significance level was set to 0.05 for all analyses.

## Subgroup analyses: sports-related injuries

Our subgroup analyses focused on ED visits for tSCI that resulted from sports-related injuries. For these analyses, ED visits for tSCI from our primary analyses were queried for recorded diagnoses of 65 distinct sports-related injuries, which were defined using ICD-10-CM codes (Supplementary Table 3) (18, 19). Next, among the subset of ED visits with sports-related injuries, visits were categorized as being attributed to "contact-collision," "limited contact," "noncontact," or "other" sports using the "*Classification of Sports According to Contact*," which was developed by the American Academy of Pediatrics Council on Sports Medicine and Fitness (18).

We then estimated the total number of ED visits for incident tSCI in each year (2016–2020), the corresponding visit rate per 100,000 children, and the percentage of ED visits leading to immediate hospitalization for the subgroup of pediatric sports-related ED visits. Similar to our primary analyses, reported estimates were stratified by age and sex. Yearly ED visit counts and rates per 100,000 children were also estimated and reported for each sport category.

Lastly, to describe sports most responsible for precipitating tSCI ED visits, all subgroup visits for years 2019 and 2020 were reported in order of decreasing prevalence by individual sport for each year. Annual rankings were further stratified by region (northeast, midwest, south, and west) (20) to characterize geographical differences in sport injury etiology.

## Software

All study analyses were completed using SAS V.9.4 (SAS Institute Inc., Cary, North Carolina, United States). Trends in ED visits were graphically depicted using GraphPad Prism Version 9.2.0 (GraphPad Software LLC, San Diego, California, United States).

# Results

## Trends in emergency department visits

Annual trends in pediatric emergency department (ED) discharges for all-cause incident traumatic spinal cord injury (tSCI) between 2016 and 2020 are shown in Figure 1. Between 1 January 2016 and 31 December 2020, there were 11,005 ED visits in the United States for tSCI among children, corresponding to an average of 2,201 visits (standard deviation (SD): ±163) per year. The number of tSCI visits was lowest in 2018 (1,981 visits) and highest in 2016 (2,370 visits). The annual ED visit rate for tSCI remained relatively stable throughout the study period, with 2.74 visits per 100,000 children observed in 2016 and 2.47 visits per 100,000 children observed in 2020 [mean: 2.55 visits per 100,000 children per year, standard deviation (SD): ±0.19 visits per 100,000 children per year], and only decreased by 1.2% between 2019 (2.50 visits per 100,000 children) and 2020, the first year of the COVID-19 pandemic (Figure 1A). Except for 2019 (68.7%), the percentage of pediatric ED visits for tSCI resulting in immediate hospitalization increased yearly between 2016 (69.6%) and 2020 (79.1%; Figure 1B).

Age-stratified trends demonstrated that the oldest children (15–20 years) were consistently responsible for the highest number of tSCI ED visits (mean: 1,501 visits, SD: ±126 visits) and the greatest annual tSCI ED visit rate over time (mean: 5.89 visits per 100,000 children per year, SD: ±0.50 visits per 100,000 children per year; Figures 1C). The average annual tSCI ED visit rate for the oldest children was 243%–597% greater than the average annual visit rate of any other examined age group. Despite the youngest children (0–4 years) having the lowest average annual ED tSCI visit rate (mean: 0.84 visits per 100,000 children per year, SD: ±0.12 visits per 100,000 children per year), they had the highest average annual hospitalization percentage (82.1%; Figure 1D). Their average annual hospitalization percentage most resembled that observed for the oldest children (77.7%). Conversely, the average annual hospitalization percentage for children ages 5–9 years and 10–14 years were similar at 55.3% and 55.2%, respectively.

The number of annual tSCI ED visits (mean: 1,489 visits, SD: ±113 visits) and the corresponding average annual ED tSCI visit rate (mean: 3.37 visits per 100,000 children per year, SD: ±0.25 visits per 100,000 children per year) for males was approximately twice the average number of annual visits (mean: 713 visits, SD: ±60 visits) and visit rate (mean: 1.69 visits per 100,000 children per year, SD: ±0.14 visits per 100,000 children per year), respectively, observed for females. Overall, the annual number of tSCI ED visits and the annual tSCI ED visit rate were relatively stable by sex over time. Although the annual percentage of ED visits resulting in immediate hospitalization was consistently higher for males compared with females, the annual hospitalization percentage for females increased by 38.7% between 2016 (56.1%) and 2020 (77.7%).

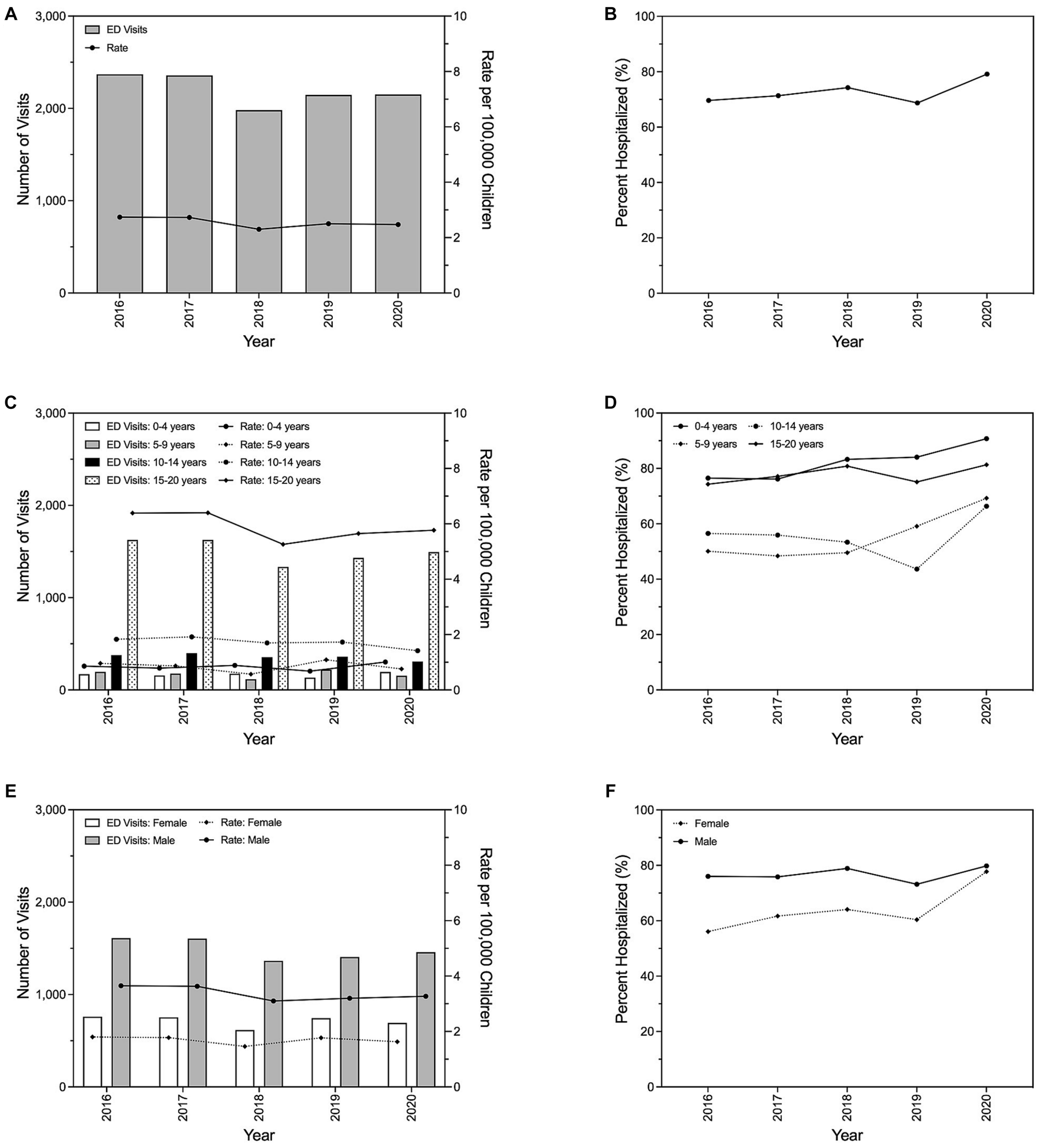


FIGURE 1
Trends in emergency department visits for pediatric traumatic spinal cord injury and subsequent hospital admissions in the United States, 2016–2020. Total number of visits and corresponding visit rate per year **(A)**, and the proportion of visits resulting in immediate hospitalization by year **(B)**. Annual emergency department visits, visit rate, and proportion of visits resulting in immediate hospitalization stratified by age **(C,D)** and sex **(E,F)**.

## Emergency department visits and hospital admissions

There were 2,146 and 2,151 pediatric ED visits for all-cause tSCI in 2019 and 2020, respectively. A total of 182 (8.5%) and 120 (5.6%) encounters were excluded from our 2019 and 2020 analyses, respectively, due to missing or unknown patient payer status, zip income quartile, race, or hospital trauma level designation. After applying study-specific exclusions, 1,964 and 2,031 pediatric ED visits remained for all-cause tSCI in 2019 and 2020, respectively. The majority (2019: 85.4%; 2020: 83.7%) of ED visits were by older children (10–20 years), while more than two-thirds of visits (2019: 66.5%; 2020: 67.3%) were by males. Most ED visits were by white children (2019: 53.5%; 2020: 49.9%) and private medical insurance (43.3%–45.1%) was the most common primary payer. Cervical injuries were most prevalent (2019: 50.6%; 2020: 46.6%) and few visits to the ED resulted in death (2019: 3.5%; 2020: 1.6%). Most tSCI ED visits occurred in the south (2019: 40.3%; 2020: 42.0%) and midwest

(2019: 25.2%; 2020: 24.1%). Children with tSCI mostly presented to level I trauma hospitals (2019: 51.8%; 2020: 58.2%) and hospitals designated as metropolitan teaching centers (2019: 86.4%; 2020: 86.1%). For our admission analyses, 1,321 (67.3%) and 1,605 (79.0%) ED visits resulted in hospital admission in 2019 and 2020, respectively.

Relative to the oldest children (15–20 years), children aged 10–14 years were significantly less likely to be admitted to the hospital immediately following a visit to the ED for tSCI in both 2019 [adjusted odds ratio (AOR) 0.28, 95% CI 0.15 to 0.51] and 2020 (AOR 0.41, 95% CI 0.20 to 0.85). Patient sex and race were not found to be associated with hospital admission. Compared with ED visits covered by private insurance, those subsidized by Medicaid in 2020 were significantly more likely to result in hospital admission (AOR 2.04, 95% CI 1.05 to 3.98). Lastly, non-trauma center ED visits were significantly less likely (2019: AOR 0.25, 95% CI 0.01 to 0.61; 2020: AOR 0.14, 95% CI 0.07 to 0.30) to end in hospital admission than visits to level I trauma centers.

### Trends in sports-related injuries

Compared with all-cause ED tSCI, similar trends in the annual number of tSCI ED visits, tSCI ED visit rates, and immediate hospitalizations were observed for the subgroup of children with sports-related injuries (Figure 2). Annual ED tSCI visits and visit rates attributed to sports-related injuries remained stable between 2016 and 2019 (0.49 visits per 100,000 children in 2016 and 0.50 visits per 100,000 children); however, a 38.0% decrease in the rate was observed between 2019 and 2020 (Figure 2A). The average annual percentage of ED visits for tSCI resulting in immediate hospitalization was lower for sports injuries (60.1%), ranging from 64.4% in 2016 to 63.6% in 2020 (Figure 2B), than was observed for all-cause tSCI (Table 1).

Few young children (0–9 years) visited the ED for tSCI resulting from sports between 2016 and 2020; therefore, associated counts and rates for this population are unable to be reported (Figure 2C). When limited to older children or stratified by sex, annual ED tSCI visits and visit rates for sports-related tSCI minimally fluctuated between 2016 and 2019, though markedly declined in 2020. The average annual ED tSCI visit rate (mean: 0.61 visits per 100,000 children per year, SD: ±0.11 visits per 100,000 children per year) for sports-related injuries among males was nearly three times the visit rate (mean: 0.23 visits per 100,000 children per year, SD: ±0.05 visits per 100,000 children per year) observed for females (Figure 2E).

Between 2016 and 2019, contact-collision and limited contact injuries were the first and second, respectively, causes of sports-related tSCI among children (Figures 2G,H). Although the rate of tSCI ED visits due to contact-collision sports was consistently the highest between 2016 and 2020, the rate sharply declined by 46.5% from 2019 to 2020, matching the rate for limited contact sports injuries (0.13 per 100,000 in 2020).

### Sports-related causes of spinal cord injury

Sports-related injuries accounted for 20.0% of ED visits for tSCI in 2019 ($n = 2,146$), but only 12.7% of similar visits in 2020 ($n = 2,151$). Sports injuries prompting tSCI ED visits among children in 2019 and 2020, including by geographic region, are described in Table 2. The total number of sports-related ED visits for tSCI decreased from 430 encounters in 2019 to 273 encounters in 2020 (36.5% decrease). American tackle football was the leading cause of sports-related tSCI among children in both 2019 and 2020, accounting for 21.1% and 16.9% of tSCI ED visits, respectively. Other sports leading to tSCI in 2019 were varied, with no individual sport accounting for more than 10% of all sports-related tSCI ED visits. Trampolining (8.2%) was second to American tackle football as the most prevalent sports-related injury in 2019. In 2020, snow sports, including skiing (alpine and downhill), snowboarding, sledding, tobogganing, and snow tubing, became the second leading sport cause of tSCI, representing 14.4% of total sports-related injuries. Variations in the prevalence of sports-related injuries were observed by region; however, for the most part, 10 or fewer tSCI ED visits were attributed to individually examined sports within each region.

## Discussion

Our primary findings were that the annual ED visit rate for tSCI remained relatively stable between 2016 and 2020, with approximately 2,200 new all-cause pediatric ED visits for tSCI per year. On average, roughly 70% of ED visits for tSCI resulted in immediate hospitalization; most ED visits for tSCI were by older children (15–20 years) and males, who were also more often admitted to the hospital. Notable secondary findings included: (a) compared with older children (15–20 years), younger children (10–14 years) were significantly less likely to be admitted to hospital immediately following a visit to the ED for tSCI; (b) relative to level I trauma centers, ED visits for tSCI at non-trauma centers were significantly less likely to result in hospital admission; (c) patient sex and race were not associated with hospital admission; (d) the proportion of ED visits for tSCI due to sports-related injuries declined between 2019 (20.0%) and 2020 (12.7%); and (f) American tackle football was the leading cause of sports-related ED visits for tSCI among children.

We report that the annual incidence of all-cause ED visits for tSCI among children remained relatively stable between 2016 and 2020 (mean: 2.55 visits per 100,000 children per year), and that the proportion of ED visits for tSCI resulting in immediate hospitalization (mean: 72.6%) marginally increased during the same period (2016: 69.6%; 2020: 79.1%). Despite our study population comprising children to age 20 years, our findings generally coincide with those from a prior NEDS study that examined trends in ED visits for tSCI among children aged 17 years and younger between 2007 and 2010 (7). In that study, investigators determined that an average of 1,308 children and adolescents visited the ED for tSCI each year in the United States, corresponding to a cumulative pediatric tSCI incidence of 1.75 per 100,000 children per year (7). Age and sex disparities in the occurrence of tSCI were reported, whereby ED visits for tSCI were more common among older and male children. Investigators also noted that, overall, 6.9% of tSCIs were attributed to sports and that 62.4% of ED visits for tSCI resulted in admission to the hospital. Compared with our study, observed differences in the cumulative tSCI incidence rate and proportion of sports-related injuries most likely reflect the older age of our study population (68.2% of visits were by children aged 15–20 years) and associated differences in behaviors and lifestyle activities of older children. Other minor differences between study findings may result from variations in case ascertainment algorithms (ICD10-CM vs. ICD-9-CM coding and study-specific primary and secondary tSCI diagnosis inclusion criteria), as well as

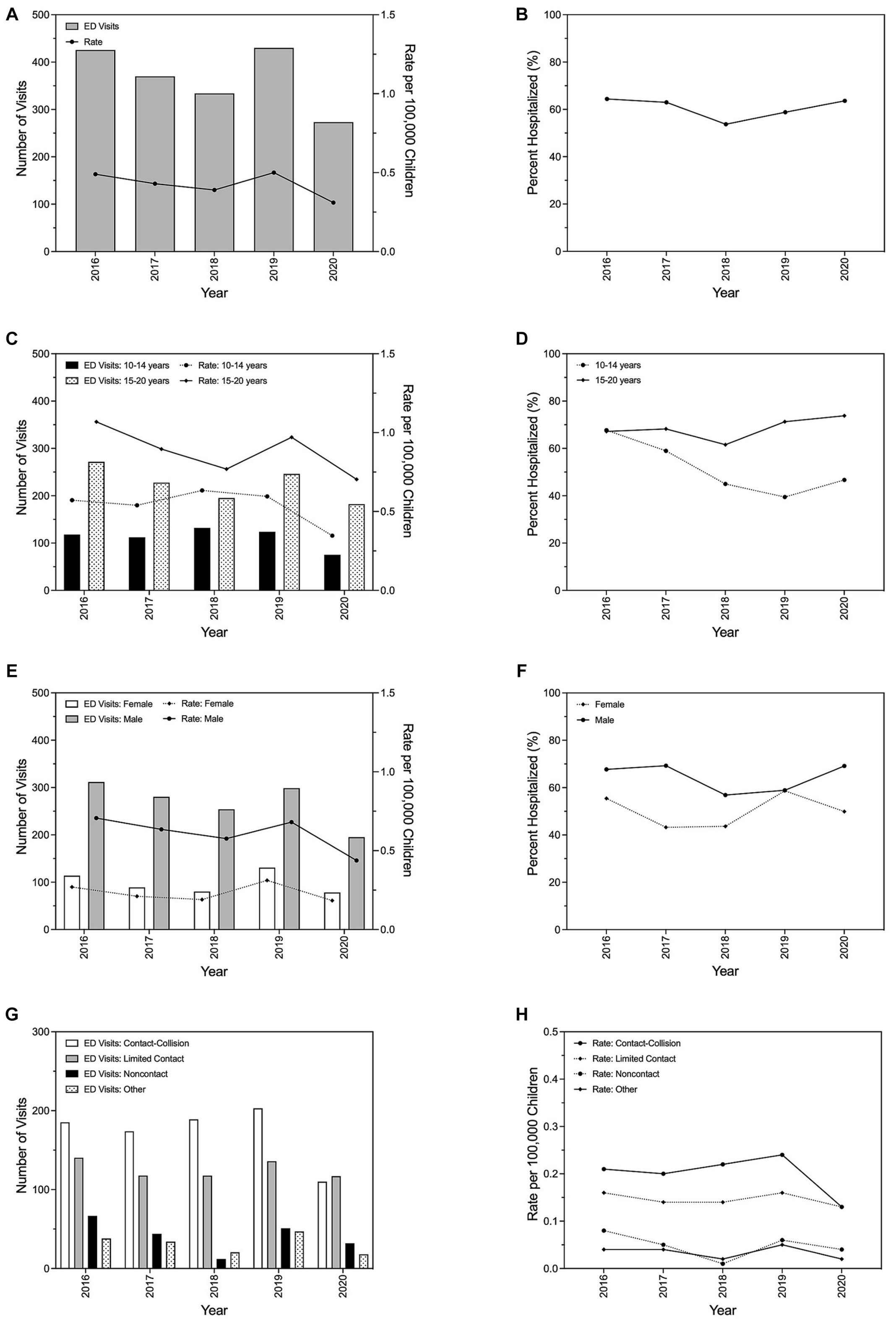


FIGURE 2
Trends in emergency department visits for pediatric traumatic spinal cord injury resulting from sports-related injuries and subsequent hospital admissions in the United States, 2016–2020. Total number of visits and corresponding visit rate per year **(A)**, and the proportion of visits resulting in immediate hospitalization by year **(B)**. Annual emergency department visits, visit rate, and proportion of visits resulting in immediate hospitalization stratified by age **(C,D)** and sex **(E,F)**. Total number of yearly emergency department visits **(G)** and corresponding annual visit rate **(H)** by sport type.

TABLE 1 Baseline characteristics and associations between select factors and immediate hospital admission for pediatric spinal cord injury by year, 2019–2020.

| | 2019 | | | | | 2020 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Admitted to hospital | | | | | Admitted to hospital | | | |
| | All ED visits *n* (%) | Yes *n* (%) | No *n* (%) | | | All ED visits *n* (%) | Yes *n* (%) | No *n* (%) | | |
| Characteristic | *n* = 1,964 | *n* = 1,321 | *n* = 643 | *p*-values[a] | AOR | *n* = 2,031 | *n* = 1,605 | *n* = 426 | *p*-values[a] | AOR |
| **Age** | | | | | | | | | | |
| 0–4 | 113 (5.8) | 96 (84.8) | 17 (15.2) | <0.01 | 2.50 (0.88–7.06) | 178 (8.8) | 164 (92.4) | 13 (7.6) | 0.01 | 2.75 (0.78–9.66) |
| 5–9 | 173 (8.8) | 83 (47.9) | 90 (52.1) | | 0.31 (0.12–0.84)* | 153 (7.5) | 106 (69.0) | 47 (31.0) | | 0.40 (0.16–1.04) |
| 10–14 | 313 (15.9) | 124 (39.6) | 189 (60.4) | | 0.28 (0.15–0.51)*** | 295 (14.5) | 196 (66.3) | 99 (33.7) | | 0.41 (0.20–0.85)* |
| 15–20 | 1,365 (69.5) | 1,018 (74.6) | 347 (25.4) | | Reference | 1,405 (69.2) | 1,139 (81.1) | 266 (18.9) | | Reference |
| **Sex** | | | | | | | | | | |
| Male | 1,307 (66.5) | 945 (72.3) | 361 (27.7) | 0.01 | Reference | 1,367 (67.3) | 1,090 (79.7) | 277 (20.3) | 0.60 | Reference |
| Female | 657 (33.5) | 375 (57.1) | 282 (42.9) | | 0.61 (0.36–1.01) | 664 (32.7) | 515 (77.5) | 149 (22.5) | | 0.94 (0.56–1.58) |
| **Race** | | | | | | | | | | |
| White | 1,052 (53.5) | 684 (65.1) | 367 (34.9) | 0.24 | Reference | 1,013 (49.9) | 790 (78.0) | 223 (22.0) | 0.70 | Reference |
| Black | 455 (23.2) | 344 (75.6) | 111 (24.4) | | 1.26 (0.62–2.59) | 479 (23.6) | 372 (77.6) | 107 (22.4) | | 0.53 (0.27–1.04) |
| Other[b] | 457 (23.3) | 292 (64.0) | 165 (36.0) | | 1.12 (0.54–2.32) | 539 (26.5) | 443 (82.2) | 96 (17.8) | | 0.95 (0.45–2.02) |
| **Primary payer** | | | | | | | | | | |
| Private insurance | 885 (45.1) | 621 (70.2) | 264 (29.8) | 0.62 | Reference | 880 (43.3) | 650 (73.9) | 230 (26.1) | 0.14 | Reference |
| Medicaid | 833 (42.4) | 537 (64.4) | 296 (35.6) | | 0.68 (0.35–1.29) | 853 (42.0) | 713 (83.6) | 140 (16.4) | | 2.04 (1.05–3.98)* |
| Other[c] | 246 (12.5) | 163 (66.2) | 83 (33.8) | | 0.75 (0.35–1.64) | 299 (14.7) | 242 (81.2) | 56 (18.8) | | 1.87 (0.77–4.50) |
| **Median household income[d]** | | | | | | | | | | |
| Quartile 4 | 388 (19.8) | 213 (55.0) | 175 (45.0) | 0.40 | -- | 291 (14.3) | 212 (73.1) | 78 (26.9) | 0.75 | -- |
| Quartile 3 | 434 (22.1) | 306 (70.5) | 128 (29.5) | | | 418 (20.6) | 327 (78.4) | 90 (21.6) | | -- |
| Quartile 2 | 529 (27.0) | 367 (69.3) | 163 (30.7) | | -- | 605 (29.8) | 477 (78.9) | 128 (21.1) | | -- |
| Quartile 1 | 612 (31.2) | 434 (71.0) | 177 (29.0) | | -- | 718 (35.3) | 588 (81.9) | 130 (18.1) | | -- |
| **Injury level** | | | | | | | | | | |
| Cervical | 993 (50.6) | 646 (65.0) | 347 (35.0) | 0.39 | -- | 947 (46.6) | 682 (72.1) | 264 (27.9) | 0.01 | -- |
| Thoracic | 670 (34.1) | 510 (76.1) | 160 (23.9) | 0.01 | -- | 729 (35.9) | 611 (83.8) | 118 (16.2) | 0.11 | -- |
| Lumbar | 332 (16.9) | 208 (62.6) | 124 (37.4) | 0.52 | -- | 464 (22.8) | 396 (85.5) | 67 (14.5) | 0.06 | -- |
| Died | 68 (3.5) | 59 (86.0) | 10 (14.0) | 0.09 | -- | 32 (1.6) | 23 (71.5) | 9 (28.5) | 0.67 | -- |
| **Hospital region** | | | | | | | | | | |
| Northeast | 243 (12.4) | 150 (61.7) | 93 (38.3) | 0.41 | -- | 254 (12.5) | 215 (84.6) | 39 (15.4) | 0.50 | -- |
| Midwest | 495 (25.2) | 353 (71.2) | 142 (28.8) | | -- | 489 (24.1) | 367 (74.9) | 123 (25.1) | | -- |
| South | 792 (40.3) | 573 (72.3) | 219 (27.7) | | -- | 853 (42.0) | 662 (77.6) | 191 (22.4) | | -- |
| West | 433 (22.1) | 245 (56.5) | 188 (43.5) | | -- | 435 (21.4) | 361 (83.1) | 74 (16.9) | | -- |

*(Continued)*

TABLE 1 (Continued)

| | 2019 | | | | | 2020 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Admitted to hospital | | | | | Admitted to hospital | | | |
| | All ED visits *n* (%) | Yes *n* (%) | No *n* (%) | | | All ED visits *n* (%) | Yes *n* (%) | No *n* (%) | | |
| Characteristic | *n* = 1,964 | *n* = 1,321 | *n* = 643 | *p*-values[a] | AOR | *n* = 2,031 | *n* = 1,605 | *n* = 426 | *p*-values[a] | AOR |
| **Hospital trauma level designation** | | | | | | | | | | |
| Not a trauma center | 262 (13.3) | 107 (41.0) | 155 (59.0) | <0.01 | 0.25 (0.10–0.61)** | 243 (12.0) | 109 (45.0) | 134 (55.0) | <0.01 | 0.14 (0.07–0.30)*** |
| Trauma center level I | 1,017 (51.8) | 741 (72.8) | 276 (27.2) | | Reference | 1,182 (58.2) | 981 (83.0) | 201 (17.0) | | Reference |
| Trauma center level II | 533 (27.1) | 388 (72.8) | 145 (27.2) | | 0.80 (0.36–1.78) | 462 (22.7) | 405 (87.7) | 57 (12.3) | | 1.30 (0.60–2.79) |
| Trauma center level III | 152 (7.7) | 85 (56.1) | 67 (43.9) | | 0.40 (0.16–1.03) | 144 (7.1) | 109 (75.7) | 35 (24.3) | | 0.52 (0.18–1.52) |
| **Teaching status of hospital** | | | | | | | | | | |
| Metropolitan non-teaching | 132 (6.7) | 82 (61.7) | 51 (38.3) | 0.11 | -- | 168 (8.3) | 114 (67.9) | 54 (32.1) | <0.01 | -- |
| Metropolitan teaching | 1,696 (86.4) | 1,175 (69.3) | 522 (30.7) | | -- | 1,748 (86.1) | 1,445 (82.7) | 303 (17.3) | | -- |
| Non-metropolitan hospital | 135 (6.9) | 64 (47.5) | 71 (52.5) | | -- | 116 (5.7) | 46 (39.9) | 70 (60.1) | | -- |

AOR, adjusted odds ratio; ED, emergency department. [a]Chi-square test. [b]Includes Hispanic, Asian or Pacific Islander, Native American, and other races. [c]Includes Medicare, private insurance, self-pay, and other payers. [d]2019—Quartile 1: $1–$47,999; Quartile 2: $48,000–$60,999; Quartile 3: $61,000–$81,999; Quartile 4: $82,000+. 2020—Quartile 1: $1–$49,999; Quartile 2: $50,000–$64,999; Quartile 3: $65,000–$85,999; Quartile 4: $86,000+. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

changes to diagnostic practices in acute clinical settings over time. The elevated proportion of children immediately hospitalized within our study is presumed to be driven by increased tSCI severity among the oldest and youngest children. However, it may also be in part associated with changes in clinical practices, the availability of inpatient beds and specialty care, and health insurance eligibility over the last decade. A separate study using pediatric HCUP inpatient data from 2009 reported that the incidence of tSCI hospitalization among children less than 21 years of age was 2.4 per 100,000 children per year (21), while our prior work using comparable 2016 data from similarly aged children suggested that the incidence of tSCI hospitalization may be as low as 1.48 per 100,000 children per year (8). Compared with our most recent findings, previously observed decreases in the annual pediatric tSCI incidence (6), whether approximated using ED or inpatient encounters, appear to have halted. Additional studies are needed to determine whether further reductions in pediatric tSCI incidence are possible, characterize tSCI etiology and severity further, and inform injury prevention strategies and health resource planning.

Our findings suggest that age and hospital trauma designation may be associated with hospital admission following tSCI among children. Specifically, we observed that children between the ages of 10–14 years were significantly less likely to be admitted to hospital following ED visits for all-cause tSCI compared with the oldest children (15–20 years). This may be due in-part to variations in the mechanisms of tSCI injury, pathology, and level of injury by age. For example, prior studies have repeatedly shown that older children are more likely to sustain sports-related and violent injuries, including those from firearms and assaults, whereas motor vehicle crashes and falls are leading causes of tSCI among younger children (7–10, 22–24). Moreover, we found that ED visits for tSCI occurring at non-trauma centers were significantly less likely to result in hospital admission compared with visits to level I trauma centers. This finding may be explained by the more rural location of select non-trauma centers, differences in distance between patient location where the injury occurred and the nearest hospital, and the often limited capacity of non-trauma centers to respond to severe injuries effectively (25, 26). Although our reported associations are exploratory, they provide valuable insight into factors associated with hospital admission following tSCI, which may in-turn serve as a crude proxy for the quality of tSCI care. Future studies should examine outcomes post-tSCI, including regional differences in inpatient care.

Other studies have repeatedly demonstrated that, following motor vehicle crashes (~37.0%), accidental falls (~20.4%), and firearm injuries (~8.7%), sports (~6.9%) are a major leading cause of tSCI among children (6, 7, 27). Between 2007 and 2010, 6.9% of all ED visits for tSCI among children (0–17 years) in the United States were attributed to sports etiologies (7); whereas between 1997 and 2012, sports injuries were associated with 29.4% and 25.7% of tSCI cases among hospitalizations for spinal injury among children (0–14 years) and adolescents (15–17 years), respectively (6). These observations have led investigators to suggest that pediatric tSCI prevention strategies focused on sports-related injuries may effectively reduce

TABLE 2 Sports-related causes of spinal cord injury by year and region in the United States, 2019–2020.

| | | Sports-related ED visits for tSCI by region^ | | | |
|---|---|---|---|---|---|
| 2019: sports-related ED visits for tSCI | All regions *n* (%)^ (*n* = 430 total) | Northeast (*n* = 80 total) | Midwest (*n* = 97 total) | South (*n* = 135 total) | West (*n* = 118 total) |
| American tackle football | 90 (21.1) | American tackle football (*n* = 16, 20.6%) | American tackle football (*n* = 24, 25.0%) | American tackle football (*n* = 33, 24.4%) | American tackle football (*n* = 17, 14.3%) |
| Trampolining | 35 (8.2) | Ice hockey (*n* = 11, 14.0%) | Wrestling (*n* = 11, 14.3%) | Trampolining (*n* = 16, 11.7%) | Snow sports+ (*n* = 14, 11.9%) |
| *Climbing, rappelling and jumping off | 33 (7.6) | Basketball[a] | Snow sports+ | Swimming (*n* = 13, 9.9%) | Soccer[a] |
| Bike riding | 29 (6.7) | Gymnastics[a] | Trampolining | *Climbing, rappelling and jumping off (*n* = 13, 9.3%) | Trampolining[a] |
| Wrestling | 26 (6.1) | *Climbing, rappelling and jumping off[b] | Bike riding[a] | Wrestling (*n* = 12, 9.1%) | Bike riding[a] |
| Snow sports+ | 24 (5.6) | Springboard and platform diving[b] | Soccer[a] | Cheerleading[a] | Rugby[a] |
| Basketball | 24 (5.5) | American flag or touch football[c] | *Climbing, rappelling and jumping off[b] | Other involving muscle strengthening exercises[a] | *Climbing, rappelling and jumping off[b] |
| Soccer | 22 (5.1) | Bike riding[c] | Springboard and platform diving[b] | Basketball[a] | Walking, marching and hiking[b] |
| Swimming | 18 (4.2) | Walking, marching and hiking[c] | Mountain climbing, rock climbing and wall climbing[b] | Bike riding[a] | Gymnastics[c] |
| Gymnastics | 18 (4.1) | Surfing, windsurfing and boogie boarding | Surfing, windsurfing and boogie boarding[c] | Water skiing and wake boarding[b] | Aerobic and step exercise[c] |
| Springboard and platform diving | 16 (3.6) | Running | Basketball[c] | Other specified sports and athletics[b] | Basketball[c] |
| Walking, marching and hiking | 15 (3.4) | | | Gymnastics[c] | Springboard and platform diving[c] |
| Ice hockey | 11 (2.6) | | | Soccer[c] | Swimming[c] |
| Rugby | -- | | | BASE jumping[c] | #Other sports and athletics played individually |
| Surfing, windsurfing and boogie boarding | -- | | | Lacrosse and field hockey[c] | |
| Running | -- | | | Running[c] | |
| Cheerleading[a] | -- | | | | |
| Other involving muscle strengthening exercises[a] | -- | | | | |
| American flag or touch football[b] | -- | | | | |
| Water skiing and wake boarding[b] | -- | | | | |
| Mountain climbing, rock climbing and wall climbing[b] | -- | | | | |
| Aerobic and step exercise[b] | -- | | | | |
| Other specified sports and athletics[b] | -- | | | | |
| #Other sports and athletics played individually[c] | -- | | | | |
| BASE jumping[c] | -- | | | | |
| Lacrosse and field hockey[c] | -- | | | | |

*(Continued)*

TABLE 2 (Continued)

| 2020: sports-related ED visits for tSCI | All regions *n* (%)^ (*n* = 273 total) | Northeast (*n* = 53 total) | Midwest (*n* = 73 total) | South (*n* = 105 total) | West (*n* = 42 total) |
|---|---|---|---|---|---|
| Percent (%) change from 2019 | −36.5 | −33.7 | −24.7 | −22.2 | −64.4 |
| American tackle football | 46 (16.9) | Snow sports[+] (*n* = 18, 33.4%) | American tackle football (*n* = 22, 29.9%) | American tackle football (*n* = 20, 18.5%) | Snow sports[+] |
| Snow sports[+] | 39 (14.4) | Ice hockey (*n* = 11, 20.6%) | Snow sports[+] (*n* = 12, 15.9%) | Swimming (*n* = 17, 16.5%) | Surfing, windsurfing and boogie boarding |
| Swimming | 24 (8.9) | Horseback riding | Basketball | Wrestling | Bike riding[a] |
| Basketball | 17 (6.0) | American tackle football[a] | Bike riding[a] | Springboard and platform diving | Gymnastics[a] |
| Bike riding | 16 (5.9) | Surfing, windsurfing and boogie boarding[a] | Cheerleading[a] | *Climbing, rappelling and jumping off[a] | Trampolining[a] |
| Wrestling | 16 (5.7) | Gymnastics | *Climbing, rappelling and jumping off[a] | Basketball[a] | Soccer[b] |
| Springboard and platform diving | 14 (5.3) | | Springboard and platform diving[a] | Bike riding | Wrestling[b] |
| *Climbing, rappelling and jumping off | 14 (5.2) | | Ice hockey[b] | #Other sports and athletics played individually[b] | Swimming[b] |
| Ice hockey | 14 (5.0) | | Swimming[b] | Roller skating (inline) and skateboarding[b] | |
| Surfing, windsurfing and boogie boarding | 11 (3.9) | | Wrestling | Other specified sports and athletics[b] | |
| Horseback riding[a] | -- | | | Cheerleading[b] | |
| Cheerleading[a] | -- | | | Other involving water and watercraft[b] | |
| Gymnastics | -- | | | Running[b] | |
| Trampolining | -- | | | Trampolining[b] | |
| #Other sports and athletics played individually[b] | -- | | | Walking, marching and hiking[b] | |
| Roller skating (inline) and skateboarding[b] | -- | | | | |
| Other specified sports and athletics[b] | -- | | | | |
| Other involving water and watercraft[b] | -- | | | | |
| Running[b] | -- | | | | |
| Walking, marching and hiking[b] | -- | | | | |
| Soccer[b] | -- | | | | |

ED, emergency department; tSCI, traumatic spinal cord injury. [+]Snow (alpine; downhill) skiing, snowboarding, sledding, tobogganing and snow tubing. *Other involving climbing, rappelling and jumping off. #Other involving other sports and athletics played individually. ^Reported percentages were based on weighted values and may therefore appear to be inaccurate. [a]Equal number of visits. [b]Equal number of visits. [c]Equal number of visits.

tSCI among children and be more manageable than interventions tailored to other tSCI mechanisms (6). Overall, our findings show that sports-related injuries were documented during 16.6% of all ED visits for tSCI among children between 2016 and 2020; 20.3% and 14.9% of all ED visits for tSCI by children ages 0–14 years and 15–20 years, respectively, were attributed to sports-related causes. We also report that the incidence of pediatric tSCI attributed to sports remained relatively stable between 2016 and 2019. Based on these findings, it is reasonable to hypothesize that reported decreases in pediatric tSCI incidence over the last two decades have been achieved through the positive effects of interventions on injury mechanisms other than sports, such as reductions in tSCI due to motor vehicle crashes (28, 29). Such decreases would explain the decreasing pediatric tSCI incidence over time and the increasing proportion of pediatric tSCI resulting from sports. Notwithstanding, it is also possible that prior approximations of tSCI among children resulting from sports were underestimated due to undocumented mechanisms of injury within health records (7). Irrespective of the causes for the observed shift in the proportion of pediatric sports-related tSCI, further reductions in tSCI incidence may be best attained through investments in public policies, education, and injury prevention initiatives that focus on sports. This may include implementing of broad interventions focused on targeted populations, such as male children or the participants (and their parents) of sports deemed to have an elevated tSCI risk, such as American tackle football, trampolining, or snow sports. It may also include the application of regional risk mitigation strategies in areas with the highest number of pediatric visits to the ED for tSCI, such as the south, or regions with the greatest annual incidence of pediatric sports-related tSCI. Ultimately, further epidemiological investigations into pediatric sport-related tSCI offer the promise of returning considerable public and population health benefits.

Changes in activities of daily living and health behaviors due to COVID-19 restrictions may explain the observed 38.0% decrease in sports-related tSCI between 2019 and 2020 despite the stable overall pediatric tSCI incidence during the same period (13). This is consistent with the reported 15% decrease in the total number of ED visits in the United States from 2019 to 2020. Moreover, the increased 2020 hospital admissions observed in our study correspond with the elevated rate of all-cause admission from the ED reported for the United States in the same year. Future studies will be required to determine how the epidemiology of pediatric tSCI has changed following the first year of the COVID-19 pandemic.

Our study has numerous strengths. Annual pediatric ED visits for tSCI and associated visit rates were estimated using NEDS datasets that are representative of all ED visits in the United States during examined calendar years. Using these datasets allowed us to precisely estimate annual ED visits for tSCI across the 5 years following the introduction of ICD-10-CM coding, including throughout the first year of the COVID-19 pandemic. The identification of eligible tSCI encounters and the classification of sport-related injuries were based on ICD-10-CM detection and categorization algorithms developed in consultation with epidemiologist and clinical experts. Additionally, the datasets included detailed sociodemographic, clinical, and care setting information, which permitted us to: examine trends in ED visits for tSCI by age, sex, and sports-related injuries; characterize immediate hospitalizations following tSCI; and account for factors presumed to confound modeled associations in our regression analyses. To our knowledge, our study is the first to report data from the last decade on trends in national ED visits for tSCI and associated hospital admissions among children in the United States. Therefore, our findings provide meaningful benchmark data that may be used to examine future temporal changes in ED visits for tSCI and assess the effectiveness of interventions targeted at reducing tSCI among children.

Certain limitations should be considered when interpreting our findings. Reported tSCI incidence rates within our study are derived using information from administrative data; they are encounter-based, lack unique patient identifiers, and do not account for children who died at a trauma scene (30). Similar to other studies using electronic health data, it is possible that diagnoses of tSCI, important details pertaining to injury mechanism, and other clinical characteristics were omitted from the administrative datasets or inadvertently misclassified as something else. Such occurrences would have led to the over or underestimation of reported counts and rates within our study and may bias reported estimates of association. Moreover, due to the unavailability of pediatric census data by broad geographic region, we were unable to compute estimates of annual ED visits for tSCI by region. This limited our ability to make specific regional tSCI prevention recommendations, especially regarding preventable sports injuries. Our reported multivariable models are exploratory; we therefore did not make adjustments for multiple comparisons. The models may also not account for all potential confounders that may bias examined associations, such as tSCI severity and household socioeconomic status. Despite these limitations, our reported findings meaningfully address major gaps in the pediatric tSCI literature by advancing existing knowledge of pediatric tSCI incidence and sports-related causes of tSCI.

Overall, we found that the rate of ED visits for pediatric tSCI in the United States was relatively stable between 2016 and 2020, with approximately 2,200 incident cases annually. On average, only approximately 70% of ED visits for tSCI resulted in immediate hospitalization. Future studies are necessary to describe the sociodemographic and clinical characteristics of children that are not hospitalized after visiting the ED for tSCI. Our findings also suggest that the proportion of sports-related tSCI ED visits may have increased in recent years. American tackle football, trampolining, and snow sports were leading causes of sports-related tSCI. Future research should further examine trends in the underlying etiologies of pediatric tSCI, while assessing the effectiveness of new and existing interventions aimed at tSCI prevention.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

## Author contributions

JCri: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition. LL: Conceptualization, Writing – original draft, Methodology, Visualization, Formal analysis. VN: Writing – review & editing, Conceptualization. NT: Writing – review & editing, Conceptualization. BK: Writing – review & editing. MD: Writing – review & editing. DT: Writing – review & editing, Conceptualization, Formal analysis, Methodology. AW: Writing – review & editing, Conceptualization, Methodology. JCra: Writing – review & editing, Conceptualization, Formal analysis, Project administration, Supervision.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1264589/full#supplementary-material

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# Assessing the reach, effectiveness, adoption, implementation, and maintenance of the ProACTIVE SCI physical activity counseling intervention among physiotherapists and SCI peer coaches during the transition from rehabilitation to community

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**Introduction:** Physical Activity (PA) levels for individuals with spinal cord injury (SCI) peak during rehabilitation and sharply decline post-discharge. The ProACTIVE SCI intervention has previously demonstrated very large-sized effects on PA; however, it has not been adapted for use at this critically understudied timepoint. The objective is to evaluate the reach, effectiveness, adoption, implementation, and maintenance of the ProACTIVE SCI intervention delivered by physiotherapists and SCI peer coaches during the transition from rehabilitation to community.

**Methods:** A single-group, within-subjects, repeated measures design was employed. The implementation intervention consisted of PA counseling training, champion support, prompts and cues, and follow-up training/community of practice sessions. Physiotherapists conducted counseling sessions in hospital, then referred patients to SCI peer coaches to continue counseling for 1-year post-discharge in the community. The RE-AIM Framework was used to guide intervention evaluation.

**Results:** Reach: 82.3% of patients at the rehabilitation hospital were reached by the intervention. Effectiveness: Interventionists (physiotherapists and SCI peer coaches) perceived that PA counseling was beneficial for patients. Adoption: 100% of eligible interventionists attended at least one training session. Implementation: Interventionists demonstrated high fidelity to the intervention. Intervention strategy highlights included a feasible physiotherapist to SCI peer coach referral process, flexibility in timepoint for intervening, and time efficiency. Maintenance:

Ongoing training, PA counseling tracking forms, and the ability to refer to SCI peer coaches at discharge are core components needed to sustain this intervention.

**Discussion:** The ProACTIVE SCI intervention was successfully adapted for use by physiotherapists and SCI peer coaches during the transition from rehabilitation to community. Findings are important for informing intervention sustainability and scale-up.

KEYWORDS

**physical activity counseling, spinal cord injury, rehabilitation, physiotherapist, SCI peers**

# Introduction

Physical activity (PA) levels for individuals who have recently incurred a spinal cord injury (SCI) peak during inpatient rehabilitation and sharply decline after discharge (1). This is unsurprising given the substantial readjustment period experienced by individuals with SCI during the transition from hospital to the community. However, patients are often motivated from seeing their progress during the rehabilitation process, leading to greater interest and commitment to being active post-discharge (2). As such, it has been suggested to promote PA immediately following discharge (2). PA interventions that address the unique needs of people with SCI during the transition between hospital to community are crucial yet understudied.

A limited number of studies have examined the effects of PA interventions at the point of discharge among people with SCI. For example, in the ReSpAct trial, PA counseling was implemented by physiotherapists or sport therapists in 18 rehabilitation centers located throughout the Netherlands (3). Prior to being discharged, patients had an initial PA consultation and subsequently received counseling for 13-weeks post-discharge from trained PA counselors. Patients with diverse disabilities (∼2% with SCI) who participated in the program exhibited an increase in their PA and sport participation levels following discharge from rehabilitation. Similarly, an intervention in the Netherlands initiated PA counseling during rehabilitation that was continued by physiotherapists or occupational therapists for 3-months after discharge and demonstrated small to medium-sized effects on PA behavior among those living with subacute SCI (4). These findings are promising; however, clinician time is often limited making the feasibility and scalability of therapist-delivered interventions challenging. There is value in examining other interventionist groups to continue PA counseling post-discharge.

The ProACTIVE SCI intervention is a PA counseling intervention that was co-developed by ∼300 end-users including healthcare providers and people with SCI. This intervention has previously demonstrated very large effect sizes for increasing PA behavior that were sustained over 6 months in the research setting (5). The intervention was co-developed with both physiotherapists (community, in-patient, and out-patient) and people with SCI who shared their lived experiences of PA across the rehabilitation continuum. Given the need for PA interventions during the transition from rehabilitation to community, we wanted to explore the adoption of the ProACTIVE SCI when delivered by clinicians and peers across this transition.

SCI peers and health service providers have been identified as preferred messengers of PA information (6). SCI peers can communicate the lived experience of a SCI and help those with a new SCI improve or maintain their PA behavior in the community-setting (7). Further, research has shown peer-delivered PA interventions to be as effective as professionally delivered interventions for increasing PA (8). Physiotherapists have the knowledge and confidence to prescribe exercise and encourage their patients to lead physically active lives (9). To date, no studies have explored the implementation of a coordinated, clinician-to-peer PA counseling service at the point of discharge.

Evaluation frameworks can be used to support implementation through systematic development and evaluation of programs and interventions. A widely used evaluation tool is the RE-AIM framework, which assesses the impact of an intervention across five domains: reach (the percentage of individuals who receive or are affected by a program), effectiveness (the positive and negative consequences of a program), adoption (the proportion of settings of intervention agents that adopt a policy or program), implementation (the extent to which a program is delivered as intended or clients' use of the intervention and implementation strategies), and maintenance (the extent to which a behavior or program becomes routine or maintained over time) (10). This framework was developed to evaluate the impact of public health programs, and now is widely used in many contexts as both a planning and evaluation guide for community interventions at the individual and community level (11). The RE-AIM framework has also been previously used to evaluate PA behavior change interventions (12). Using the RE-AIM framework, the purpose of this study was to evaluate the reach, effectiveness, adoption, implementation, and maintenance of an evidence-based PA intervention for people with SCI delivered by physiotherapists and SCI peer coaches during the transition from rehabilitation to community.

# Materials and methods

## Participants

Interventionists (physiotherapists and SCI peer mentors/SCI peer coaches) were recruited via email from a rehabilitation hospital (GF Strong) and provincial SCI organization (Spinal Cord Injury BC) in Vancouver, BC, Canada. Relevant staff physiotherapists (i.e., those working in the spine or neuromusculoskeletal unit) and SCI peer staff members were contacted by each site's leadership [participant recruitment has been described previously in Ma et al. (5)].

## Study design

This study used a hybrid implementation-effectiveness study design which is the simultaneous testing of an implementation strategy and a clinical intervention (13). A single-group within-subjects, repeated measures design was used. Details of the study design have been previously reported (14). The implementation evaluation is discussed here. The effectiveness (clinical) study evaluates the impact of the ProACTIVE SCI Intervention on patient PA levels and is reported elsewhere (Olsen et al., *in preparation*). Ethics approval for the protocol was granted by the Behavioral Research Ethics Board at the University of British Columbia (H19-02694).

## Implementation intervention

Physiotherapists and SCI peer coaches received an initial, in-person 2-h training (March 2020) on how to deliver the ProACTIVE SCI intervention and were provided with PA counseling forms tailored for each setting. A follow-up two-hour training session for dedicated practice and feedback was conducted 1 month later. It was intended to be conducted in-person, but was conducted via Zoom due to the restrictions of the COVID-19 pandemic. Physiotherapists and SCI peer coaches who attended the initial training session were supported by activities delivered by the champions (dedicated individuals who facilitate implementation) including monitoring, feedback, prompts to continue PA counseling, and problem solving. A prompt was added to physiotherapists' patient-oriented discharge summaries to cue the PA conversation as part of their typical workflow. A third training session (November 2020) was added to re-launch the study after research activities were halted due to the COVID-19 pandemic. Four follow-up training/community of practice sessions were completed over the course of 2 years. See Ma et al. (14) for further details.

## Physical activity counseling and referral procedure

Following the initial training, physiotherapists conducted PA counseling sessions with patients during rehabilitation. Briefly, counseling sessions, grounded in motivational interviewing and the Health Action Process Approach model, involved a discussion to understand client's readiness for PA, goals, barriers, activity preferences, and access to PA resources to then co-develop a PA plan (15, 16). During initial sessions physiotherapists completed a PA counseling form, which was forwarded to SCI peer coaches who would continue counseling sessions with patients for 1-year post-discharge in the community. However, due to the COVID-19 pandemic, counseling in the community did not occur for a 10-month period (March 2020–November 2020). Physiotherapists continued to send PA counseling referrals during this time, but all counseling was delayed in accordance with Public Health recommendations. In November of 2020 the study was re-launched to include the SCI peer coach PA counseling, and the first community counseling session delivered by a SCI peer coach took place in January 2021.

## Measures and analyses

### RE-AIM

The RE-AIM framework was used to guide the evaluation of the reach, effectiveness, adoption, implementation, and maintenance of the intervention. Descriptions of the RE-AIM elements and how these data were operationalized are described in Table 1.

### Client discharge summaries

Client discharge summaries (CDS) were reviewed by physiotherapist champions to monitor which patients received PA counseling and determine intervention reach. Physiotherapists documented the date the form was completed, if a PA counseling conversation was offered (Yes/No), and reasons as to why PA conversations did not occur (if applicable). The total number of patients who received a full or partial PA conversation (numerator), was divided by the total number of patients with SCI admitted to the rehabilitation hospital during the study duration (denominator) to determine a reach percentage.

### Semi-structured interviews

Individual semi-structured interviews were conducted over the phone or via Zoom 6-months post training with physiotherapists and SCI peer coaches. Implementation interventions require researchers to strategically combine and borrow from established qualitative approaches to meet the specific needs of the study, which is inherently pragmatic in nature (17). Therefore, a pragmatic qualitative approach was used, in which emphasis is placed on the intersubjectivity of findings (i.e., the idea that there is neither complete objectivity nor subjectivity when interpreting results) (18). Further, a pragmatic approach allowed us to prioritize the translation, co-production of knowledge, and applicability of findings to real world settings (18). Interviews explored factors that affected the effectiveness (i.e., patient benefits), implementation (i.e., intervention timing, feasibility, and impact on interventionist time) and maintenance of the intervention (e.g., program sustainability and scale-up to other rehabilitation centers). Analysis of implementation barriers and facilitators reported in these interviews is reported elsewhere (Lin et al., *in preparation*). Interviews were recorded and transcribed verbatim using Zoom audio transcription software. Zoom-produced transcripts were manually checked by the first author (KO) for accuracy. Interviews were coded using an iterative inductive content analysis approach to map onto the elements within the RE-AIM framework (19). NVivo was used to code transcripts (KO). Codes were then compared by a co-author (JM) to provide feedback and engage in discussion to refine the codes. Member checking was used to confirm and refine the interpretation of the findings.

TABLE 1 Reach, effectiveness, adoption, implementation, and maintenance domains and measurements.

| RE-AIM element | Domains as described in Glasgow et al. (10) p. 3–4 | Measurement of domain |
|---|---|---|
| Reach | The absolute number, proportion, and representativeness of individuals who are willing to participate in a given initiative, intervention, or program | Client discharge summary forms |
| Effectiveness | The impact of an intervention on important outcomes, including potential negative effects, quality of life, and economic outcomes | Interventionist interviews |
| Adoption | The absolute number, proportion, and representativeness of: a) settings; and b) intervention agents (people who deliver the program) | Training attendance sheets |
| Implementation | The intervention agents' fidelity to the various elements of an intervention protocol, including consistency of delivery as intended and the time required. It also includes adaptations made and the costs of the implementation | Interventionist interviews, physical activity counseling forms |
| Maintenance | The extent to which: (a) behavior is sustained 6 months or more after treatment or intervention; and (b) a program or policy becomes institutionalized or part of the routine organizational practices and policies. Includes proportion and representativeness of settings that continue the intervention and reasons for maintenance, discontinuance, or adaptation | Interventionist interviews, physical activity counseling forms |

RE-AIM, reach, effectiveness, adoption, implementation, maintenance; CDS, client discharge summary.

TABLE 2 Client discharge summary completion: intervention reach.

| | | |
|---|---|---|
| Total # of patients | 141 | |
| Total number of patients who did not have PA conversation | 25 | - |
| Total number of patients who had partial PA conversation | 42 | - |
| Total number of patients who had PA conversation | 74 | - |
| Total patient reach (# of patients who had the full PA conversation/total # of patients) | 52.48% | - |
| Adjusted patient reach (# of patients who had partial OR full PA conversation/total # of patients) | 82.27% | - |
| Reason for not having PA conversation | N | % |
| **Did not have PA conversation** | | |
| Not appropriate due to level of injury | 12 | 17.91% |
| Missed due to staffing issues | 9 | 13.43% |
| Patient did not have a SCI | 2 | 2.99% |
| Patient was moving out of province | 1 | 1.49% |
| Patient withdrew from therapy | 1 | 1.49% |
| **PA conversation initiated but terminated before complete** | | |
| Other medical concerns | 3 | 4.48% |
| Patient was not ready to discuss PA | 10 | 14.93% |
| No access to phone | 1 | 1.49% |
| Patient was already very motivated to be physically active on their own (not interested in having conversation) | 3 | 4.48% |
| Patient declined | 24 | 42.11% |
| Patient already arranged for private physiotherapy | 1 | 1.49% |

CDS, client discharge sheet; PA, physical activity; SCI, spinal cord injury.

## Training attendance sheets

The number of staff who were eligible to participate in the ProACTIVE SCI training was collected using recall from the physiotherapist clinical practice lead (CC-L) at the rehabilitation hospital and the executive director of the provincial SCI peer organization (CM) to determine intervention *adoption*. The number of interventionists attending the training was collected using attendance sheets. Adoption was calculated by taking the number of interventionists who attended the training sessions (numerator), compared to the total number of individuals who were eligible to attend the training sessions (denominator).

## Physical activity counseling forms

Physiotherapists completed a standardized PA counseling/referral form to document the use of the

TABLE 3 Interventionist interview categories and illustrative quotes.

| RE-AIM domain | Interview prompt | Category | Example quotes |
|---|---|---|---|
| Effectiveness | Do you perceive that your clients are seeing benefits from physical activity counseling (using the Proactive toolkit)? In other words, is it being used or understood? Why or why not? | Patients are understanding the benefits of PA and PA counseling | *"Yeah, I think the majority of clients if the conversation is had you know, in the right way I think they see the value in it. I think a lot of them feel overwhelmed, about going home and having to do this on their own. But I think making that plan and having the conversation is, is a great way to sort of try and overcome that."*<br>*-Sharon (physiotherapist)* |
| Implementation | How feasible has it been to refer patients to SCI BC? Should there be a more formal referral process to SCI BC? What should that look like? | Emailing or dropping off a physical copy of the PA counseling form to the SCI peer office on site was perceived as a feasible referral process | *"I think it's been great and should be easy to start. I just scan the form and I can email it through and it's the easiest thing in the world to do. I don't find the conversation that time consuming and I can just have it bit by bit with people. I think it's, it's a very easy process."*<br>*-Harry (physiotherapist)* |
| | What are your thoughts on the timing of using the toolkit with your clients (before in-patient discharge or during outpatient physiotherapy)? | Patients have unique needs and optimal times to deliver PA counseling; it's important to at least start the conversation | *"A lot of them are not ready. Lots of them are. You, at least have the conversation, like, do you want to have this conversation. Are you ready for this? And for someone that's just absolutely not. For other ones, it's like, start the conversation, it makes them super anxious and that's not great. And other ones it's like yeah, I'm not really sure but like maybe I would do this."*<br>*-David (physiotherapist)* |
| | Apart from training sessions and COP meetings, were there any impacts on your time beyond your usual practice before the implementation? | Implementing PA conversations did not impact time beyond usual practice | *"I would say, it slots in very well into what we do here, you know, it's a quick conversation to have with the client and it's not a large amount of time to put aside for them to do the plan, we would always do a home exercise program anyway on discharge so any, you know, documentation like a, you know, exercise plan sheet with, you know, drawings and instructions of physical activity would always happen anyways I think it just complements the process quite well."*<br>*-Candice (physiotherapist)* |
| | Has the use of the toolkit changed your discharge planning and how? | No change to discharge planning, but increased use of the SCI PA guidelines | *"It's changed that about physical activity after discharge. Beyond providing the client with some research in the context of, you know, this is how much physical activity as a minimum and then you can progress to this, having that on the form, you know the 20 min, you know, two times a week of moderate time to high intensity exercise, that particular part of evidence backing up what we are saying is quite helpful."*<br>*-David (physiotherapist)* |
| Maintenance | Do you foresee any issues with the uptake of this intervention in other rehab centers? | Resource accessibility and interventionist adoption may be prospective barriers to the expansion of the ProACTIVE SCI intervention to other rehabilitation centers | *"No, just the resource to be the thing. I think just access to resources would be the biggest thing. We have [accessible gym], which is a good resource for us here. I don't think that every rehab center in Canada has access, close access, for clients to an accessible gym."*<br>*-Julia (physiotherapist)* |

*(Continued)*

TABLE 3 (Continued)

| RE-AIM domain | Interview prompt | Category | Example quotes |
|---|---|---|---|
| | | | *"You know I'd say the problem would be just the implementation, you just have to a) talk to the physios, and then b) find out if they had buy in. If they had buy in for the importance of it. Then, then kind of, but you wouldn't target that many people right so the problem is if you only have a few spinal cord injury patients that pop up in [Health Authority] once in a while. Having a physical activity conversation will get forgotten."* <br> *-Cameron (physiotherapist)* |
| | | Potential to use the PA counseling forms with other populations | *"You know I think in other rehab centers it would be nice to not just have you know a SCI physical activity form. That it would just be for all of our clients. You know what I mean. So, I think that there's research, they're looking at this for amputees for example, it would just be nice to have it for across the board because, looking at that form, it could be for my patients with amputations, my patients who have rheumatoid arthritis or any kind of neuromuscular disease transfers, there's so many, you know, I think if you want it to be applied to a variety of rehab centers."* <br> *-Emily (physiotherapist)* |
| | If you had the resources to continue sustaining the intervention, what do you feel are the key components that should be kept? | Physical activity counseling form, refresher meetings and ongoing practice sessions are essential implementation intervention components needed to sustain PA counseling delivery | *"I like the idea of having periodic meetings I can't remember what we call them, but we have meetings lunch meetings where [team member] comes in and sort of gives people a little bit of a refresher on the conversation."* <br> *-Julia (physiotherapist)* <br> *"I think just the practice is helpful like what we'll do on the 24th similar to last time, because yeah, all the things we've done the number one thing with the team liked was actually sitting down and trying to do the coaching."* <br> *-Rebecca (SCI peer coach)* <br> *"I like the sheet or like just a framework of clients verbalizing what their expectations are and intentions are and what they are planning I think it's a good conversation, and so having the sheets or like a framework to go through is valuable. Just so you have what's in your mind and verbalize it and write it down. So, it's a bit more of kind of really flushing out what someone's plan is afterwards, and they can get a better understanding of it. There is value in that."* <br> *-Sharon (physiotherapist)* |

Pseudonyms were used as place holders for participant names.

ProACTIVE SCI intervention components (i.e., discuss current PA levels, goal setting, PA preferences, resources, barriers, and conduct problem-solving and action planning) with patients prior to discharge. SCI peer coaches completed a similar counseling form when conducting PA counseling in the community.

Intervention fidelity (within the *implementation* domain) was assessed by reviewing the use of the initial intake session forms

TABLE 4 Physical activity counseling forms: intervention component use frequencies.

| Form component | Frequency of component usage by physiotherapists | Frequency of component usage by SCI peer coaches during first counseling session |
|---|---|---|
| Are you interested in being more physically active? | 100% | 95% |
| What are your goals? | 100% | 100% |
| What are you currently doing for physical activity? | 30.9% | 100% |
| Benefits of physical activity | 8.5% | N/A |
| SCI physical activity guidelines | 0% | N/A |
| What types of activity do you enjoy/are you interested in doing? | 91.5% | 88% |
| What resources do you have available to you? | 95.8% | 96% |
| Things that could get in the way (barriers) of your goals? | 90.1% | 100% |
| Your plan/timetable | 81.7% | 90% |

A total of 71 PA counseling forms were completed by the Physiotherapists. A total 28 PA counseling forms were completed by SCI peer coaches during their initial exercise counseling sessions with patients. N/A, not applicable.

for both physiotherapists and SCI peer coaches. Each section of the form was marked as "yes" if used, and "no" if left blank. Intervention fidelity was calculated by dividing the summed number of form components completed across the forms (as indicated by "yes") completed by physiotherapists and SCI peer coaches separately, divided by the total number of times these components could have been used. The higher the completion score (0–100%), the greater the fidelity of delivery. Follow-up SCI peer coach PA counseling forms were evaluated as described above but were also summarized for each follow-up session timepoint.

## Sample size

Given the pragmatic nature of the study, we aimed to recruit all eligible physiotherapists ($n$ = 13) and SCI peer coaches ($n$ = 2). Of note, the SCI peer coaches participating in the study had their regular duties shifted to participate in this role. This limited the recruitment of SCI peer coaches to what was feasible for the organization.

# Results

## Client discharge summaries

Reach percentages were calculated at the patient level (Table 2). One-hundred and forty-one patients were admitted to the rehabilitation hospital with a SCI during the time of recruitment for the study. Of these, 24 patients did not have a PA conversation due to extenuating circumstances, 42 had a partial PA conversation, and 74 of these patients had a full PA conversation with their physiotherapist. Of these 74 conversations, 28 patients consented to participate in the study and receive further PA counseling.

## Semi-structured interviews

Analysis of semi-structured interviews resulted in identifying categories within the RE-AIM domains of effectiveness, implementation, and maintenance (Table 3). For effectiveness, both physiotherapists and SCI peer coaches perceived that their patients understood the benefits of PA and receiving PA counseling, as they observed that the information being delivered was effectively used and comprehended by the patients. Four categories were identified related to implementation: (1) physiotherapists found the referral process to the SCI peer organization to be feasible; (2) interventionists identified that there was no single best timepoint for intervening and was instead dependent upon the individual, (3) implementing PA conversations was time efficient for physiotherapists and did not impact their time beyond usual practice; and (4) conducting PA counseling did not change the process of discharge planning for patients, but led to an increase in the use of the SCI PA guidelines by physiotherapists. Three categories were identified within maintenance: (1) resource accessibility and interventionist buy-in are potential barriers to expanding the ProACTIVE SCI intervention to other rehabilitation centers; (2) interventionists anticipated the potential for PA counseling forms to be used among diverse populations beyond SCI; (3) physical activity counseling forms, refresher meetings and ongoing practice sessions are essential implementation intervention components needed to sustain PA counseling delivery.

## Training attendance sheets

All practicing physiotherapists in the relevant units at the rehabilitation hospital who were eligible for the training attended the initial ProACTIVE SCI training session in March, 2020. Eighty-five percent of the attendees of the first training session attended the second session. Further, 77% of these physiotherapists attended the refresher training in November 2020. All of the designated SCI BC peer coaches received the ProACTIVE training and attended all training sessions.

### Physical activity counseling forms

Physiotherapists PA referral/counseling forms showed that the most frequently used components of the forms included: whether the patient was interested in discussing PA, goal setting, activity preferences, resources available, potential barriers, and action planning (Table 4). The least used components of these forms were discussing the benefits of PA, current PA levels, and the SCI PA guidelines (Table 4). PA counseling forms, completed by SCI peer coaches, showed that all sections of the forms were used by peer coaches during initial counseling sessions, but the use of these components decreased over time (Figure 1). Specifically, peer coaches consistently discussed patients' PA and goal setting/action planning across all sessions. Discussing barriers to being active was consistently used during sessions 1–5, and slowly decreased in use for the remaining sessions (i.e., sessions 6–10). Lastly, developing a plan/solution for being active dropped substantially in use between the first and second session, and was only occasionally used (i.e., <30% of the time) beyond the third session. Further, this section was not used at all beyond the seventh follow-up session for any patient.

## Discussion

This study aimed to evaluate the reach, effectiveness, adoption, implementation, and maintenance of an evidence-based PA intervention for people with SCI that was delivered by physiotherapists and SCI peer coaches during the transition from rehabilitation to community. Results showed that the ProACTIVE SCI intervention reached the majority of patients who were admitted to the rehabilitation hospital, suggesting successful adaptation for use during this transitional period. Implementation was supported by high fidelity to the PA counseling intervention components and interview findings suggest the feasibility of the intervention with respect to minimal impacts on time beyond usual practice or discharge planning. Further, the coordination of program delivery between physiotherapists and SCI peer coaches was deemed feasible. This coordinated referral approach along with core intervention components such as ongoing training with opportunities for practice and a PA counseling form is suggested to be integral to the long-term maintenance of the ProACTIVE SCI intervention. While these finding are context-specific, we suggest strategies for future sites to adopt the ProACTIVE SCI at this critically understudied timepoint. More broadly, findings can support the integration of a clinician to peer mentor/coach referral system that links clients from rehabilitation to community in rehabilitation institutes across Canada.

### Reach

This intervention reached 82% of patients admitted to the participating rehabilitation hospital. This is in line with previous research examining the delivery of PA counseling interventions to the general population who were using primary care clinics, which found that 77% of patients were reached by the program (12). The high level of reach in the current study could be due to the ease with which patients could receive this program. PA counseling was integrated into the standard of care patients would receive from their physiotherapist by adding a prompt to their existing patient-oriented discharge summaries. Semi-structured interviews with physiotherapists highlighted that integrating PA counseling conversations was time efficient and naturally fit into the scope of their practice, further supporting the high level of patient reach. However, the initial reach of the program did not directly translate to participating in continued PA counseling in the community program. Specifically, less than half of the patients who received a PA counseling session from their physiotherapist consented to participate in the full intervention (i.e., continue the PA counseling in the community). As mentioned, the time following discharge can be an overwhelming readjustment leading to decreases in PA (1). PA often does not take priority after rehabilitation with competing concerns like housing, accessibility, family, and financial considerations (20). Further, individuals with SCI often face barriers like lack of time, energy, and motivation to be physically active post-injury, making it especially challenging to participate in PA (21). While the intervention reach to patients was high in-hospital, it is possible that not all patients are ready to prioritize PA during the transition to community and further examination is warranted to better support this transition (6).

### Effectiveness

Interviews revealed that both physiotherapists and SCI peer coaches held positive attitudes toward the intervention and highlighted positive perceived benefits for patients participating in PA counseling, including increased planning for PA and increased awareness for managing PA barriers. Theories of behavior change have previously supported the link between attitudes and intention formation, and later behavioral enactment (e.g., Theory of Planned Behavior and the Health Action Process Approach) (22, 23). Interventionists held positive attitudes toward the intervention, which may have contributed to the improved counseling behaviors over time (Shu et al., *under review*). The importance of attitudes in predicting counseling behaviors has been previously supported. Results of a study that investigated the voluntary delivery of HIV counseling among schoolteachers using the theory of planned behavior showed that intention to deliver this counseling was significantly predicted by attitudes toward the intervention (24).

### Adoption

The ProACTIVE SCI intervention was successfully adopted by all physiotherapists at the rehabilitation hospital and all eligible SCI peer coaches. We used an integrated knowledge translation (IKT) approach whereby physiotherapists and people with SCI were involved in the development, delivery and analysis of the research. This allowed for evidence from both research and practice contexts to bi-directionally inform intervention decision-making, and is consistent with the IKT Guiding Principles for

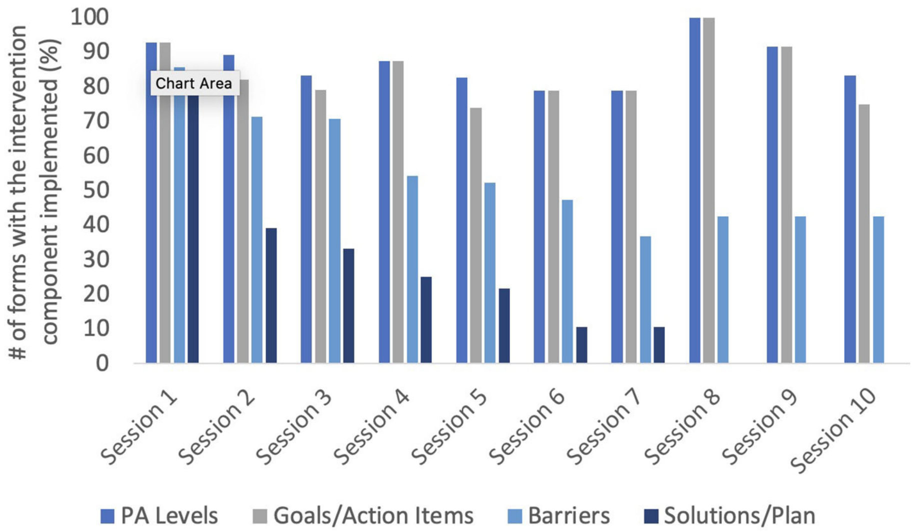


FIGURE 1
Frequency of PA counseling behaviors delivered by SCI peer coaches during follow-up counseling sessions over time. Not all patients elected to receive all 10 offered sessions (4 patients attended 2 sessions; 1 patient attended 4 sessions; 4 patients attended 5 sessions; 3 patients attended 7 sessions; and 12 patients attended all sessions). Further, 4 patients withdrew from the study after their second counseling session. Therefore, values are reported as percentages relative to the number of patients who attended the session.

conducting SCI research in partnership (25). Interventions that are designed and implemented together with stakeholders are often more likely to be adopted within existing delivery systems (26). For example, an effectiveness-implementation trial compared the adoption of physical activity programs that were iteratively and interactively developed with stakeholders to programs that were unidirectionally disseminated (26). Comparison of the two program design types demonstrated that the two designs showed similar effects on PA behavior, however, programs that involved end-users in development reported significantly greater adoption rates, intentions to sustain program delivery, and participant reach. Organizations wanting to increase adoption rates and potentially support implementation sustainability should seek to meaningfully engage delivering partners as best practice when designing and implementing programs.

## Implementation

When designing clinical interventions, interventionists need to be able to implement these programs into their standard-of-care practice. In the current study, PA counseling was incorporated into typical patient discharge planning, which resultantly had minimal impact on time beyond usual workload. Incorporating non-treatment PA advice during normal consultations has previously shown to be perceived as more feasible than creating a separate PA counseling session (9).

Beyond incorporating the PA counseling conversation into their regular discharge planning, use of PA counseling forms and referral to SCI peer coaches to continue PA counseling post-discharge were critical aspects of the successful intervention implementation. As highlighted in the interviews, physiotherapists found the structure provided by the counseling forms to be helpful in providing a framework when delivering PA counseling (supported by the high fidelity to the core components outlined in the forms), but also offered flexibility to tailor their delivery to the individual. Transferability of interventions to new contexts is often uncertain, and interventions need to be adapted to be successful and effective (27). A systematic review of the adaptation of programs implemented in community settings found the most common intervention adaptations were adding or removing elements to tailor the program to each individual (28). Similarly, SCI peer coaches delivered PA counseling in the community with high fidelity. However, follow-up counseling sessions often employed fewer components of these forms over time as needed. For example, discussing barriers to PA and providing solutions to these barriers was used less frequently in the later counseling sessions. This is unsurprising, as over time, patients likely needed less problem solving as barriers typically are addressed in the earlier counseling sessions. These findings are in line with a previous examination of the behavior change techniques employed using the ProACTIVE intervention in the research setting, where the time spent delivering behavior change techniques related to goals and planning decreased in the follow-up sessions as compared to the initial session (29).

## Maintenance

Interventionists perceived the intervention could be used in other sites as well as among other populations with disability. However, they noted the primary barriers to scaling this intervention to other centers included access to facilities designed to promote accessible PA and interventionist buy-in. Options for PA may be unusable by some clients with SCI due to lack of transportation, building/facility access, inclusiveness amongst programs, or knowledge of staff, as examples (30, 31). With respect to interventionist buy-in, interventionists voiced that maintaining PA counseling as a priority is challenging, though ongoing trainings may help address this challenge. Professionals who are committed to ongoing learning and training have previously been shown to be more effective teachers, and those resistant to receiving training show low levels of program implementation (32). Lastly, while not examined in this study, interventionists foresaw the opportunity for the ProACTIVE SCI intervention to be adapted for use among other populations. Use of physical activity counseling in clinical settings is well-studied among other populations (33–35). However, examination of coordinated referral to peer services from rehabilitation is limited and warrants further study in other clinical populations.

## Strengths and limitations

To our knowledge, this is the first study to examine coordinated PA counseling between physiotherapists and SCI peer coaches at the point of hospital discharge. In Canada, each province has an equivalent SCI advocacy organization. These findings may support the case for modeling this coordinated referral process across the country. Another strength of this work is the integrated knowledge translation approach. Representatives from all involved parties were involved in decision-making from the point of research question inception through to implementation. The importance of this collaborative approach is highlighted by the sustained use of this intervention beyond the project lifecycle as both the rehabilitation hospital and provincial SCI organization have adopted this intervention into standard practice.

As limitations, due to restrictions during the COVID-19 pandemic, any new staff hired onto the spine unit at the rehabilitation hospital were not trained to deliver the ProACTIVE SCI intervention. This may have led to fewer patients having PA counseling conversations and subsequently being referred to SCI peer counseling. Despite a break in the study, the majority of patients did receive PA counseling as reflected in the high reach levels observed in this study. Another limitation was in interpreting the fidelity to the intervention by examining use of the PA forms. Analysis of these forms revealed infrequent discussion of the benefits of PA or the SCI PA guidelines. As these sections were summarized in a diagram, there was no text required to record whether these sections were discussed within the referral form. Other form components (e.g., goal setting) require a text entry from the provider. Therefore these sections may have been delivered to patients, but were undocumented. Lastly, reach data was collected by champions who would periodically review client discharge summaries with the group of physiotherapists to report whether they delivered the ProACTIVE SCI intervention with each patient. It is possible that social pressures may have influenced the reporting or even acted as an intervention component (e.g., social influences) itself. Lastly, the intervention was delivered by only two SCI peer coaches. Since completing the study, additional SCI peer coaches have been trained and it would be valuable to examine the implementation and effectiveness of this interventions amongst a greater diversity of SCI peer coaches.

In conclusion, this study demonstrated that the ProACTIVE SCI Toolkit can be adapted for use by physiotherapists and SCI peer coaches during the transition from rehabilitation to community, a critical and understudied timepoint for PA intervention. Findings are important for informing intervention sustainability and scale-up to other institutions and interventions. Future studies should continue to monitor program maintenance of the ProACTIVE SCI intervention beyond the 6-month period.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Behavioral Research Ethics Board at the University of British Columbia (H19-02694). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

KO: Writing—original draft, Conceptualization, Formal analysis, Writing—review & editing. KM: Conceptualization, Writing—review & editing, Funding acquisition, Methodology, Supervision. SL: Writing—review & editing, Formal analysis, Methodology. CM: Writing—review & editing, Conceptualization, Funding acquisition. KW: Writing—review & editing, Conceptualization, Funding acquisition, Project administration. CL: Writing—review & editing, Conceptualization, Funding acquisition, Methodology, Resources. RCo: Writing—review & editing, Conceptualization. TP: Writing—review & editing, Conceptualization. AB: Writing—review & editing, Conceptualization. TT: Writing—review & editing, Conceptualization, Project administration. RCl: Writing—review & editing, Conceptualization, Project administration. RB: Writing—review & editing, Conceptualization, Project administration. JM: Writing—review & editing, Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Enabling knowledge translation: implementation of a web-based tool for independent walking prediction after traumatic spinal cord injury

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**Introduction:** Several clinical prediction rules (CPRs) have been published, but few are easily accessible or convenient for clinicians to use in practice. We aimed to develop, implement, and describe the process of building a web-based CPR for predicting independent walking 1-year after a traumatic spinal cord injury (TSCI).

**Methods:** Using the published and validated CPR, a front-end web application called "Ambulation" was built using HyperText Markup Language (HTML), Cascading Style Sheets (CSS), and JavaScript. A survey was created using QualtricsXM Software to gather insights on the application's usability and user experience. Website activity was monitored using Google Analytics. Ambulation was developed with a core team of seven clinicians and researchers. To refine the app's content, website design, and utility, 20 professionals from different disciplines, including persons with lived experience, were consulted.

**Results:** After 11 revisions, Ambulation was uploaded onto a unique web domain and launched (www.ambulation.ca) as a pilot with 30 clinicians (surgeons, physiatrists, and physiotherapists). The website consists of five web pages: Home, Calculation, Team, Contact, and Privacy Policy. Responses from the user survey ($n = 6$) were positive and provided insight into the usability of the tool and its clinical utility (e.g., helpful in discharge planning and rehabilitation), and the overall face validity of the CPR. Since its public release on February 7, 2022, to February 28, 2023, Ambulation had 594 total users, 565 (95.1%) new users, 26 (4.4%) returning users, 363 (61.1%) engaged sessions (i.e., the number of sessions that lasted 10 seconds/longer, had one/more conversion events e.g., performing the calculation, or two/more page or screen views), and the majority of the users originating from the United States (39.9%) and Canada (38.2%).

**Discussion:** Ambulation is a CPR for predicting independent walking 1-year after TSCI and it can assist frontline clinicians with clinical decision-making (e.g., time to surgery or rehabilitation plan), patient education and goal setting soon after injury. This tool is an example of adapting a validated CPR for independent walking into an easily accessible and usable web-based tool for use in clinical practice. This study may help inform how other CPRs can be adopted into clinical practice.

KEYWORDS

**clinical prediction rule, knowledge translation, prognosis, risk calculator, spinal cord injury, web-based tool**

## Introduction

Accurate prognostication, defined as the probability of a person developing a particular state of health or outcome over a specific time (1), can enable clinicians to provide appropriate advice and initiate timely patient-centered management and rehabilitation strategies (2, 3). For spinal cord injury (SCI) this is an active area of research (4–6), that can provide crucial evidence to inform the translation of biomedical and health-related research into better patient outcomes (7).

Prognostic studies can be categorized into four distinct but interrelated themes: fundamental prognosis research, prognostic factor research, prognostic model research, and stratified medicine research (7). In prognostic model research, multiple variables ("predictors") to estimate a patient's prognosis are considered (1). The result is a prognostic model, also known as a clinical prediction rule (CPR), that combines influential variables to predict the risk of future clinical outcomes in patients, and can be used in various settings for clinical, research and health systems planning applications (1).

Despite the proliferation of CPRs in medical literature, their implementation into clinical practice is limited (8). In general, research suggests that only a small minority of published evidence is translated into clinical practice, and this change occurs slowly over nearly two decades (9). There is a wealth of literature describing potential barriers to account for this, including lack of time, skills, and institutional support to implement clinical practice guidelines (10, 11). Barriers specific to the clinical use of CPRs have recently been discussed in the SCI literature (4). Khan et al. suggested that novel CPRs presented in publications need to be made for accessible to end-users (4). This discrepancy between knowledge creation and knowledge application can be framed as an issue with knowledge translation (KT). KT is a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge, and an approach focusing on closing the gaps between knowledge and practice (12, 13). KT supports moving beyond the dissemination of knowledge (i.e., conducting and publishing prognostic model research) and into the actual use of the knowledge (i.e., the adoption and application of CPRs in the clinical setting). Although the field of KT in SCI is in its early stages, initial evidence supports that KT interventions may change clinician behavior and, ultimately, improve patient outcomes (14). For example, with prognosis research, better translation of published CPRs into clinical practice could guide the clinicians' discussions with patients using reliable evidence-based estimates on the course of their condition. This could help address the variability in information provided by spine surgeons to patients, and the resultant uncertainty in patient expectations regarding outcomes (15).

Examples of non-SCI CPRs that have been successfully adopted into clinical settings include: the Nottingham Prognostic Index for the management of breast cancers (16), Framingham Risk Score for estimating the 10-year Cardiovascular Disease Risk (17), and CHADS (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, and stroke) score to calculate a patient's risk of having a stroke secondary to atrial fibrillation (18). Reasons for the successful implementation of these CPRs into clinical practice are likely multifactorial, including support from leading professionals in the field and the urgency of the clinical need being addressed; however, these examples also support the notion that CPRs that are easy-to-use are more readily incorporated into clinical practice.

How a CPR is used by its end-users (e.g., clinicians, patients, or researchers) is shaped by its presentation format (19). Various model formats exist for CPRs, including regression formulas, nomograms, score charts, and web-based formats, but there is no consensus on the preference of certain formats over others for optimal communication and use (19). A recent trend toward CPRs being presented as web-based calculators has been noted (20), and several online medical calculators exist, such as MDCalc Medical Calculator (https://www.mdcalc.com). MDCalc offers healthcare professionals with a broad range of clinical tools to support decision-making. The calculators are designed in a practical, easy-to-use format that provide concise, targeted, expert-written content. Thus, in anticipation of the ongoing digitalization in healthcare (21), e.g., with electronic decision support systems and electronic medical records (EMRs), such web-based formats could promote the transportability of CPRs (e.g., by integrating with existing hospital systems) and enable the easy availability of predictions at the point-of-care. Further, our groups' experience in developing and validating the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) Algorithm (https://www.isncscialgorithm.com), supports the use of web-based platforms in SCI clinical practice. The ISNCSCI Algorithm (22), developed by the Praxis Spinal Cord Institute in collaboration with the International Spinal Cord Society (ISCoS), is a free, user-friendly, computerized application designed to convert raw ISNCSCI test scores into accurate classification scores for the SCI now using the revised 2019 ISNCSCI scoring rules. The Algorithm was developed to reduce the high error rates in ISNCSCI exam classification, thus supporting SCI education, research and clinical care (23).

The development and validation of CPRs are only the first steps in KT process. For CPRs to be successfully translated into clinical practice and inform decision-making, they need to be available in a format that can be easily adopted by their end-users. For SCI, given that mobility after injury has been cited by patients as one of their top functional recovery priorities (24), a number of studies have published CPRs for the prediction of independent walking ability after injury (25–29). However, to our knowledge, none are in an easy-to-use format to support adoption into clinical practice. In this study, we aimed to develop a web-based calculator, called Ambulation, using the simplified CPR for prognosticating independent walking after traumatic SCI (TSCI) developed by Hicks et al. (25). The specific objectives were to (1) design and develop the web-based calculator, (2) test and pilot Ambulation with a small group of users, and (3) summarize the feedback from the user-survey and website analytics data. Findings from this study may assist others in the development of novel web-based tools for SCI, incorporating additional research findings in SCI CPRs to make them more accessible and useful for clinicians and patients.

## Materials and methods

In alignment with an integrated KT approach (30), Ambulation was designed to bridge the KT gap, taking a validated CPR for independent walking prediction and transforming it into a user-friendly clinical tool. The following sections describe the steps involved in Ambulation's website design, development, implementation, and monitoring process:

- Planning.
- Design and development.
- Delivery.
- Dissemination.
- Maintenance.

## Planning

Ambulation was co-designed with potential end-users to ensure engagement and adoption with the target audience from the start. In total, a core team of seven clinicians and researchers, and 20 other professionals from different disciplines were consulted. This included, persons with lived experience of SCI, communications and marketing professionals, web developers and IT technicians, as well as a privacy lawyer.

## Design and development

We first considered the operating system, supporting software, and hardware available for the targeted primary end-users (i.e., healthcare professionals such as spine surgeons and allied health professionals treating patients with SCI). Because these end-users would typically have access to a computer or smartphone with internet access (e.g., in the physician's office or at the bedside), Ambulation was implemented to operate on a web browser as a front-end web application.

Initially Ambulation was conceptualized as a one-page website. However, to enhance the user experience, the calculator and other supporting information were designed to be divided across the website as individual pages. The graphical user interface for Ambulation was designed to include five pages, each with a simple layout, consisting of a manageable number of actions, and targeting a specific function. These were the Home, Calculation, Team, Contact, and Privacy Policy page. The Home page and Calculation pages included all the essential information and functionality needed to use the calculator for its intended purpose, i.e., inputting patient data to receive a predicted probability based on the CPR. The Privacy Policy, the Team, and the Contact Us pages contained additional information. Where appropriate, pop-up pages would be included to add additional information that the team deemed was important for the user to read before proceeding further. For example, to ensure that the information generated on Ambulation was appropriately used, a pop-up "User Agreement, Disclaimer, and Consent" was included before the user could access the Calculation page. In this pop-up, users would be informed of the calculator's intended purpose and limitations (i.e., advised that the website is only intended to be used as a tool to assist clinicians in understanding how certain clinical variables relate to walking outcome after TSCI).

We developed Ambulation using HyperText Markup Language (HTML; a markup language), Cascading Style Sheets (CSS; a design language), and JavaScript (a programming language). Together, these three foundational tools in web development enabled the formatting, design, and programming of a lightweight front-end web application. We supplemented this with Bootstrap, a free and open-source CSS framework, to ensure a uniform appearance for prose, tables, and form elements across web browsers (e.g., Chrome, Safari, Internet Explorer, Firefox or Edge). As the calculations to be performed on Ambulation (i.e., the predictions provided by the CPR) are entirely reliant on user input, there was no need to develop a backend with a supporting database which would use more sophisticated web development frameworks. This also ensures that any data entered would not be stored or subject to privacy laws.

When implementing the calculation that would enable the user to estimate the probability of walking independently one-year after TSCI, the mathematical equations from the regression model published in Hicks et al. (25) were extracted. Using this CPR, the end-user entered three patient data points: age (dichotomized at the 65-year-old threshold), highest (left or right) ISNCSCI motor score of the L3 myotome (quadriceps femoris muscle), and highest (left or right) ISNCSCI light touch sensory score of the S1 dermatome completed within 15 days of TSCI (31). The calculation is based on the weighted coefficients to generate a total score (range: −10 to 20). The total score is then used in the regression formula to compute the predicted probability (range: 0 to 1).

The regression formula is as follows:

$$\frac{\exp\left(-1.763 + 0.125 \times score\right)}{1 + \exp\left(-1.763 + 0.125 \times score\right)} \quad (1)$$

where "score" is the total score. The resultant probability is communicated to the end-user, with precision to two decimal places. In addition, we applied the 0.5 cut-off value used by Hicks et al. to translate the probabilities into the functional outcome of interest. That is, if a person's probability of walking is predicted to be $\geq$0.5, then they are classified as someone likely to have walking ability; if a person's probability of walking is predicted to be $<$0.5, then they are classified as likely not to have independent walking ability (26). Both the probability (ranging from 0 to 1) and the final outcome (walk or not walk) rendered by the CPR would be communicated to the end-user (i.e., the clinician), providing flexibility to interpret the results and make optimal use of the data to inform their patients and their clinical decision making. Moreover, information about the definition of "independent walking" would be provided in the calculator's output. Independent walking ability was defined according to the Functional Independence Measure (FIM) (32), a standardized tool for measuring disability, and corresponded to a score of 6 (modified independence) or 7 (complete independence) and a mode of locomotion as walk or both walk and wheelchair (26). These details would allow the results to be interpreted in the context of the original study's definition of independent ambulation.

The calculator was tested using manually derived test cases ($n$ = 10) created for debugging purposes, i.e., a process of detecting and removing errors in software code that can cause it to behave unexpectedly or crash. If an unexpected output was observed or a revision was made for improved user experience, the code base was checked, and the identified errors or changes were fixed. The test cases were then applied again until accurate generation of all correct responses was ensured.

To supplement the Calculation page, a section with frequently asked questions was developed. These questions aimed to provide more details regarding Ambulation, including who the intended end-user is, how and when the calculator should be used, and how results should be interpreted. Moreover, other content included a cookie notification pop-up, the Privacy Policy page, the Contact Us page and the Team page.

## Delivery

We planned a pilot launch of Ambulation to gather early utilization data and feedback from targeted end-users. We implemented two systems to monitor website utilization and gather ongoing feedback. Google Analytics (GA, https://analytics.google.com/) was used to monitor real-time website utilization starting from the pilot launch (February 7, 2022). GA data included number of users, average time spent, geographic distribution, user activity trends, and application utilization metrics (clicks, desktop vs. mobile, etc.). In addition, a short user-survey was included using Qualtrics$^{XM}$ (http://www.qualtrics.com/). The survey consisted of four key questions regarding Ambulation's design, utility, and comprehensibility, as well as an open text field for any additional feedback (Supplementary Appendix 1). Upon using the calculator, users are presented with the option to provide their feedback by clicking on the survey link and consenting to the survey.

## Dissemination

For the pilot, several strategies were used to disseminate Ambulation. This included peer-to-peer outreach within existing clinical networks, direct emailing to 30 SCI clinicians, and presentations at SCI conferences i.e., the Canadian Spine Society (CSS) 2022 Annual General Meeting, the "Spinal Columns" CSS Newsletter, American Spinal Injury Association (ASIA) 2022 Annual Scientific Meeting, and GF Strong Research Day-Technology in Rehabilitation 2022.

## Maintenance

GA metrics were monitored monthly to observe trends in website utilization data and identify opportunities for quality improvement on an ongoing basis.

## Data analysis

Descriptive statistics were performed to characterize the survey responses and the GA data. Frequencies and proportions were used to analyze categorical data. Responses to open-ended questions were summarized narratively.

# Results

## Ambulation, a web-based calculator

Ambulation was designed and developed as a front-end web site that incorporated the simplified CPR for predicting independent walking ability 1-year after TSCI by Hicks et al. (25). Ambulation underwent 11 revisions to clarify communication and calculator output, improve the design, layout, and site navigation for the end-user. The final version consisted of five pages (Figures 1–5). On February 7th, 2022 Ambulation was uploaded onto its own unique domain: http://www.ambulation.ca.

A typical workflow for a user begins with the Home Page (Figure 1). Upon entering, per local and international data privacy laws, the user is informed that the website uses cookies in the form of a pop-up notification. The window appears along the bottom of the webpage without any action from the user. The user is provided with a brief description of the web-based calculator, and the option to proceed to the calculator by clicking "Continue to Calculator." Additionally, there are eight "frequently-asked-questions" displayed in a drop-down list of responses pertaining to each question. The drop-down feature was intentionally chosen to maintain simplicity and only show information that the user is actively seeking. When proceeding to the calculator, the user encounters a second pop-up with the "User Agreement, Disclaimer, and Consent" (Figure 2A). The user must read and agree to terms before proceeding. Importantly, users are advised that the website is only intended to be used as a tool to assist clinicians in understanding how certain clinical variables relate to walking outcome after TSCI. Further, non-clinician users are advised to always consult their clinician, or other healthcare provider, if they have questions or concerns regarding their health and functional recovery. The calculator requires three input variables (Figure 2B) as described previously. Additionally, on this page links to external resources, such as the ISNCSCI assessment, are provided. These were included to equip the clinician with adequate background information to perform an appropriate assessment of their patient, to ultimately increase the likelihood that accurate patient information is entered into the calculator. If the required input data were entered correctly (i.e. within a range of valid scores), clicking "calculate" will provide the results of the CPR (Figure 2C). Each input parameter has a range of valid scores that are shown to the user. If any input data was entered incorrectly, the user is notified that specific information needs to be changed (e.g., the following field is empty or invalid: motor score L3 must be $\geq$0 and $\leq$5) in order for the calculation to be performed. Users are invited to complete a feedback survey each time a calculation is performed. Other options on the calculator include "Recalculate" to update the results if input data were changed, "Clear" to reset input data, or a "Show calculation" option to display how the probability estimates from the CPR are calculated. The Privacy Policy Page (Figure 3), the Team Page (Figure 4), and the Contact Us Page (Figure 5), contain supplementary information that can be sought via links at the bottom of the webpage (Privacy Policy Page) or in the top-left corner (Team Page, Contact Us Page).

In total, 15 external links were included throughout Ambulation, providing additional guidance to the user

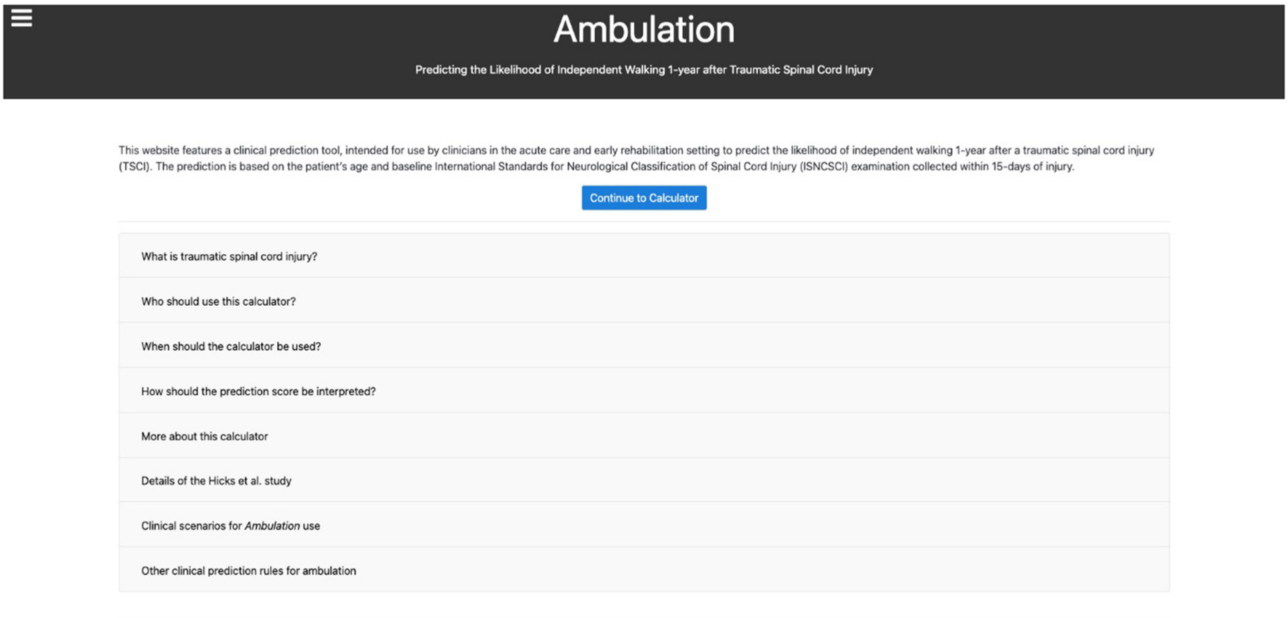



FIGURE 1
The Ambulation home page. Users are first greeted with a pop-up notification informing them that the website uses cookies and that by continuing they agree to the use of cookies outlined in the Privacy Policy. On this page, a brief description of the web-based calculator is presented, followed by eight "frequently-asked-questions" to important topics before proceeding to the Calculator Page.

regarding peer-reviewed publications related to the CPR, information about the ISNCSCI assessment required to use the calculator, or more information about the sponsoring institution (Praxis).

## Survey results

February 7th 2022, Ambulation was piloted by 30 test-users, which included spine surgeons, physiatrists and physiotherapists. Six survey responses were received (20% response rate). Based on question one, using the 5-item Likert scale, most respondents thought Ambulation was easy to navigate, use and understand (Table 1). Most respondents (66.7%) would prefer to use Ambulation on a desktop PC or MacBook, rather than using a smartphone. All six respondents said they would recommend Ambulation to others. When asked to indicate why, responses were: "*Helpful and basic*"; "*Prediction value. Easy to use*"; "*Easy to use and provides great information for discharge planning*"; "*Simple and quick*"; and "*Planning for rehab.*"

Two respondents gave additional feedback on their experience using Ambulation.

> Respondent 1: "*I think there should be clarification on the website what independent ambulation means. From my take on the Hicks paper, they used a 50 m distance with or without aids (i.e., FIM of 6 or 7), whereas Middendorp used 10 m as their distance on the SCIM. I have concerns that the individual prediction of a population may not fully represent real scenarios. The model really downgrades older people. For example, any older person with even minor spinal cord injury (e.g., grade 5 motor power and grade 1 sensation) is predicted not able to walk. I question the face validity of this.*"
>
> Respondent 2: "*I trialed this tool using a patient who is now 2 years post TSCI. I used the ISNCSCI that was completed in ICU 2 days post injury. The patients score was 35.87%. The Ambulation Tool was correct in its prediction of independent ambulation. Even after a year of outpatient physiotherapy working on the patient's goal of ambulation this individual is not an independent ambulator.*"

## Google analytics data traffic

From February 7th, 2022 to February 28th, 2023, Ambulation had 594 total users, 565 (95.1%) new users, 26 (4.4%) returning users (Table 2). These refer to unique visits and repeat visits, respectively. In addition, there were 363 (61.1%) engaged sessions (i.e., the number of sessions that lasted 10 seconds/longer, or had one/more conversion events or two/more page or screen views). In terms of engagement with different pages, 213 users visited the Ambulation home page, and 164 users visited the calculation page. For specific tracking of the "calculate" and "re-calculate" buttons, 167 and 67 users were clicking these, respectively. The "calculate" button had an average event count of 1.29 times, and the "re-calculate" button had an average event count of 2.57 times, meaning that on average these 67 users pressed "re-calculate" at least 2.5 times.

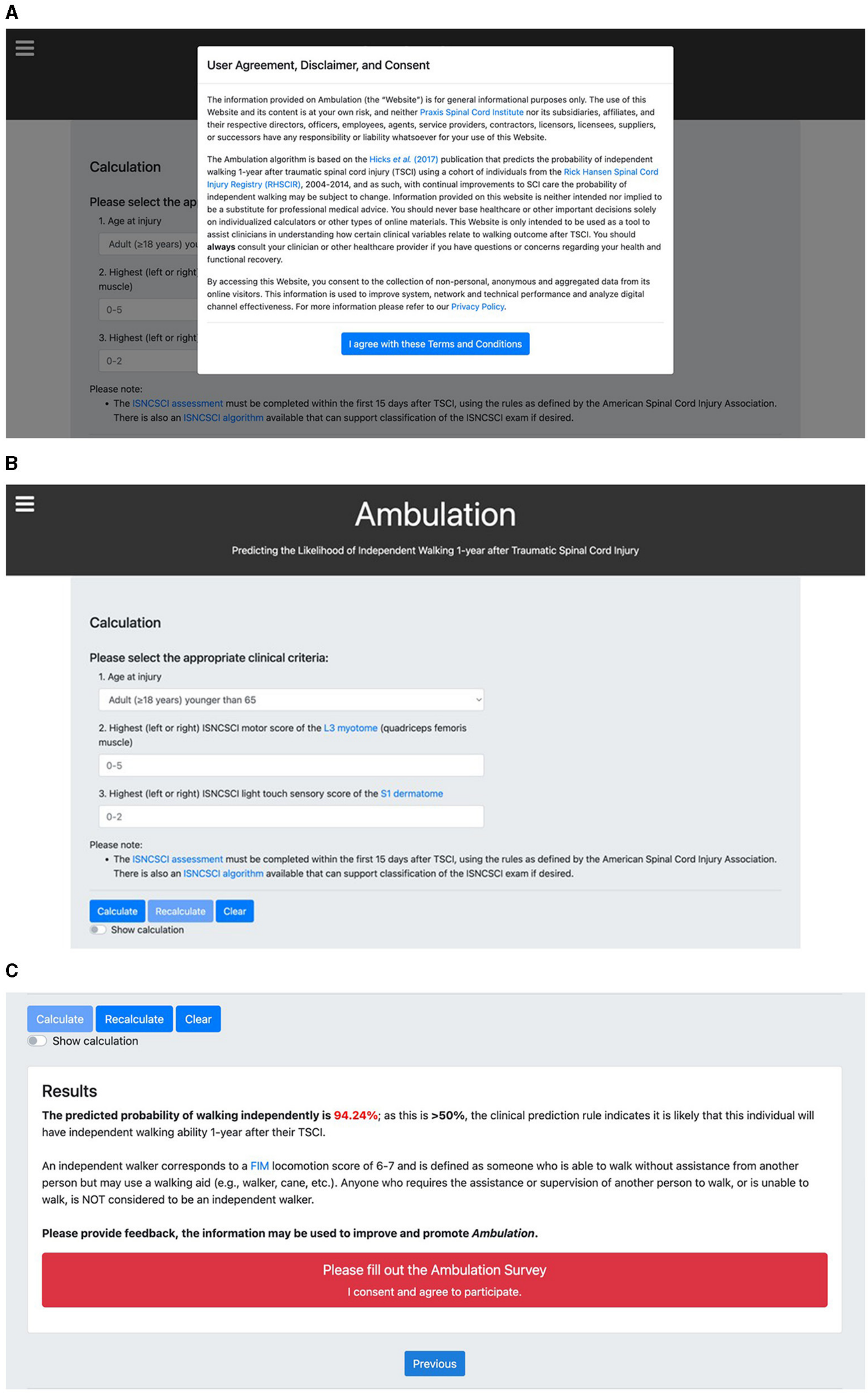
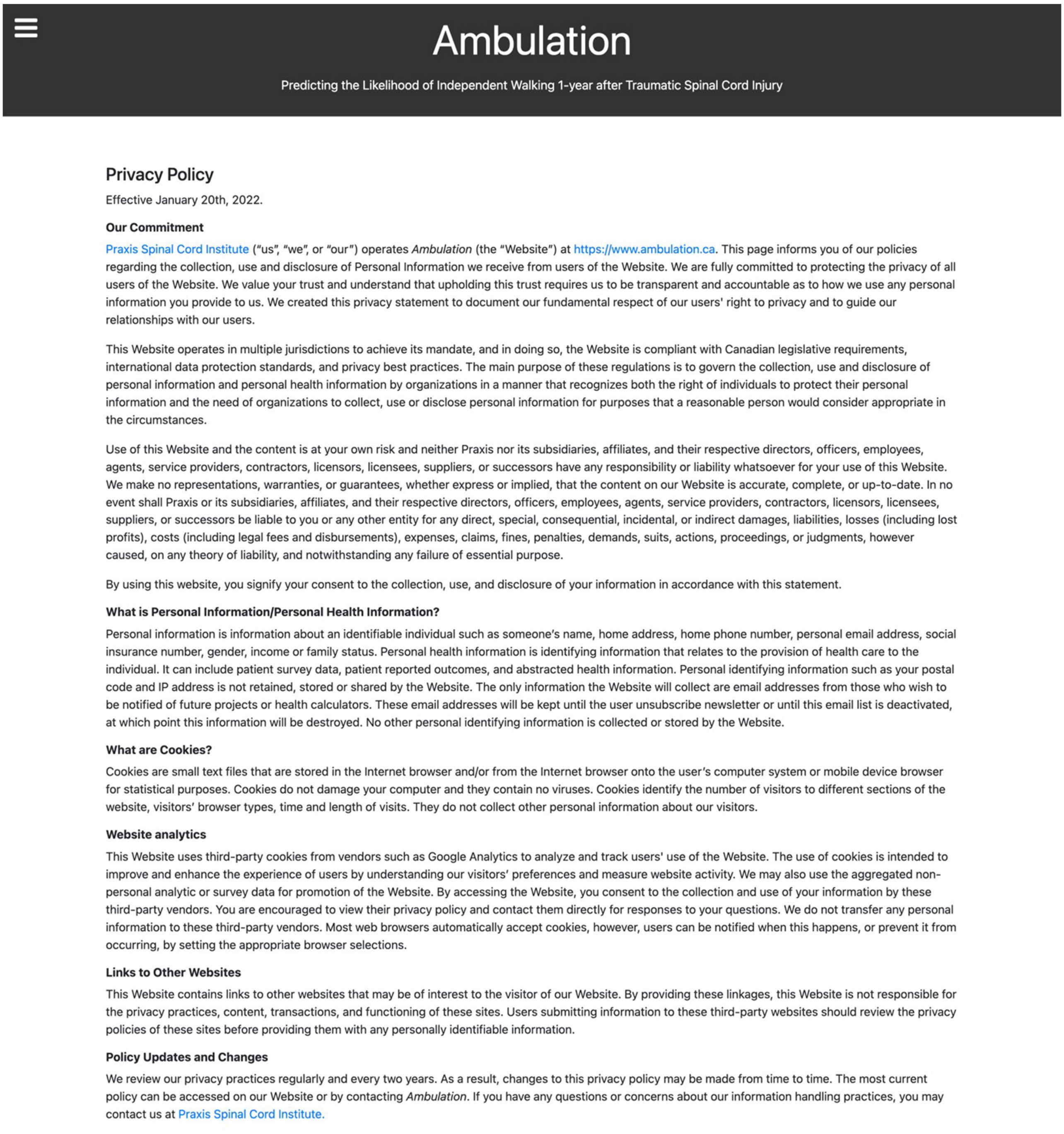



FIGURE 2
The Ambulation calculator page. **(A)** Upon entering the Calculator Page, a "User Agreement, Disclaimer and Consent" pop-up notification appears. The user must agree to terms and conditions before proceeding to the calculation. **(B)** The calculation is based on the clinical prediction rule (CPR) by Hicks et al. (25). The calculation requires the user to input three patient-related variables: age at injury dichotomized at 65 years old and two items from the ISNCSCI assessment completed within the first 15 days after TSCI. **(C)** The CPR result and interpretation are provided to the user and a link to the feedback survey on Qualtrics is presented.



# Ambulation

Predicting the Likelihood of Independent Walking 1-year after Traumatic Spinal Cord Injury

## Privacy Policy

Effective January 20th, 2022.

**Our Commitment**

Praxis Spinal Cord Institute ("us", "we", or "our") operates *Ambulation* (the "Website") at https://www.ambulation.ca. This page informs you of our policies regarding the collection, use and disclosure of Personal Information we receive from users of the Website. We are fully committed to protecting the privacy of all users of the Website. We value your trust and understand that upholding this trust requires us to be transparent and accountable as to how we use any personal information you provide to us. We created this privacy statement to document our fundamental respect of our users' right to privacy and to guide our relationships with our users.

This Website operates in multiple jurisdictions to achieve its mandate, and in doing so, the Website is compliant with Canadian legislative requirements, international data protection standards, and privacy best practices. The main purpose of these regulations is to govern the collection, use and disclosure of personal information and personal health information by organizations in a manner that recognizes both the right of individuals to protect their personal information and the need of organizations to collect, use or disclose personal information for purposes that a reasonable person would consider appropriate in the circumstances.

Use of this Website and the content is at your own risk and neither Praxis nor its subsidiaries, affiliates, and their respective directors, officers, employees, agents, service providers, contractors, licensors, licensees, suppliers, or successors have any responsibility or liability whatsoever for your use of this Website. We make no representations, warranties, or guarantees, whether express or implied, that the content on our Website is accurate, complete, or up-to-date. In no event shall Praxis or its subsidiaries, affiliates, and their respective directors, officers, employees, agents, service providers, contractors, licensors, licensees, suppliers, or successors be liable to you or any other entity for any direct, special, consequential, incidental, or indirect damages, liabilities, losses (including lost profits), costs (including legal fees and disbursements), expenses, claims, fines, penalties, demands, suits, actions, proceedings, or judgments, however caused, on any theory of liability, and notwithstanding any failure of essential purpose.

By using this website, you signify your consent to the collection, use, and disclosure of your information in accordance with this statement.

**What is Personal Information/Personal Health Information?**

Personal information is information about an identifiable individual such as someone's name, home address, home phone number, personal email address, social insurance number, gender, income or family status. Personal health information is identifying information that relates to the provision of health care to the individual. It can include patient survey data, patient reported outcomes, and abstracted health information. Personal identifying information such as your postal code and IP address is not retained, stored or shared by the Website. The only information the Website will collect are email addresses from those who wish to be notified of future projects or health calculators. These email addresses will be kept until the user unsubscribe newsletter or until this email list is deactivated, at which point this information will be destroyed. No other personal identifying information is collected or stored by the Website.

**What are Cookies?**

Cookies are small text files that are stored in the Internet browser and/or from the Internet browser onto the user's computer system or mobile device browser for statistical purposes. Cookies do not damage your computer and they contain no viruses. Cookies identify the number of visitors to different sections of the website, visitors' browser types, time and length of visits. They do not collect other personal information about our visitors.

**Website analytics**

This Website uses third-party cookies from vendors such as Google Analytics to analyze and track users' use of the Website. The use of cookies is intended to improve and enhance the experience of users by understanding our visitors' preferences and measure website activity. We may also use the aggregated non-personal analytic or survey data for promotion of the Website. By accessing the Website, you consent to the collection and use of your information by these third-party vendors. You are encouraged to view their privacy policy and contact them directly for responses to your questions. We do not transfer any personal information to these third-party vendors. Most web browsers automatically accept cookies, however, users can be notified when this happens, or prevent it from occurring, by setting the appropriate browser selections.

**Links to Other Websites**

This Website contains links to other websites that may be of interest to the visitor of our Website. By providing these linkages, this Website is not responsible for the privacy practices, content, transactions, and functioning of these sites. Users submitting information to these third-party websites should review the privacy policies of these sites before providing them with any personally identifiable information.

**Policy Updates and Changes**

We review our privacy practices regularly and every two years. As a result, changes to this privacy policy may be made from time to time. The most current policy can be accessed on our Website or by contacting *Ambulation*. If you have any questions or concerns about our information handling practices, you may contact us at Praxis Spinal Cord Institute.

FIGURE 3
The Ambulation privacy policy page. To comply with local and international data privacy laws, this page describes how the website collects, uses, and manages the personal information received from all users.

Users were primarily from the United States (236, 39.9%), Canada (226, 38.2%), and China (48, 8.1%), and were accessing Ambulation using a desktop (463, 77.9%) or mobile (130, 21.9%) device.

## Discussion

In an effort to bridge the KT gap for SCI prediction models, we implemented and designed a simple front-end website CPR for

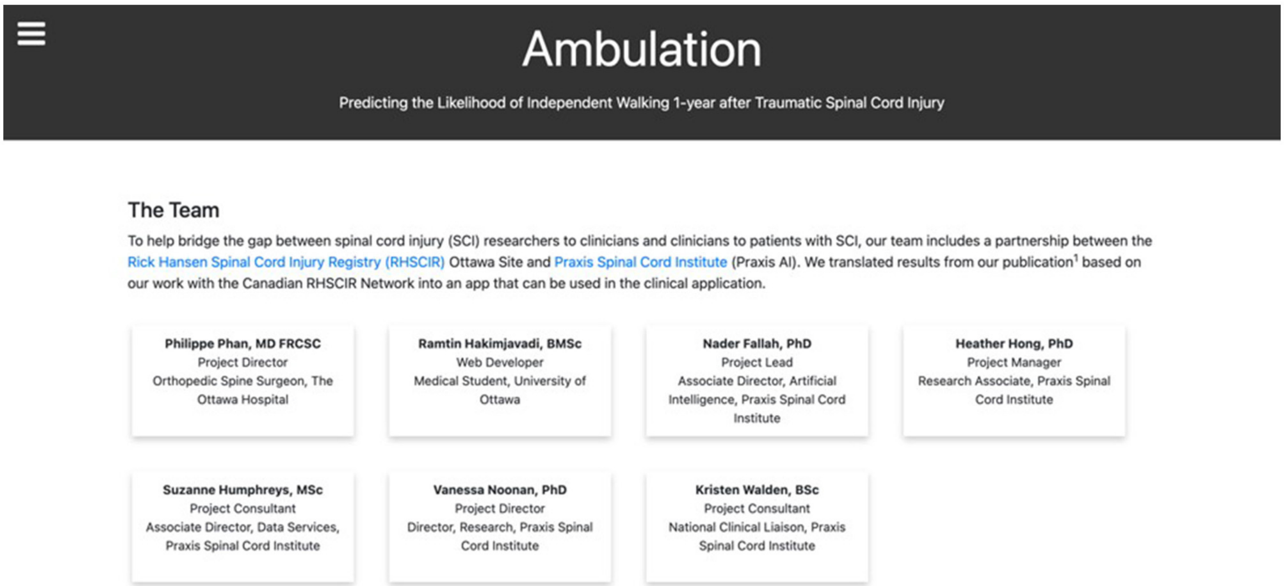



FIGURE 4
The Ambulation team page. An overview of the development team and their roles.

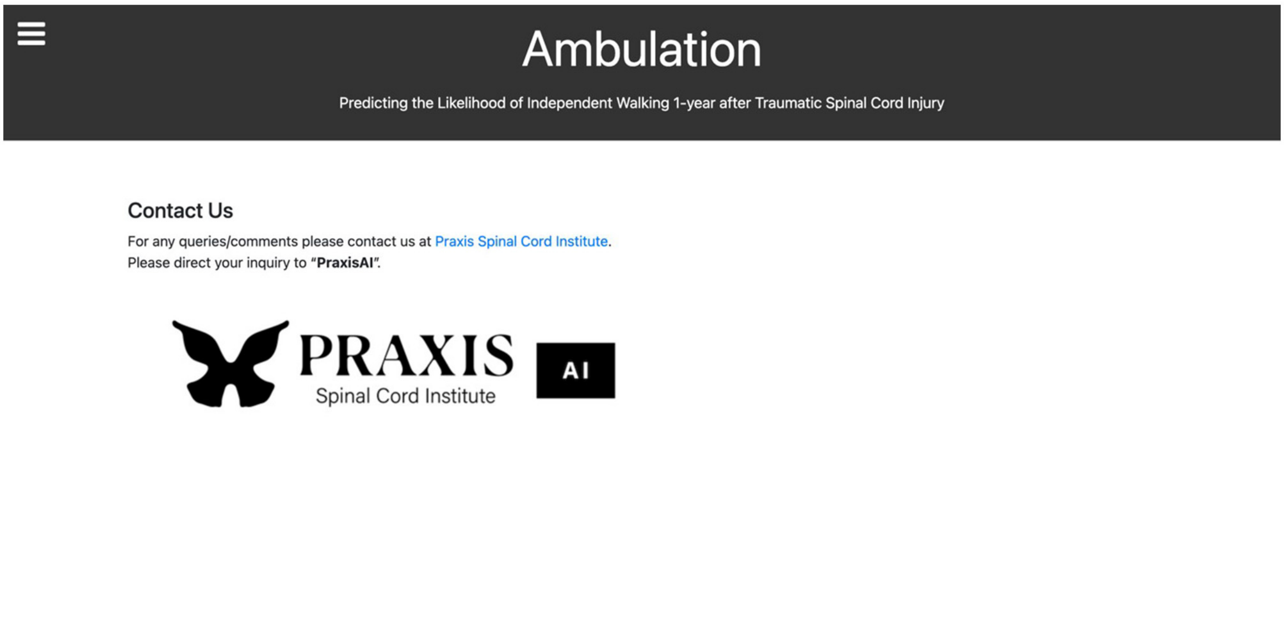



FIGURE 5
The Ambulation contact us page. For users to easily contact the Ambulation team for any comments or suggestions.

predicting independent walking ability 1-year after TSCI using the model by Hicks et al. (25). Ambulation was successfully developed, piloted, and launched. Within its first year, GA data demonstrated that Ambulation steadily gained new users over time. Peaks in new users coincided with presentations at local and international conferences. Overall, the majority of users originated from the United States and Canada. Of note, from the 234 unique users that eventually performed a calculation during the study period, 67 (28.6%) users clicked the re-calculate button on average >2.5 times (Table 2), suggesting further utility of the CPR beyond an initial calculation.

In addition to developing the CPR as an application, our experience with developing Ambulation demonstrates the importance of additional considerations when developing web-based KT tools. These include the engagement of professionals in IT, communications, marketing, privacy policy, and persons with

TABLE 1 Question 1 survey responses using the 5-item Likert scale ranging from strongly agree to strongly disagree.

| | Strongly agree | Somewhat agree | Neither agree, nor disagree | Somewhat disagree | Strongly disagree | Total |
|---|---|---|---|---|---|---|
| Ambulation's website is easy to navigate | 5 (83.3%) | 0 | 0 | 0 | 1 (16.6%) | 6 |
| Ambulation's external website links to other sources, such as the ISNCSCI 2019 publication or ISNCSCI algorithm, are helpful | 3 (60.0%) | 1 (20%) | 0 | 0 | 1 (20%) | 5 |
| Ambulation's design, layout, color and contrast are visually appealing | 3 (60.0%) | 1 (20%) | 0 | 0 | 1 (20%) | 5 |
| Ambulation, the calculation page is easy to use | 5 (83.3%) | 0 | 0 | 0 | 1 (16.6%) | 6 |
| Ambulation, the result generated is easy to understand | 4 (66.7%) | 1 (16.7%) | 0 | 0 | 1 (16.7%) | 6 |
| Ambulation is applicable for clinical use | 3 (50%) | 1 (16.7%) | 1 (16.7%) | 0 | 1 (16.7%) | 6 |
| Ambulation's prediction score for independent walking 1-year after TSCI is helpful in guiding patient management | 3 (50%) | 1 (16.7%) | 1 (16.7%) | 0 | 1 (16.7%) | 6 |

lived experience along with targeted end-users, bringing a diverse array of knowledge and skill sets to help design appropriately for users' needs; and the inclusion of additional web pages to meet privacy requirements and support end-users. We engaged end-users as active participants across the design, development, and testing phases of Ambulation through user-centered design principles (33). This helped promote the usability and applicability of the web-based calculator in the clinical setting, for example, by better understanding the technologies available to them and their clinical workflows. Moreover, it was particularly important to precisely identify and engage with the targeted end-user in developing content for each of the web pages. This was needed to effectively tailor the information provided on the website. For example, the first question on the Home Page (Figure 1), "What is traumatic spinal cord injury?", was kept brief assuming that clinicians using the website would already have some level of expertise on TSCI. Similarly, on the Calculator Page (Figure 2), resources for detailed information on how to perform the ISNCSCI assessment were provided. This would not be needed if, for example, the Ambulation calculator was designed for direct use by persons living with SCI. Defining and engaging the end-user early in the implementation process, a key component of the knowledge-to-action (KTA) cycle (12) and integrated KT (30), helps ensure that the tool being developed is ultimately relevant to users' needs.

The process of translating knowledge to practice is iterative and dynamic (12, 13). The development of Ambulation represents one phase of Knowledge Creation, which is part of the KTA cycle (34). Knowledge Creation involves (1) knowledge inquiry, (2) synthesis of knowledge, and (3) the production of knowledge tools. The methods described in this paper primarily encompass the third phase, with the creation of the web-based calculator as a KT tool, whereas the former two were accomplished with the development and validation of the CPR by Hicks et al. (25). While commentators have raised a variety of issues related to the translation of prognosis research into practice, a recurring theme is the lack of tools to simplify the complexity of prognostic models for daily use in clinical settings and the failure to recognize prognostic models as healthcare technologies that require deliberate implementation strategies (1, 2). These claims align with the current state of SCI research.

In a systematic review of KT initiatives in SCI research, Noonan et al. identified a paucity of KT interventions for SCI (14). Moreover, and perhaps unsurprisingly, none of the few interventions identified were related to implementing CPRs into clinical practice. As machine learning driven prognostic studies become more important in spine research (4), there will be a pressing need to create web-based tools that incorporate these complex models and make them more accessible to potential end-users, given the novelty of these techniques compared to traditional regression-based CPRs. Therefore, the focus on the production of knowledge tools presented here (Phase 3 of Knowledge Creation), addresses an important gap in the KTA cycle for prognosis research generally, and SCI prognostic models specifically. The development of CPRs in easy-to-use CPR presentation formats, such as Ambulation, could provide the means for implementing KT tools and better promote their adoption in clinical settings. We intended our approach to the design and development of Ambulation to be simple and with minimal resource requirements. This was done for two reasons: (1) to promote the reproducibility of our methods for other researchers seeking to develop web-based calculators alongside new CPRs and (2) to enable its transportability and integration with hospital-based systems in the future. While input from IT professionals and software engineers can be useful, the first steps to building web-based KT tools can be initiated by researchers with minimal technical expertise.

Concurrent with the pilot launch of Ambulation, several feedback mechanisms were integrated into the development of the website to provide means of evaluating the process of implementation and potential barriers or facilitators to the use of the CPR. These were the online feedback survey, the website traffic data collected through Google Analytics, and the Contact page where users could find information to email comments or suggestions. Through the survey, users provided feedback on how specific predictions provided through the calculator compared with their clinical intuition and experience. This provided insights about the face validity of the Hicks et al. (25) CPR. Encouraging this feedback is critical to the adoption of CPRs, if experts do not accept the results from the web-based calculator, they are less likely to adopt the tool and use it to inform discussions with patients. Future updates or

TABLE 2 Ambulation google analytics data, report February 7, 2022 to February 28, 2023.

| Data variable | Data element definition | *N* (%) |
|---|---|---|
| Users | The total number of active users | 594 |
| New users | The number of users who interacted with your site or launched your app for the first time (event triggered: first_open) | 565 (95.1) |
| Returning users | Users who have initiated at least one previous session | 26 (4.4) |
| Users by country | The country from which the user activity originated | 1. United States, 236 (39.9)<br>2. Canada, 226 (38.2)<br>3. China, 48 (8.1)<br>4. Saudi Arabia, 13 (2.2)<br>5. Australia, 10 (1.7) |
| Users by Canadian City | The city from which the user activity originated | 1. Toronto, 53 (11.6)<br>2. Ashburn, 30 (6.6)<br>3. Columbus, 19 (4.2)<br>4. Ottawa, 18 (3.9)<br>5. Vancouver, 17 (3.7)<br>6. Hamilton, 16 (3.5)<br>7. Montreal, 15 (3.3) |
| Sessions—direct search by new users | This is most often the result of a user entering a URL into their browser or using a bookmark to directly access the site | 411 |
| Session—organic search | This refers to sessions from users who found the website via an organic search, i.e., they found the website after clicking on the website's link in the search engine results page | 174 |
| Event count | The number of times your users triggered an event | 4,525 |
| Event name by total users | The name of the triggered event | 1. page_view, 568<br>2. session_start, 568<br>3. user_engagement, 356<br>4. first_visit, 565<br>5. scroll, 325<br>6. Calculate button Click, 167<br>7. Recalculate button click, 67 |
| Average engagement time | Average engagement time per active user for the time period selected | 53 s |
| Engaged sessions per user | Average session count per active user for the time period selected | 0.61 |
| Users by platform | The platform on which your app or website ran; e.g., web, iOS, or Android | Web, 594 (100) |
| Users by operating system | The operating systems used by visitors to your app or website. Includes mobile operating systems such as Android | 1. Windows, 333 (56.1)<br>2. Macintosh, 123 (20.7)<br>3. iOS, 89 (15.0) |
| Users by browser | The browsers used to view the website | 1. Chrome, 397<br>2. Safari, 113<br>3. Edge, 38 |
| Users by device category | The type of device: desktop, mobile, or tablet | 1. Desktop, 423 (79.4)<br>2. Mobile, 109 (20.5)<br>3. Tablet, 1 (0.2) |

refinements of the CPR to optimize its clinical usefulness, such as modifying the risk threshold for classifying patients as able to walk or not based on the estimate of risk (20), can be also implemented and tested in this way. The integrated GA metrics (Table 2) supplemented survey feedback by allowing continuous monitoring of user behavior on the website. Even with our small sample and limited study period, these feedback mechanisms revealed critical insights into the implementation process and provided data to the research team in real-time to facilitate improvements to the design of the web-based calculator. This iterative approach to implementation allows for early identification of usability issues, prompt redesign, and further testing—principles that promote the successful design and implementation of digital health innovations (33).

## Limitations

This study has several limitations. First, the response rate to the feedback survey was low (six of 30, 20%). However, the purpose of soliciting feedback was to assess usability issues and improve the overall design, thus achieving a reasonable number of responses (rather than a high rate of response) was our goal. Research suggests that as few as three to five users can identify the most important issues for usability testing (35, 36), therefore the six respondents may be adequate to provide baseline feedback for improving Ambulation. Second, test users were limited to clinicians in Canada. Engaging users from diverse healthcare settings could offer new learning points for design and implementation and improve the generalizability of Ambulation's implementation. Third, we did not assess which clinical settings and at which timepoints during the clinical workflow Ambulation was tested among users. Collecting these data will facilitate workflow analysis and help promote the adoption and sustained use of Ambulation by clinicians treating persons with TSCI over time. Lastly, the clinical utility of Ambulation is limited to the setting and populations in which the CPR by Hicks et al. (25) was developed and validated: adult patients with TSCI managed in acute care and rehabilitation hospitals across Canada (26).

## Future research directions

We presented the process of developing and piloting Ambulation, however, it is yet to be elucidated how to effectively integrate this web-based CPR into routine clinical practice. To do this, further engagement with the KTA cycle proposed by Straus et al. (12) is needed. This will entail evaluating the adoption or customization of the KT tool to the local context; assessing the determinants of use; and determining strategies for ensuring sustained use. This can be facilitated through conducting a focused implementation study guided by validated frameworks such as the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) or Promoting Action on Research Implementation in Health Services (PARIHS) (37). Furthermore, there is an opportunity to develop other SCI web-based calculators using our experience from Ambulation, similar to the work being pursued by the SORG Orthopedic Research Group (https://sorg.mgh.harvard.edu/predictive-algorithms/), who have developed several predictive algorithms for patient outcomes after orthopedic surgery (38). Here, different tools have been made accessible for a variety of conditions and clinical decisions. For SCI, we plan to develop a library of web-based CPRs to bridge the KTA gap that covers the spectrum of clinical care including prediction of survival (39), functional capabilities besides walking (e.g., bowel and bladder function) (40, 41), life satisfaction, quality of life, and readmission or discharge disposition. These KT tools will align to the priorities of people with lived experience as well as clinicians and will focus on those developed or validated with Canadian data to ensure applicability in a Canadian context. Finally, future work should consider feedback from a larger group of clinicians from centers in other countries. The easy accessibility of Ambulation could also provide means for conducting external validation of the Hicks et al. CPR in under-researched settings (e.g., low-to-middle countries). The results of this study already demonstrate the use of this tool in three continents (Table 2). With further dissemination of the Ambulation website to both Low- and Middle-Income Countries (LMICs) and High-Income Countries (HICs), an emerging focus of future research may be comparative analysis of CPR utilization in diverse healthcare economies and the differences in therapeutic attitudes that these data may reflect.

In conclusion, Ambulation, a web-based CPR for independent walking 1-year after TSCI, was developed and successfully launched. Here we describe the steps to developing Ambulation and provide initial results from the pilot study among SCI clinicians. Feedback from the user survey suggests that clinicians believe Ambulation is useful in practice, easy-to-use, and may be of assistance for discharge planning. These findings outline some feasible options for developing web-based CPRs and some challenges that should be addressed to enable the implementation of CPRs in clinical care. We anticipate that our experiences with developing and launching Ambulation will promote and inform the development of other web-based presentation platforms and help improve future prediction model digital implementation efforts.

## Data availability statement

The datasets presented in this article are not readily available because of the Rick Hansen Spinal Cord Injury Registry (RHSCIR) Data Use and Disclosure Policy which is administered by the Praxis Spinal Cord Institute. Requests to access the datasets should be directed to the Praxis Spinal Cord Institute, dataservices@praxisinstitute.org.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## Author contributions

RH, HH, NF, VN, and PP were involved with conceptualization, methodology, and project design. RH and HH developed and wrote the original draft, and prepared figures and tables. All authors revised the draft of the paper, contributed to the article, and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1219307/full#supplementary-material

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# Pattern of neurological recovery in persons with an acute cervical spinal cord injury over the first 14 days post injury

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**Introduction:** Following a traumatic spinal cord injury (SCI) it is critical to document the level and severity of injury. Neurological recovery occurs dynamically after injury and a baseline neurological exam offers a snapshot of the patient's impairment at that time. Understanding when this exam occurs in the recovery process is crucial for discussing prognosis and acute clinical trial enrollment. The objectives of this study were to: (1) describe the trajectory of motor recovery in persons with acute cervical SCI in the first 14 days post-injury; and (2) evaluate if the timing of the baseline neurological assessment in the first 14 days impacts the amount of motor recovery observed.

**Methods:** Data were obtained from the Rick Hansen Spinal Cord Injury Registry (RHSCIR) site in Vancouver and additional neurological data was extracted from medical charts. Participants with a cervical injury (C1–T1) who had a minimum of three exams (including a baseline and discharge exam) were included. Data on the upper-extremity motor score (UEMS), total motor score (TMS) and American Spinal Injury Association (ASIA) Impairment Scale (AIS) were included. A linear mixed-effect model with additional variables (AIS, level of injury, UEMS, time, time$^2$, and TMS) was used to explore the pattern and amount of motor recovery over time.

**Results:** Trajectories of motor recovery in the first 14 days post-injury showed significant improvements in both TMS and UEMS for participants with AIS B, C, and D injuries, but was not different for high (C1–4) vs. low (C5–T1) cervical injuries or AIS A injuries. The timing of the baseline neurological examination significantly impacted the amount of motor recovery in participants with AIS B, C, and D injuries.

**Discussion:** Timing of baseline neurological exams was significantly associated with the amount of motor recovery in cervical AIS B, C, and D injuries. Studies examining changes in neurological recovery should consider stratifying by severity and timing of the baseline exam to reduce bias amongst study cohorts. Future studies should validate these estimates for cervical AIS B, C, and D injuries to see if they can serve as an "adjustment factor" to control for differences in the timing of the baseline neurological exam.

KEYWORDS
**acute cervical spinal cord injury, motor recovery trajectory, baseline neurological assessment, upper-extremity motor score, total motor score**

## Introduction

The clinical evaluation of acute traumatic spinal cord injury (SCI) utilizes the widely accepted International Standards for the Neurological Classification of SCI (ISNCSCI) examination to characterize the degree of neurological impairment (1). This exam provides a standardized way to report the level and severity of injury and has been used to predict neurological recovery and outcome (2). It is recommended that the ISNCSCI exam is done following the SCI (1, 3). However, the challenge in the acute setting is that the SCI itself is evolving from the moment that it happens. Many patients, for example, will describe a period of complete paralysis at the scene of the accident when the initial injury occurs, with subsequent improvement to varying degrees of incomplete motor/sensory recovery observed in the ensuing hours and days. Because this is a dynamic process, how one interprets recovery will invariably be influenced by when the neurological assessment is actually done (i.e., when the "snapshot" of neurological impairment is actually taken). For example, if a patient begins at the scene of the accident (prior to any formal ISNCSCI examination) with a motor score of 0, and at 1-month post-injury has a motor score of 25, how one interprets this amount of recovery will depend upon when the first formal ISNCSCI examination actually occurred. Perhaps this patient had a motor score of 5 on arrival in hospital 4 h later, and then by the time magnetic resonance imaging (MRI) was conducted and the patient was taken to the operating room, ∼12 h post-injury, the motor score was 10. If the clinical team was able to assess an ISNCSCI examination at 4 h post-injury, it would be interpreted that at 1 month the recovery was 20 points. But if the ISNCSCI was performed at 12 h, motor recovery would be deemed to be 15 points (25% less), just due to the timing of the baseline examination.

Studies investigating neurological recovery following SCI vary in terms of when the baseline neurological exam is conducted and have ranged from 2 h up to 30 days (4–14) (see Table 1). Practically, the precise timing of the examination is often not documented and this lack of recorded time further complicates the understanding of neurological recovery following the initial assessment. Because the time of the baseline neurological assessment is not standardized in registries, this issue may confound studies where investigators use specific inclusion criteria for the intervention group but use a control group from a registry where the timing of the first neurological exam varies from one day to one-month post injury. Bias can be introduced into the analysis if exams performed earlier post-injury (i.e., before the possibility of spontaneous neurological recovery) are grouped with later examinations that may have been taken after or during spontaneous neurological recovery (15). In this case, participants in the "earlier exam" group may falsely exhibit greater neurological improvement in response to the intervention than the "later exam" group. It is also important that the examiners are trained and have experience to ensure the exam results are reliable and valid (16, 17).

Furthermore, most of the evidence on neurological recovery is based on a cross-sectional or longitudinal study design with only a few time points (e.g., at admission and scheduled follow-ups). Given the nature of neurological recovery, a longitudinal study design that includes multiple data points (e.g., on admission, following surgery, on admission to rehab, at discharge) temporally recorded would help describe neurological recovery following injury and allow researchers to more appropriately adjust for the differences between groups (e.g., cases and controls). Finally, earlier work by our research group and others has highlighted the importance of controlling for heterogeneity of SCI by appropriately stratifying study participants into categories by both neurological severity and level of injury, recording the number of study participants, and reporting the mean baseline motor scores for each study participant category (15, 18).

To understand the trajectory of neurological recovery following SCI, we examined the relationship between the timing of neurological assessment and motor recovery over the first 14 days post injury using a longitudinal study design in persons with cervical SCI, as this is the average time frame reported in SCI studies (4–6, 8–11, 13, 19). The specific study objectives were to: (1) describe the pattern and amount of motor recovery in persons with an acute cervical SCI over the first 14 days (including taking into consideration the neurological level and severity of the SCI); and (2) evaluate if the timing of the first neurological examination over the first 14 days biases the amount of motor recovery observed.

## Materials and methods

### Study design

A retrospective cohort analysis using a longitudinal study design was used. For this study, we focused on motor recovery following cervical SCI, given this is often an outcome used for SCI clinical trials (20, 21).

### Study cohort

Patients were enrolled in the Vancouver site of the Rick Hansen SCI Registry (RHSCIR), a pan-Canadian prospective observational registry of 30 major acute and rehabilitation hospitals, between 2004–2012. Full details of the RHSCIR have been described elsewhere (22). Eligibility for the study included participants with an acute cervical SCI (C1–T1) who had a minimum of two neurological exams with upper-extremity motor score (UEMS), total motor score (TMS) and American Spinal Injury Association (ASIA) Impairment Scale (AIS) data conducted within the first 2 weeks of injury (at least one in each week except AIS which was just for the first exam), and a final exam with the same data elements (UEMS, TMS, AIS) within RHSCIR.

### Participant, injury and care management data variables

Demographic and injury data on RHSCIR participants included age, sex, mechanism of injury (i.e., assault, fall, sport, transport, or other) (23), a total count of medical comorbidities based on the Charlson Comorbidity Index (24, 25), and additional injuries to other body regions using the Injury Severity Score (ISS) (26). Data describing the provision of care consisted of the time to

TABLE 1 Comparing distribution of first neurological exam in cervical SCI studies.

| References | Number of participants | First ISNCSCI exam post injury (approximate time) | Follow-up ISNCSCI exam | Neurological level of injury (approximate time) | Neurological severity (AIS) |
|---|---|---|---|---|---|
| Maynard et al. (4) | 114 | 72 hours | 1 year | Frankel classification | A–D: based on Frankel classification |
| Marino et al. (5) | 482 | 7 days | 1 year | C1–L5 | A–D: based on Frankel classification and AIS |
| Burns et al. (6) | 103 | 48 hours | 1 year | Not available | A–D |
| Fawcett et al. (7) | Review paper so NA | 30 days | 1 year | C1-L5 | A–D |
| Curt et al. (8) | 1140 | 14 days | 48 weeks | Tetraplegic, paraplegic | A–D |
| Van Middendorp et al. (9) | 161 | 15 days | 6 months—1 year | C1–T11 | A–D |
| Marino et al. (10) | 125 | 7 days | 1 year | C1–C8 | A–D |
| Steeves et al. (11) | 305 | 72 hours—7 days | 1 year | C4–C7 | A |
| Kirshblum et al. (12) | 187 | 30 days | 1 year | C1–L5 | A |
| Evaniew et al. (13) | 85 | 48 hours | 1 year | C1–T1 | A |
| Balbinot et al. (14) | 748<br>440 (subset) | 4 weeks<br>7 days | 48 weeks for all | C1–C8 | A–D |

AIS, American Spinal Injury Association (ASIA) Impairment Scale; ISNCSCI, International Standards for the Neurological Classification of Spinal Cord Injury; NA, not applicable.

the acute hospital (Vancouver General Hospital), spine procedures (number receiving surgery, timing of surgery), admission to rehabilitation (GF Strong Rehabilitation Center), and acute as well as rehabilitation length of stay.

Neurological impairment was assessed using the ISNCSCI (1, 3, 27). The date and time of these examinations (recorded in days post injury) were obtained from RHSCIR. The neurological exams were conducted by the clinical team who are trained on how to complete the ISNCSCI exam including physical therapists, nurses, spine residents/fellows and spine surgeons. Data from the ISNCSCI included the neurological level of injury (NLI), AIS to describe the injury severity, and the UEMS and TMS. The AIS classifies persons with SCI as having a motor-sensory complete injury (AIS A), a motor complete and sensory incomplete injury (AIS B), or a motor-sensory incomplete injury (AIS C or AIS D). The UEMS includes five muscles groups scored out of 5 per extremity, for a total score of 50 and a TMS of 100 (1, 3). The AIS grade assignment was verified using the Praxis ISNCSCI Algorithm which provides an AIS grade based on the motor and sensory data, including voluntary anal contraction (VAC) and deep anal pressure (DAP) (2). Neurological severity (AIS A, B, C, D), level of injury (high cervical C1–C4; low cervical C5–T1), the UEMS and TMS were obtained. A hospital chart review was conducted to obtain additional neurological exam data during the individuals' acute in-patient admission.

## Statistical analysis

First, a descriptive analysis of the data was conducted. Continuous variables were reported using mean and standard deviation, and categorical variables were described using a frequency (percentage). Missing data was not imputed. Trajectories of neurological recovery using motor scores (UEMS, TMS) from the first day up to 14 days post injury and a final exam prior to discharge, were created for subgroups AIS A, B, C and D.

Data was then stratified by neurological severity (AIS A, B, C, D) and level of injury (high cervical C1–C4; low cervical C5–T1) to determine if there were any differences in recovery between these groups. To explore the pattern and amount of motor recovery over time (up until the last exam) as well as the effect of when the exam was conducted over 14 days post injury (at least one exam was done in the first week and at least one exam was done in the second week), a linear mixed-effect model was used. In all of the linear mixed-effect models, a fixed-effects model was used first and the complexity of the model was increased in steps by adding random effects and additional variables [i.e., time (linear form), time$^2$ (quadratic form), AIS, level of injury, and motor score (UEMS, TMS)]. This process was continued until there was no improvement in the log-likelihood value, AIC and BIC goodness of fit criteria. The rate of conversion of AIS grade from the first to final assessment was also calculated and compared to the literature. A $p$-value of $<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (version 27) and Rx64 (version 3.3).

# Results

Between 2004 and 2012, a total of 849 individuals were admitted to Vancouver General Hospital, and enrolled in the Rick Hansen Spinal Cord Injury Registry (RHSCIR), among these participants, 234 individuals had cervical spinal cord injury spanning from C1–T1. Sixty-six participants were excluded because they did not have at least two neurological examinations, resulting in a study cohort of 168 individuals (see Figure 1 for the study consort diagram). The mean age at the time of injury was 45.3 (SD = 17.8) years, 78% were

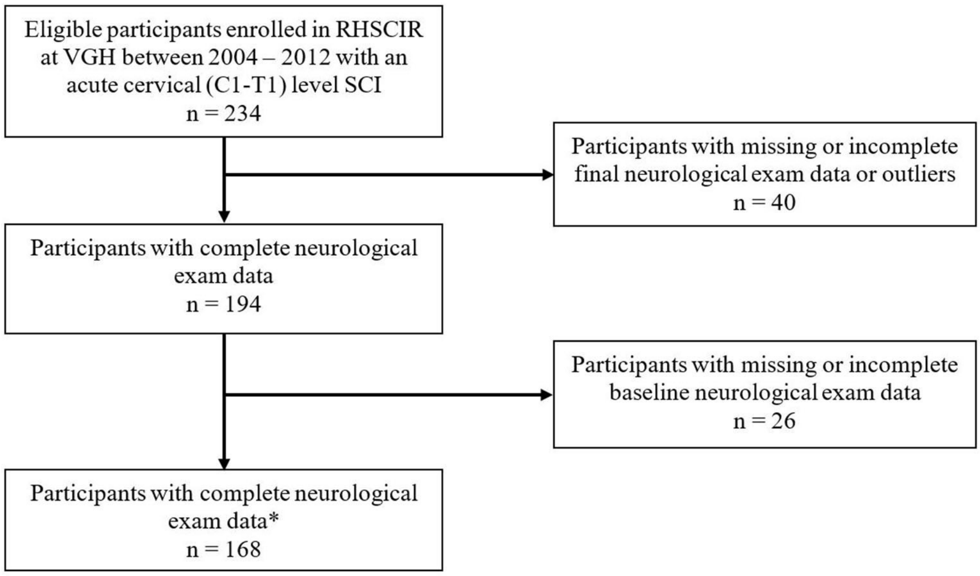


FIGURE 1
Study Consort Diagram of 849 individuals who were assessed for eligibility. *Neurological exam data included: UEMS, upper-extremity motor score; TMS, total motor score; and AIS, American Spinal Injury Association (ASIA) Impairment Scale. VGH, Vancouver General Hospital.

male, and the average time to the acute care hospital was 3.29 h (SD = 4.07; see Table 2A). On average, participants had 10 neurological exams, with a range of 3–15, over the study period which spanned from 1 to 365 days. Over half (50.6%) had their first exam within 24 h, 84% had their first exam within 48 h, and 94% had their first exam within 72 h. As mentioned previously, in addition to the initial neurological exam in the first week, all participants had at least one exam in the second week post injury. The distribution of neurological severity on admission was 72 (42.9%) AIS A, 33 (19.6%) AIS B, 47 (28%) AIS C, and 16 (9.5%) AIS D (Table 2A). Of the participants who were classified as AIS A on admission, 25.9% converted to AIS B, and 14.8% to AIS C or D by their discharge (Table 2B). More than half (59.4%) of the participants who were classified as AIS B on admission converted to AIS C or D (Table 2B). Further cohort details are included in Tables 2A, 2B.

Trajectories of motor recovery starting at 1 day up to 14 days post injury were visualized (see Figures 2, 3). Patterns and amount of motor recovery over the first 14 days were examined using a linear mixed-effect model. For the participants with AIS A injuries, UEMS and TMS were stable and not significantly different over 14 days post-injury. There were significant differences in the change in UEMS and TMS over 14 days for participants with a neurological severity AIS B, C, D, and stratified for neurological level (Table 3A), when compared to individuals with an AIS A injury. The changes in UEMS over 14 days post injury were most pronounced in individuals with AIS D injuries ($p < 0.001$ for UEMS and TMS; Table 3B).

Next, we explored the effect of timing of the neurological examination over 14 days, neurological severity (AIS A, B, C, D) and level of injury (high cervical and low cervical) on UEMS and TMS using a mixed-effect model. Specifically, we assessed whether the timing of the first neurological exam had an association with neurological recovery for each of the cervical AIS and neurological level of injury subgroups [i.e., high (C1–C4) vs. low cervical (C5–T1)]. For the cervical AIS A group (high and low cervical), there was no significant effect of timing of the exam on neurological recovery (i.e., motor score change) during the first 14 days post-injury (Table 3A). In the cervical AIS B group, the time of examination significantly impacted the UEMS (4.50; $p$-value = 0.02) and TMS (5.32; $p$-value = 0.05) over 14 days (Figures 2, 3 and Tables 3A, 3B). Furthermore, the effect of time in a linear form as well as a quadratic form (time$^2$) were tested in the model and only the linear form (0.15; $p$-value < 0.001) was significant for the AIS B group. For the cervical AIS C group, there were significant differences in UEMS (3.61; $p$-value = 0.05) and TMS (15.74; $p$-value < 0.001) recovery over the first 2 weeks and they were most pronounced around 72 h post-injury. For this group, the timing of the neurological exam was significant in both linear and quadratic form (time, time$^2$) using a mixed-effects model. Finally, the results for the AIS D group revealed that the timing of the initial examination was significantly related to changes in both UEMS (21.56; $p$-value < 0.001) and TMS (64.19; $p$-value < 0.001). The AIS D subgroup demonstrated the highest slope of change (i.e., improvement in UEMS and TMS) when compared to the other AIS subgroups. The injury location (high vs. low cervical) and time interaction term was not significant for AIS B, C, and D injuries in the first 14 days post injury.

These results illustrate that the timing of neurological exams and injury severity were important factors. For individuals with the most severe injuries (AIS A group), the timing of the neurological exam did not have a significant impact on the observed neurological recovery. For AIS, B, C, and D injuries, the recovery curve was nonlinear and recovery began immediately after injury, with the most significant changes happening up to 72 h after the injury. Finally, for individuals with the least severe injuries (AIS D group), the timing of the exam was especially important, and they had the

TABLE 2A Participant characteristics for the analysis cohort ($n = 168$).

| Variable | |
|---|---|
| Age at injury; mean years (SD) | 45.3 (17.8) |
| Male *n* (%) | 131 (78) |
| Mechanism of injury *n* (%) | |
| Falls | 64 (38.1) |
| Transport | 54 (32.1) |
| Sports | 36 (21.4) |
| Other | 14 (8.3) |
| Charlson Comorbidity Index *n* (%) | |
| 0 | 136 (81) |
| 1–2 | 27 (16.1) |
| 3+ | 5 (2.9) |
| Injury Severity Score mean (SD) | 25.7 (11.6) |
| Neurological severity of injury on admission (AIS) *n* (%) | |
| A | 72 (42.9) |
| B | 33 (19.6) |
| C | 47 (28) |
| D | 16 (9.5) |
| Neurological injury level *n* (%) | |
| High cervical (C1–C4) | 80 (47.6) |
| Low cervical (C5–T1) | 88 (52.4) |
| UEMS change over 14 days post-injury; mean motor score units (SD) | |
| AIS A | 1.7 (4.6) |
| AIS B | 1.07 (5.1) |
| AIS C | 4.3 (7.5) |
| AIS D | 7.1 (11.4) |
| TMS change over 14 days post-injury; mean motor score units (SD) | |
| AIS A | 1.30 (4.9) |
| AIS B | 3.43 (9.97) |
| AIS C | 9.18 (12.99) |
| AIS D | 16.2 (14.22) |
| Time to acute hospital; mean hours (SD) | 3.29 (4.07) |
| Surgery *n* (%) | 153 (91) |
| Time of surgery; mean hours (SD) | 36.67 (71.62) |
| Received rehabilitation *n* (%) | 147 (87.5) |
| Acute length of stay; mean days (SD) | 56.33 (41.1) |
| Rehabilitation length of stay; mean days (SD) | 144.39 (71.79) |

AIS, American Spinal Injury Association (ASIA) Impairment Scale; SD, standard deviation; TMS, total motor score and UEMS, upper-extremity motor score.

highest level of recovery starting at 1 day which continued up to 2 weeks, compared to the other groups. These results demonstrate that individuals who had their first examination at day 1 had more room for improvement than individuals who had their first examination at day 3 post-injury, and the same pattern was observed comparing day 3 to day 14. A general formula based on the regression model is described in the Appendix.

TABLE 2B AIS conversion between admission and discharge.

| Admission AIS | Discharge AIS (% conversions) | | | | |
|---|---|---|---|---|---|
| | A | B | C | D | E |
| A | 48 (59.3) | 21 (25.9) | 10 (12.3) | 2 (2.5) | 0 |
| B | 2 (5.4) | 13 (35.1) | 10 (27.0) | 12 (32.4) | 0 |
| C | 0 (0) | 3 (5.7) | 7 (13.2) | 43 (81.1) | 0 |
| D | 0 (0) | 0 (0) | 0 (0) | 21 (91.3) | 2 (8.7) |

AIS, American Spinal Injury Association (ASIA) Impairment Scale.
The discharge time for the AIS was mean = 173.34 days, SD = 102.7 days, median = 170.5 days.

## Discussion

To better understand the neurological trajectory following cervical SCI, we analyzed longitudinal upper-extremity and total motor score data, stratified by neurological severity and level of injury, from day one after SCI up to 14 days. Our results demonstrate that for cervical AIS B, C, and D injuries there is substantial neurological recovery beginning within the first day post-injury and continues up to 14 days post-injury for AIS C and D injuries. Given these changes, clinical studies including subjects with a SCI graded as an AIS B, C, or D should ensure the baseline ISNCSCI assessment for the intervention and control cohorts are completed at the same time post-injury. For cervical AIS A injuries, our results suggest that following the first neurological exam motor score does not change significantly in the first 2 weeks post injury.

Using these models, it is possible to quantify the variation in neurological recovery due to the timing of the examination in the first 14 days following injury which can inform the analysis of registry data or design of clinical trials recruiting participants with a cervical SCI (C1–T1). For example, at one day post injury we can determine the expected natural recovery (e.g., TMS) at 10-day post injury using the regression equation in a patient with a cervical AIS C injury (high and low cervical). The "time" variable is 10 days and after subtracting the TMS from day one (i.e., the motor score at injury) it equals 4.4 and represents the amount of TMS recovery expected at 10 days post injury. A second example includes an individual with an AIS B (high cervical). The "time" variable is 10 days and based on the equation this equals 1.75, which corresponds to the amount of motor score recovery for the AIS B high cervical group at 10 days post injury. Comparing AIS B and C, the effect of time is evident; the change in TMS is 1.75 for AIS B and 4.4 for AIS C. Similar results can also be obtained for UEMS from the linear mixed-effect model.

The literature (see Table 1) reports a large variation in the timing of what is considered a "baseline" examination time and spontaneous neurological recovery is a phenomenon that has likely been underestimated or overlooked previously. Conducting an

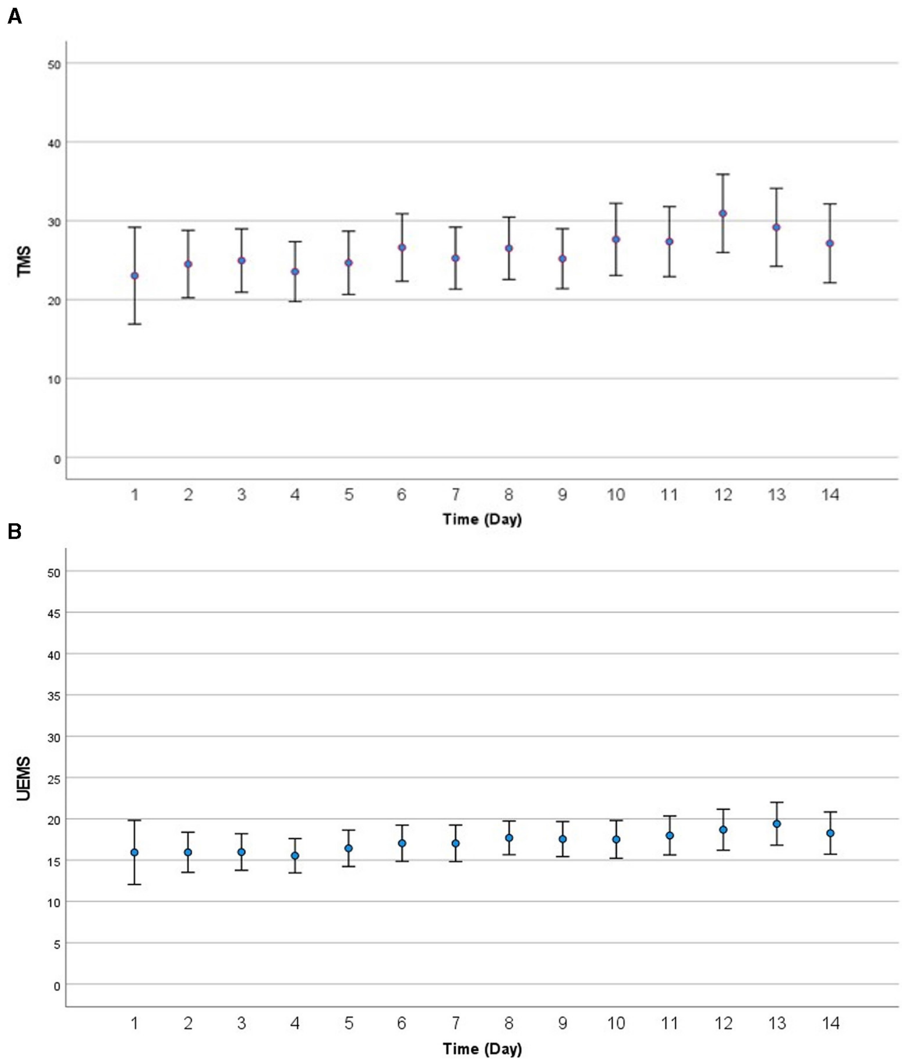


FIGURE 2
**(A)** Visualization of motor recovery using TMS for the first 14 days after injury for AIS A to D. **(B)** Visualization of motor recovery using UEMS for the first 14 days after injury for AIS A to D. AIS, American Spinal Injury Association (ASIA) Impairment Scale; TMS, total motor score; UEMS, upper-extremity motor score.

ISNCSCI exam immediately following injury can be challenging given issues with triage, the need to stabilize the patient and manage polytrauma and a decreased level of consciousness. However, when one considers that "recovery" is measured as the amount of change between an ISNCSCI examination done at a later post-injury time point vs. the ISNCSCI examination done "at baseline," it is surprising that the timing of that baseline examination and how this might influence the quantification of recovery has not been well studied. In the literature, the recommendation was to conduct a neurological exam any time after 72 h post-injury (28), between 72 h to 1-month post-injury (5, 29) or anywhere between 2 weeks post-injury as the baseline assessment (30). Our findings strongly suggest that individuals who have sustained a SCI (ranging from AIS A to D) should promptly undergo a neurological examination (31), rather than adhering to the commonly recommended practice of scheduling it after the 72-h mark. Even for individuals with AIS A injuries, a number convert to an incomplete injury (AIS B to D) and might have the potential to have significant improvement in motor score (UEMS and TMS). Research studies including individuals (AIS A to D) should have the time of their ISNCSCI neurological exam recorded and be matched to within the same day to ensure the recovery potential is equivalent in studies using SCI registry data as a control or in planning a prospective study (e.g., randomized control trial or observational study) to account for spontaneous recovery. Furthermore, studies should consider using a longitudinal study design rather than a cross-sectional study design. Although a longitudinal study design presents challenges due to the increased cost and time for repeated clinical examinations, it enables a more detailed examination of how the variable(s) of interest change over time, at both the group and individual level. This will allow gradual changes in neurological recovery that may occur in the first few days post injury to be observed.

Results from this study can also be used to "adjust" for differences between the control and intervention group based upon

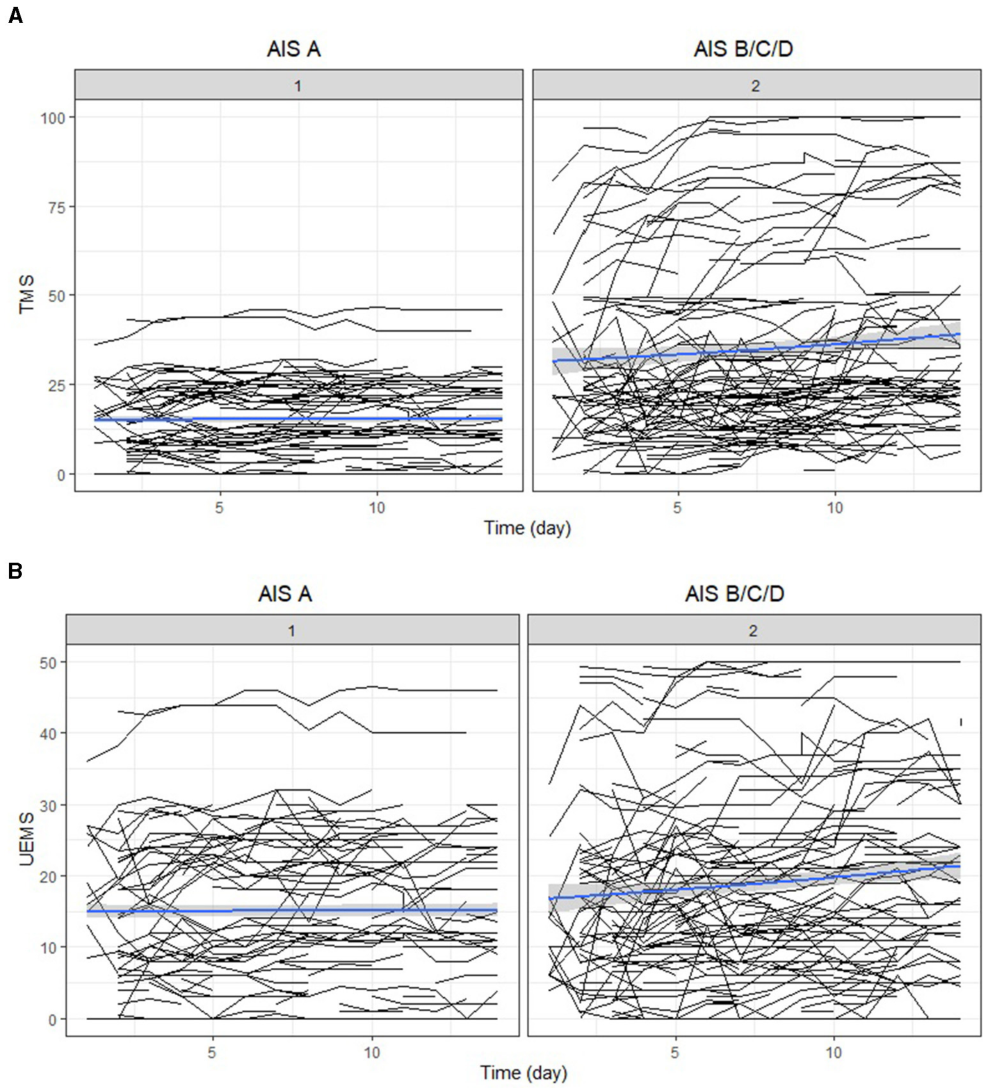


FIGURE 3
**(A)** Individual trajectory and mean change of total motor score recovery for the first 14 days after injury (Panel 1 AIS A; Panel 2 AIS B, C, D). **(B)** Individual trajectory and mean change of upper-extremity motor score recovery for the first 14 days after injury (Panel 1 AIS A; Panel 2 AIS B, C, D). AIS, American Spinal Injury Association (ASIA) Impairment Scale; TMS, total motor score; UEMS, upper-extremity motor score.

the timing of neurological exams. The regression equations enable the amount of neurological improvement each day post injury to be quantified and so two groups can be matched (e.g., artificially match the intervention group and control group for time of neurological exam). However, further research is needed to validate our results in other countries with SCI registries before these adjustment estimates should be used in future research.

Our previous findings (15) suggested that participants in observational studies should be stratified by neurological severity and level of injury given the heterogeneity of SCI. In this current study where we measured the first 14 days post injury, we were not able to show a difference between upper and lower cervical injuries. However, the effect of level of injury should be explored in studies with larger sample sizes since 43% of our sample has an AIS A injury and this study may be under powered to show a difference between upper and lower cervical injuries. Failure to stratify and/or use an appropriate control group can lead to incorrect conclusions regarding efficacy of a treatment, especially if there are small cohort sizes. Stratification can improve the study efficiency by decreasing the variance and increasing statistical power and so it is suggested individuals are stratified for neurological severity and level of injury. Based on these results, it is also important to record the time of the baseline neurological examination and ensure that control and intervention groups are matched on this variable.

Although this study provides new information on the neurological recovery patterns for cervical SCI, it is important to consider the limitations. Our study examined neurological data reported in days, however, future research should include more precise times reported within hours of injury (e.g., 0–4 h, 4–8 h etc.) and determine if these changes are clinically significant. In this study, AIS conversion was only measured at baseline and at the final neurological exam. As a result, we cannot comment on the timing of the neurological exam as it relates to AIS conversion. Future studies including biomarker and imaging data will provide

TABLE 3A Linear mixed effects model for total motor score (TMS) as the outcome.

| Characteristics | Entire cohort | |
|---|---|---|
| | Estimate (95% CI) | *p*-value |
| Time, day | 0.04 (0.00 to 0.07) | 0.04 |
| $Time^2$, day | 0.00002 (0.00 to 0.00) | 0.68 |
| Baseline AIS | | |
| A | Ref | — |
| B | 5.32 (0.06 to 10.58) | 0.05 |
| C | 15.74 (10.93 to 20.55) | <0.001 |
| D | 64.19 (57.12 to 71.26) | <0.001 |
| Baseline level of injury | | |
| Upper cervical | Ref | — |
| Lower cervical | 9.60 (5.65 to 13.55) | <0.001 |
| Baseline AIS * time, day | | |
| A | Ref | — |
| B | 0.15 (0.07 to 0.22) | <0.001 |
| C | 0.42 (0.35 to 0.48) | <0.001 |
| D | 0.69 (0.52 to 0.87) | <0.001 |
| Baseline AIS * $time^2$, day | | |
| A | Ref | — |
| B | −0.0002 (0.00 to 0.00) | 0.17 |
| C | −0.0009 (0.00 to 0.00) | <0.001 |
| D | −0.0067 (−0.01 to 0.00) | <0.001 |

TABLE 3B Linear mixed effects model for upper-extremity motor score (UEMS) as the outcome.

| Characteristics | Entire cohort | |
|---|---|---|
| | Estimate (95% CI) | *p*-value |
| Time, day | 0.0647 (0.04–0.09) | <0.001 |
| $Time^2$, day | −0.0003 (0.00–0.00) | 0.02 |
| $Time^3$, day | 0.000001 (0.00–0.00) | 0.04 |
| Baseline AIS | | |
| A | Ref | — |
| B | 4.50 (0.66–8.34) | 0.02 |
| C | 3.61 (0.10–7.11) | 0.05 |
| D | 21.56 (16.43–26.68) | <0.001 |
| Baseline level of injury | | |
| Upper cervical | Ref | — |
| Lower cervical | 12.22 (9.37–15.07) | <0.001 |
| Baseline AIS * time, day | | |
| A | Ref | — |
| B | 0.04 (0.01–0.07) | 0.02 |
| C | 0.10 (0.07–0.13) | <0.001 |
| D | 0.21 (0.15–0.26) | <0.001 |

AIS, American Spinal Injury Association (AIS) Impairment Scale.

more precise information on changes in neurological recovery and factors such as age, concurrent injuries, infections, and surgical management that can influence recovery should be considered. In addition, this study focused on cervical injuries and future studies should conduct longitudinal studies in individuals with thoracic and thoracolumbar injuries. Data used in this study is comparable to previous, similar studies examining neurological recovery (8) in participants with cervical SCI, although the number of conversions of AIS A injuries in our cohort is slightly higher (15). This may be due to "spinal shock" which may affect the reliability of neurological examinations at very early timepoints post injury. It is recognized that the concept of "spinal shock" complicates the early assessment of acute SCI patients and can make it quite difficult to discern the true extent of the neurological impairment. This issue is inherently problematic in the clinical evaluation of neuroprotective treatments which must be delivered as soon as possible after injury and therefore do not afford investigators the luxury of just waiting until spinal shock resolves and a reliable neurological examination can be conducted. Our findings highlight the dynamic nature of the injury in the first 14 days, and emphasizes the need to account for the timing of baseline neurological assessment in the interpretation of neurological recovery related to early interventions. Further research into the trajectory of sensory and autonomic scores should also be considered as it is important for neurological and functional recovery as well as further classifying the severity of the spinal fracture using the AO Spine Classification (32).

In summary, we analyzed the trajectories of motor score improvement when multiple examinations were conducted and observed that trajectories are different in the first 2 weeks following a SCI among AIS A, B, C, and D injuries. We demonstrated the need for comparable baseline neurological assessment times within study groups to prevent biasing the interpretation of neurological recovery. These results can help improve the design of future clinical SCI studies by increasing the efficiency, robustness and statistical power (7, 33–35). Future studies should validate these estimates of neurological recovery for the first 14 days in AIS B to D injuries to see if they can serve as an "adjustment factor" to control for any bias due to differences in the timing of the exams.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: access to deidentified data used for this study is available via the RHSCIR Data Use and Disclosure Policy which is administered by the Praxis Spinal Cord Institute. Requests to access these datasets should be directed to dataservices@praxisinstitute.org.

## Ethics statement

The studies involving humans were approved by Vancouver Coastal Health Research Institute and the University of British Columbia Clinical Research Ethics Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent was not required from the participants or the participants/next of kin in accordance with local legislation and our institutional requirements.

## Author contributions

NF: Conceptualization, Formal analysis, Writing—original draft. VN: Conceptualization, Writing—original draft, Funding acquisition. ZW: Writing—review & editing. RC-M: Writing—review & editing. CD: Writing—review & editing. CC: Writing—review & editing. TA: Writing—review & editing. ND: Writing—review & editing. SP: Writing—review & editing. JS: Writing—review & editing. CF: Conceptualization, Writing—review & editing. MD: Conceptualization, Writing—review & editing. BK: Conceptualization, Writing—original draft.

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## Conflict of interest

NF, VN, ZW, and CC are employees of the Praxis Spinal Cord Institute.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



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## Appendix

We used the statistical models from Tables 3A, 3B to construct the statistical equations for each outcome (TMS and UEMS). The equation below is for TMS, where the Time variable represents the neurological exam time and $Y$ represents the respective motor score for that time point.

$$Y_{\text{motor score at any given time}} = \text{Intercept} + \beta_1 * \text{Time} + \beta_2 * \text{Time}^2 + \beta_3 * \text{AIS (A/B/C/D)} + \beta_4 * \text{High cervical/Low cervical} + \beta_5 * \text{Time} * \text{AIS (A/B/C/D)} + \beta_6 * \text{Time}^2 * \text{AIS (A/B/C/D)}$$

For a particular timepoint, such as 10 days post-injury, we can forecast the expected natural recovery specifically for that day for each American Spinal Injury Association (ASIA) Impairment Scale (AIS) grades. In this scenario, the Time variable in our equation can be assigned the value of 10 days and the β values used in this equation are derived from the regression model presented in Table 3A for TMS. The $\beta_1$ corresponds to the Time variable, and in our model, it has a value of 0.04. A similar methodology can be applied to predict upper-extremity motor score (UEMS) recovery by utilizing the regression coefficients provided in Table 3B.

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# Network analysis of multimorbidity and health outcomes among persons with spinal cord injury in Canada

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**Introduction:** Multimorbidity, defined as the coexistence of two or more health conditions, is common in persons with spinal cord injury (SCI). Network analysis is a powerful tool to visualize and examine the relationship within complex systems. We utilized network analysis to explore the relationship between 30 secondary health conditions (SHCs) and health outcomes in persons with traumatic (TSCI) and non-traumatic SCI (NTSCI). The study objectives were to (1) apply network models to the 2011–2012 Canadian SCI Community Survey dataset to identify key variables linking the SHCs measured by the Multimorbidity Index-30 (MMI-30) to healthcare utilization (HCU), health status, and quality of life (QoL), (2) create a short form of the MMI-30 based on network analysis, and (3) compare the network-derived MMI to the MMI-30 in persons with TSCI and NTSCI.

**Methods:** Three network models (Gaussian Graphical, Ising, and Mixed Graphical) were created and analyzed using standard network measures (e.g., network centrality). Data analyzed included demographic and injury variables (e.g., age, sex, region of residence, date, injury severity), multimorbidity (using MMI-30), HCU (using the 7-item HCU questionnaire and classified as "felt needed care was not received" [HCU-FNCNR]), health status (using the 12-item Short Form survey [SF-12] Physical and Mental Component Summary [PCS-12 and MCS-12] score), and QoL (using the 11-item Life Satisfaction questionnaire [LiSAT-11] first question and a single item QoL measure).

**Results:** Network analysis of 1,549 participants (TSCI: 1137 and NTSCI: 412) revealed strong connections between the independent nodes (30 SHCs) and the dependent nodes (HCU-FNCNR, PCS-12, MCS-12, LiSAT-11, and the QoL score). Additionally, network models identified that cancer, deep vein thrombosis/pulmonary embolism, diabetes, high blood pressure, and liver disease were isolated. Logistic regression analysis indicated the network-derived MMI-25 correlated with all health outcome measures (*p* <0.001) and was comparable to the MMI-30.

**Discussion:** The network-derived MMI-25 was comparable to the MMI-30 and was associated with inadequate HCU, lower health status, and poor QoL. The MMI-25 shows promise as a follow-up screening tool to identify persons living with SCI at risk of having poor health outcomes.

KEYWORDS

spinal cord injury, machine learning, network analysis, multimorbidity, outcomes

## Introduction

A spinal cord injury (SCI) occurs when the spinal cord is damaged either by trauma (e.g., car crash, falls; referred to as traumatic SCI [TSCI]) or through internal damage (e.g., degenerative, neoplastic, or infectious conditions; referred to as non-traumatic SCI [NTSCI]). The resulting injury can impair motor, sensory, and autonomic functions (1–4), and multiple body systems can be affected. Following a SCI individuals may experience complications such as spasticity, urinary tract infections, pneumonia, pressure injuries, and pain (5–7). More than 90% of persons living with SCI will experience at least one complication and more than half experience three or more complications which often require ongoing management (8).

The World Health Organization defines multimorbidity as the coexistence of two or more chronic health conditions in the same individual (9). Multimorbidity is a growing health concern as the population ages resulting in increased healthcare utilization (HCU) and poorer health outcomes (10). In 2014, Noonan et al. (11), developed a Multimorbidity Index (MMI) that assessed the presence of 30 secondary health conditions (SHCs), that included both complications following SCI and pre-existing comorbidities, and found that the MMI-30 significantly correlated with self-reported HCU using the 7-item HCU questionnaire (12), physical and mental health status as measured by the 12-item Short Form-12 (SF-12) Physical (PCS-12) and Mental Component Summary (MCS-12) scores, and quality of life (QoL) measured using Life Satisfaction-11 (LiSAT-11) first question and a single item QoL measure. A higher MMI score was associated with lower PCS-12 and MCS-12 scores, as well as significantly lower LiSAT-11 and overall QoL scores. More recently, the same MMI-30 was validated in persons with NTSCI and demonstrated similar relationships with HCU, PCS-12, MCS-12, LiSAT-11, and QoL scores (13).

Network analysis is a powerful tool used to visualize complex relationships among variables (i.e., nodes) and examine the importance of each variable in the network structure via connections (i.e., edges) (14). In healthcare, network analysis has been broadly applied to describe, explore, and understand structural and relational aspects of health. Examples include modelling disease outbreaks (15), resource utilization (16), as well as understanding multimorbidity (17). In SCI, the use of network analysis can identify important nodes and relationships among SHCs and health outcomes (18).

Depending on the data type, certain statistical models can be applied to create the network model. The pairwise Markov Random Field (MRF) is a broad class of statistical modelling, characterized by undirected edges between nodes that indicate conditional dependence between nodes (19). Common examples of MRF include the Gaussian Graphical Model (GGM) for continuous normally distributed data (20) and ordinal data (21); the Ising Model for binary data (22); and the Mixed Graphical Model (MGM) for mixed data consisting of both categorical and continuous variables (23). Within these networks, an undirected edge reflects an association between two nodes, and the edge weighted reflects a quantitative value which indicates the reliability of the interaction.

Network centrality provides insight into the relative importance of each node in the context of the other nodes in the network by assigning a score to each node. Different centrality indices, such as strength, closeness, or betweenness, can provide insights into different dimensions of centrality (14). High centrality nodes have strong connections to many other nodes, and act as hubs that connect otherwise disparate nodes to one another. Low centrality nodes exist on the periphery of the network, and have fewer and weaker connections to other nodes within the network (14). Thus, the network properties can help identify relevant sub-structures within a network and inform which nodes to target, thereby creating a more concise screening tool for determining connections between medical diagnoses and health outcomes.

In this study, network analysis was used to explore the relationships between the 30 SHCs included in the MMI-30 with HCU, health status (PCS-12, MCS-12), and QoL (LiSAT-11, QoL score) in persons with SCI, with the intent to refine the MMI-30 for clinical use. Specifically, the objectives were to (1) apply three network models (GGM, Ising, and MGM) to the 2011–2012 Canadian SCI Community Survey dataset (24, 25) to identify key variables important in each network, (2) create a short form of the MMI-30 using network analysis, and (3) compare the network-derived MMI to the MMI-30 in persons with TSCI and NTSCI.

## Materials and methods

### Data source

This study used the 2011–2012 Canadian SCI Community Survey data, described in full by Noreau et al. (24, 25). In brief, the survey was designed to better understand the service-related needs, service utilization and health outcomes in persons with TSCI and NTSCI living in the community.

### Measures

The 2011–2012 Canadian SCI Community Survey data included self-reported personal (e.g., age, sex), injury (e.g., level, completeness, and type of SCI), and environmental factors (e.g., living setting). The level and completeness of SCI was determined indirectly using the participants' answers about their lesion and sensorimotor and mobility capabilities and classified according to the American Spinal Cord Injury Association (ASIA) Impairment Scale (AIS) as per the International Standards for Neurological Classification of SCI (ISNCSCI) (25).

### Multimorbidity

Participants were asked about the presence or absence of 30 SHCs within the past 12 months (Supplementary Table 1). The SHCs included comorbidities (present prior to the SCI) and secondary complications following the injury. Participants who answered, "do not know" were considered as "do not have the condition." The MMI was the sum of 30 SHCs, ranging from 0 to 30, a higher score indicating more SHCs present (11).

### Healthcare utilization

Participants reported their HCU within the past 12 months using the 7-item Health Care Utilization questionnaire (12). HCU included contact with healthcare professionals (HCP), the number of HCP seen, the number of visits, type of HCP, rehospitalization, and hospital length of stay. Furthermore, participants were asked "During the past 12 months, was there ever a time when you felt that you needed healthcare but did not receive it?." If "Yes," participants were classified as "felt needed care was not received" (FNCNR), and asked to report the frequency, type of care was needed but not received, and the reason for not receiving care. If "No," participants were classified as "felt needed care was received" (FNCR) (13). In this study the response to the HCU related to FNCNR (HCU-FNCNR) was used in the analysis.

### Health status

The SF-12 was included to measure physical and mental health status (26, 27). The SF-12 measures eight health domains to provides a PCS-12 and a MCS-12 score (26). For PCS-12, a score of ≤50 has been recommended as a cut-off to determine a physical condition, while a score of ≤42 on the MCS-12 may be indicative of mental health conditions (28).

### Quality of life

Regarding the assessment of QoL, two distinct measures were employed. First, the LiSAT-11 measures satisfaction in 10 specific domains as well as overall life satisfaction asking about "My life as a whole is." Respondents were asked to rate their satisfaction levels on a scale ranging from "very dissatisfied" (coded as 1) to "very satisfied" (coded as 6) (11). In this study just the first question asking about overall life satisfaction was used. Second, the 5-point single-item QoL measure, "How do you rate your overall QoL?," where 1 is rated as "poor" is rated as 5 being "good," was used (11). To simplify the analysis, the LiSAT-11 responses were dichotomized. Responses falling within the range of 1–4 were categorized as "not satisfied" (coded as 0), while those rated 5–6 were classified as "satisfied" (coded as 1) (11). Similarly, the single-item QoL measure on a scale of 1 (poor) to 5 (good) was coded as "not satisfied"/"poor" (coded as 0) or "satisfied"/"good" (coded as 1) (11).

## Network analysis

Three weighted undirected biological networks were constructed using the GGM (for continuous data with multivariate gaussian distribution), Ising Model (for binary variables), and MGM (for mixed data with continuous and discrete variables). Depending on the type of network, nodes represented the 30 SHCs and the health outcome measures (HCU-FNCNR, PCS-12, MCS-12, LiSAT-11, and QoL scores), and edges represented the relationships between these nodes. The edge weight or partial correlation coefficients, which ranged from −1 to 1, represented the conditional independence associations. To enhance prediction accuracy and interpretability of the models, the L1 logistic Least Absolute Shrinkage and Selection Operator (LASSO) regression was applied to each node to estimate the connections between the node and other nodes (i.e., neighbor sets) (29). The Extended Bayes Information Criterion (EBIC) was also used to choose the best neighbor set with the lowest EBIC (29). Furthermore, the hyperparameter $\gamma$ determined model sparsity, a higher $\gamma$ led to a smaller number of false positives and therefore a sparser network.

In addition, three centrality measures were performed (i.e., descriptive statistics of a nodes' influence and its role in the network). Strength centrality is the absolute sum of a nodes' edge weights, a higher value or $Z$ score indicates a stronger connection. Expected Influence (EI) is a node's importance in activating or deactivating other nodes in the network that have negative edges, greater $Z$ scores indicate influential nodes (30). Betweenness centrality is the number of times a node is in the shortest path between two other nodes which represents its role in connecting the communities of nodes.

The GGM shows which variables predict one-another, allowing for sparse modeling of covariance structures, and may highlight potential causal relationships between observed variables (31). It estimates a network of partial correlation coefficients (i.e., the correlation between two variables after conditioning on all other variables in the dataset) (32). In the Ising Model, continuous variables such as PCS-12, MCS-12, and age were removed when fitting this model. In contrast, in the MGM, direct associations between heterogenous variables and the joint probability density allowed arbitrary probabilistic questions of the data to be explored (33).

For additional information comparing the three network models and their reliability, please see Supplementary Material Section 2.

## Statistical analyses

To compare TSCI and NTSCI, descriptive and bivariate analyses were performed using the Chi-square test (Fisher's exact test if the expected cell counts were less than five) or T-test (Mann–Whitney U-test for non-normal data), and depending on the data distribution, either the Pearson or Spearman correlation were used. Both statistically significant and clinically relevant factors (e.g., age, sex, incomplete SCI, and the MMI) were included in regression models to examine their effect on the measures (HCU-FNCNR, PCS-12, MCS-12, LiSAT-11, and the QoL score). For PCS-12 and MCS-12 (continuous variables) multiple linear regression models were used, and for HCU-FNCNR, LiSAT-11, and the QoL score (categorical variables) logistic regression models were used. Further side-by-side comparisons of the network-derived MMI and the MMI-30 were performed. All statistical analyses were performed using SAS software, Version 9.4 of the SAS System for Windows (Copyright © 2013, SAS Institute Inc., Cary, NC.). Value of $ps$ <0.05 were considered statistically significant. Networks were estimated and visualized using RStudio (version 3.4) using the "bootnet" package (CRAN; https://cran.r-project.org/) (32).

# Results

## Baseline participant characteristics

Of 1,549 participants, 1,137 (73.4%) were participants with TSCI and 412 (26.6%) were participants with NTSCI. Table 1 summarizes the demographic, clinical, and outcome comparisons between participants with TSCI and NTSCI, as described in the paper by Noreau et al. (24). Age at injury, sex, AIS, and lesion severity significantly differed among participants with TSCI and NTSCI. In response to HCU question "During the past 12 months, was there ever a time when you felt that you needed healthcare but did not receive it?" (i.e., HCU-FNCNR), in total, 292 (25.7%) and 89 (21.7%) participants with TSCI and NTSCI, respectively, answered "yes" to feeling needed care was not received (Table 1).

## Bivariate analysis

The Supplementary Table 1 shows hypothesis testing of the 30 SHCs for the health outcome measures: HCU-FNCNR, PCS-12, MCS-12, LiSAT-11 and the QoL scores in persons with TSCI and NTSCI. In the TSCI dataset, only deep vein thrombosis/pulmonary embolism (DVT) and diabetes did not significantly differ across any of the measures. For the NTSCI dataset, cancer, DVT, diabetes, high blood pressure and liver disease did not significantly differ across any of the measures. All other SHCs had significant associations with the health outcome measures ($p < 0.05$).

## Network analysis

### Gaussian graphical model

In the TSCI dataset, the GGM showed that five nodes (liver disease, DVT, cancer, heart disease and kidney stones) were independent, i.e., missing an edge (Figure 1A). The strongest connections were between depression and MCS-12 (edge weight 0.3), elbow/wrist problems and shoulder problems (edge weight 0.297), and the QoL score and LiSAT-11 (edge weight 0.282). The network structure also indicated that (1) HCU-FNCNR (labeled as "Care") negatively correlated with PCS-12, MCS-12 and the QoL score, and positively correlated with light headedness/dizziness and fatigue; (2) the QoL score negatively correlated with depression, light headedness/dizziness, HCU-FNCNR and trouble sleeping, and positively correlated with LiSAT-11, PCS-12 and MCS-12; and (3) LiSAT-11 positively correlated with the QoL score, MCS-12 score and PCS-12 score, and negatively correlated with neuropathic pain. Overall, the GGM had a medium stability of estimation, strength and edge weight had centrality stability (CS)-coefficient values >0.5, and estimations of EI were unstable. The centrality indices: strength, betweenness, and EI for the TSCI GGM indicated that MCS-12 had the strongest strength, autonomic dysreflexia (AD) had the highest betweenness, and both AD and the QoL score had high EI (Figure 2A). HCU-FNCNR had lower strength and EI was significantly different from around one third of the nodes. The QoL score ranked first in betweenness, while most nodes had zero betweenness, including the other four health outcome measures (HCU-FNCNR, PCS-12, MCS-12, and LiSAT-11 scores).

For the NTSCI dataset, the GGM network structure was sparse (Figure 1B). Only one third of the nodes were connected and the connections were weak. The strongest connections were between elbow/wrist problems and shoulder pain (edge weight 0.272), followed by the QoL score and LiSAT-11 (edge weight 0.199), and the QoL score and MCS-12 (edge weight 0.14). Additionally, depression and MCS-12 had an edge weight of–0.107, which was significantly different from all other edges. Notably, HCU-FNCNR was not connected to any other nodes, and had zero strength, betweenness and EI. LiSAT-11 was positively associated with the QoL score and MCS-12, and the QoL score positively correlated with PCS-12, MCS-12, and LiSAT-11. All centrality measures and edge weights indicated an unstable estimation, the CS-coefficients were $< 0.5$. The QoL score and LiSAT-11 had a significantly larger strength and EI than around half of the nodes, the QoL score also had the largest betweenness. MCS-12 had a significantly higher strength than around two thirds of the nodes and a medium EI that was only significantly different from that of LiSAT-11, the QoL score, shoulder pain, and elbow/wrist pain. Moreover, the PCS-12 had a low strength and EI that was significantly different from less than 10 nodes.

### Ising model

In the TSCI dataset, the Ising Model showed six independent nodes (cancer, liver disease, DVT, high blood pressure, heart disease, and diabetes) (Figure 1C). The strongest connections were between the QoL score and LiSAT-11, elbow/wrist problems and shoulder problems, and the QoL score and depression with edge weights of 2.165, 1.795, and-1.08, respectively. Both the QoL score, and LiSAT-11 had a negative relationship with depression. A negative association was identified between the QoL score and HCU-FNCNR, trouble sleeping, neurological deterioration, and light headedness/dizziness. LiSAT-11 was negatively associated with depression, fatigue, neuropathic pain, constipation, and joint contractures. Additionally, HCU-FNCNR was negatively associated with the QoL score, but positively associated with depression and fatigue. Based on the CS-coefficient of strength, EI, and edge weight (all >0.5), AD had the strongest strength, betweenness and EI, suggesting that it had importance in the network and the strongest connection to other nodes. The QoL score and LiSAT-11 had high strength and medium EI, but the QoL score showed more significant differences than LiSAT-11 for both measures. HCU-FNCNR had a medium absolute value of strength and EI and the values were significantly different from around one third of the nodes.

In the NTSCI dataset, the Ising Model showed four nodes (degenerative arthritis/osteoarthritis, ulcer/gastric esophageal reflux disease, HCU-FNCNR, and osteoporosis) were independent (Figure 1D). Moreover, three node pairs were separate from the main network cluster, i.e., shoulder pain and elbow/wrist pain (edge weight 1.834), cancer and heart disease (edge weight 1.272), as well as high blood pressure and diabetes (edge weight 0.842). Within the main cluster, the strongest connection was between the QoL score

TABLE 1 Demographic and clinical characteristics of participants with traumatic spinal cord injury (TSCI) and non-traumatic spinal cord injury (NTSCI), adapted from Noreau et al. (24, 25), Noonan et al. (11), and Hong et al. (13).

| Variables | TSCI *n* = 1,137 | NTSCI *n* = 412 | *p* value |
|---|---|---|---|
| Age at injury, years (mean, SD)* | 48.3 ± 13.3 | 53.1 ± 14.9 | **<0.001** |
| Years since injury, (mean, SD)* | 18.5 ± 13.1 | 18.7 ± 17.1 | NS |
| Sex, male (*n*, %)* | 806 (70.9) | 235 (57.0) | **<0.001** |
| Ethnicity (Caucasian), *n* (%)* | 1,052 (92.5) | 377 (91.5) | NS |
| Region of residence (*n*, %)* | | | |
| Quebec | 275 (24.2) | 121 (29.4) | NS |
| Ontario | 245 (21.5) | 101 (24.5) | |
| British Columbia | 227 (20.0) | 69 (16.7) | |
| Other (Prairies and Atlantic provinces) | 390 (34.3) | 121 (29.4) | |
| Self-reported current neurological classification (*n*, %)*# | | | |
| Tetraplegia AIS A or B | 229 (21.3) | 14 (3.7) | **<0.001** |
| Paraplegia AIS A or B | 361 (33.6) | 81 (21.4) | |
| Tetraplegia AIS C or D | 301 (28) | 69 (18.2) | |
| Paraplegia AIS C or D | 184 (17.1) | 215 (56.7) | |
| Missing | 62 | 33 | |
| Lesion severity (*n*, %)* | | | |
| Complete | 444 (39.1) | 72 (17.5) | **<0.001** |
| Incomplete | 693 (61) | 340 (82.5) | |
| Area of residence (population) | | | |
| <10,000 | 244 (21.9) | 77 (19.5) | NS |
| 10,000–100,000 | 196 (17.6) | 53 (13.4) | |
| >100,000 | 431 (38.7) | 176 (44.6) | |
| Large cities | 242 (21.7) | 89 (22.5) | |
| Missing | 24 | 17 | |
| Education level* | | | |
| Less than high school | 157 (13.8) | 59 (14.3) | NS |
| High school | 249 (22) | 87 (21.3) | |
| College/university | 561 (49.6) | 205 (50.1) | |
| Graduate studies | 92 (8.1) | 27 (6.6) | |
| Others | 73 (6.5) | 31 (7.6) | |
| No record | 5 | 3 | |
| Marital status* | | | |
| Married | 466 (41.2) | 181 (44.9) | NS |
| Common-law | 107 (9.5) | 43 (10.7) | |
| Widowed, separated or divorced | 205 (18.1) | 77 (19.1) | |
| Single, never married | 353 (31.2) | 102 (25.3) | |
| Undeclared | 6 | 9 | |
| Current living setting* | | | |
| Own home | 793 (70) | 256 (63.8) | NS |
| Rental housing | 233 (20.6) | 99 (24.7) | |
| Assisted-living | 24 (2.1) | 13 (3.2) | |
| Hospital/long-term care facility | 17 (1.5) | 5 (1.2) | |
| Others | 66 (5.8) | 28 (7) | |
| Missing | 4 | 11 | |

*(Continued)*

TABLE 1 (Continued)

| Variables | TSCI $n = 1{,}137$ | NTSCI $n = 412$ | $p$ value |
|---|---|---|---|
| Multimorbidity measure, mean (SD)[†] | | | |
| MMI-30 | 13.1 (4.3) | 12.4 (4.9) | **0.015** |
| Health outcome measures, mean (SD)[†] | | | |
| PCS-12 score | 33.5 (8.6) | 33.5 (8.5) | NS |
| MCS-12 score | 51.6 (11.4) | 48.5 (11.6) | **<0.001** |
| Life Satisfaction-11, question 1 score | 4 (1) | 3.9 (1) | NS |
| Overall QoL score | 3.8 (0.9) | 3.7 (0.9) | **0.001** |
| Had a contact with an HCP, yes, *n* (%) | 1,017 (89.4) | 360 (87.3) | NS |
| Number of HCPs seen, mean (SD) | 3.9 ± 2.5 | 4 ± 2.5 | NS |
| Frequency of any HCP seen, mean (SD) | 44.4 ± 138 | 47.5 (101.7) | NS |
| Re-hospitalized, yes, *n* (%) | 297 (26.1) | 103 (25) | NS |
| Number of nights spent in hospital, mean (SD) | 23.5 (46.7) | 27.4 (47.3) | NS |
| Felt needed care was not received, yes, *n* (%) | 292 (25.7) | 89 (21.7) | NS |
| Number of times needed care could not be received, mean (SD) | 9.8 (35.7) | 24.2 (112.6) | **0.023** |

*Demographic and clinical characteristics between persons with TSCI or NTSCI adapted from Noreau et al. (24, 25).
[†]Multimorbidity, health status, and healthcare utilization in the past 12 months for persons with TSCI and NTSCI adapted from Noonan et al. (11) and Hong et al. (13), respectively.
[‡]The American Spinal Injury Association (ASIA) Impairment Scale (AIS) was evaluated indirectly from participants' answers about their lesion and sensorimotor and mobility capabilities.
Bold font indicates statistical significance.
AIS, American Spinal Injury Association (ASIA) Impairment Scale; MMI-30, Multimorbidity Index consisting of 30 secondary health conditions; SF-12, Short Form 12-item survey; PCS-12, Physical Component Summary score; MCS-12, Mental Component Summary score; HCP, healthcare professional, LiSAT-11, Life Satisfaction-11; QoL, Quality of Life measure; SD, standard deviation; NS, not significant.

and LiSAT-11 (edge weight 1.81), of which LiSAT-11 was also negatively associated with trouble sleeping, neurological deterioration, and sexual dysfunction. However, the network was unstable (all CS-coefficients were < 0.5). While kidney stones had the largest strength and EI, the significance test suggested that the strength and EI were not significantly different than that of other nodes. LiSAT-11 had a relatively large strength and a medium EI where the strength was only significantly different from four nodes and EI showed no significant differences from other nodes. The QoL score had a low strength and EI, and the significance test showed that the values were only different from very few nodes, four for strength and two for EI.

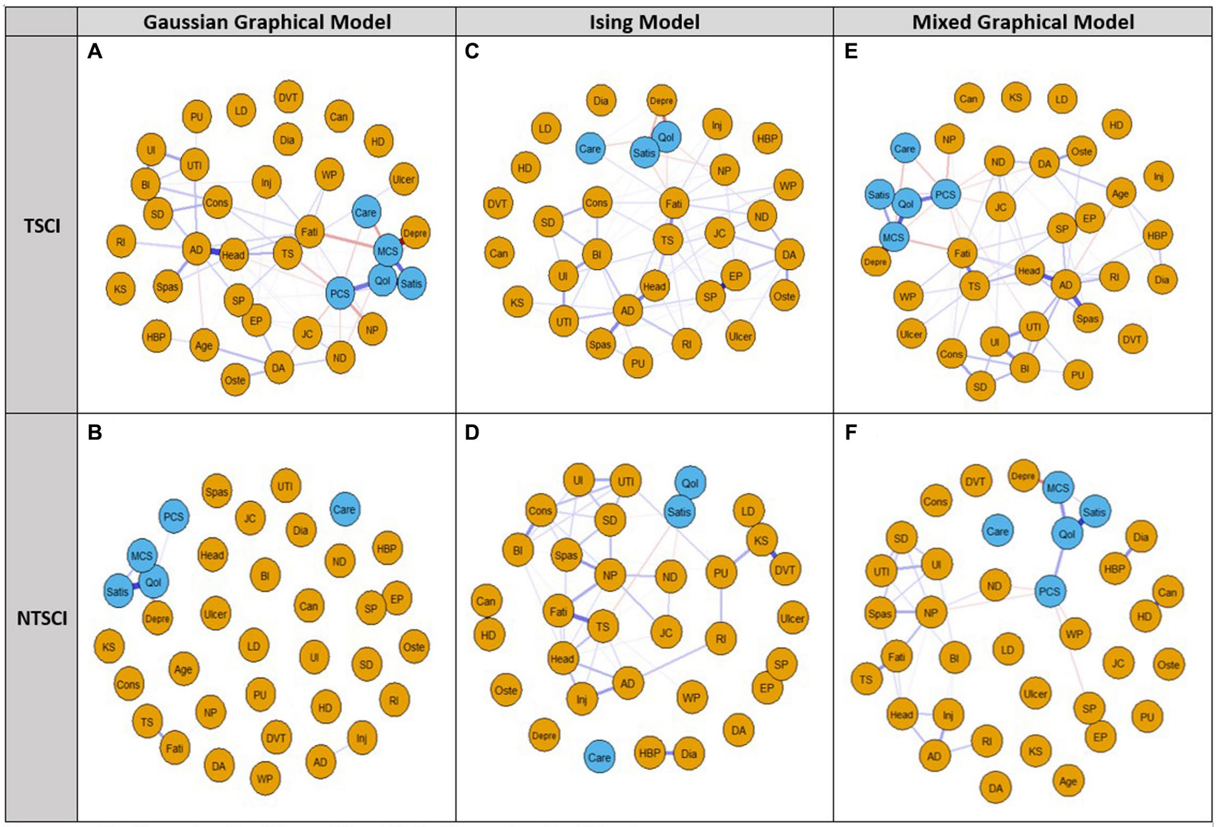
### Mixed graphical model

For TSCI, the MGM showed cancer, kidney stone, liver disease, heart disease, DVT and injuries caused by loss of sensation (e.g., burns from carrying hot liquids in the lap or sitting too close to a heater or fire) were independent (Figure 1E). The strongest connection was between elbow/wrist problems and shoulder problems (edge weight 0.825). A negative correlation was apparent between HCU-FNCNR, PCS-12, and MCS-12, whereas LiSAT-11 was positively correlated with the QoL score, PCS-12, and MCS-12, and the QoL score was positively correlated with LiSAT-11, PCS-12, and PCS-12. The stability of edge weight, strength and EI were good (CS-coefficient > 0.5), while betweenness indicated instability (CS-coefficient 0.206) which may be caused by weak connections between nodes. Interestingly, AD had the strongest strength, betweenness and EI and was the most powerful node in the network (Figure 2A). Its strength and EI were significantly different from most nodes in the network. The node HCU-FNCNR (labeled as "Care") had poor performance in all centrality indices, its strength and EI were significantly smaller than the other nodes. PCS-12 and MCS-12 had significantly larger strength, but medium EI, while the QoL score, and LiSAT-11 had significantly larger strength and EI.

For NTSCI, the MGM network was sparse (Figure 1F). Of the health outcome measures, HCU-FNCNR was independent. The strongest connections were between elbow/wrist problems and shoulder pain (edge weight 0.998), LiSAT-11 and the QoL score (edge weight 0.758), followed by cancer and heart disease (edge weight 0.61). LiSAT-11 was positively associated with MCS-12, and the QoL score was also positively associated with MCS-12 and PCS-12. Despite this, the three centrality measures and edge weight showed an unstable network (CS-coefficient < 0.5). The strength and betweenness of many nodes were estimated to be zero. The QoL score had the largest strength and EI, and neuropathic pain had the best performance for betweenness (Figure 2B). Depression had a medium EI but was significantly different from all other nodes except PCS-12 and MCS-12. LiSAT-11 had a medium strength and EI that were significantly different from a third of the nodes, while MCS-12 had significantly larger strength but lower EI. The PCS-12 also had significantly lower EI and larger strength; however, its strength was only significantly different from age and the QoL score.

## Comparison of network models between TSCI and NTSCI

The three network models between persons with TSCI and NTSCI presented a similar pattern (Figures 1, 2); however, the consistency of results among the three network analyses in the TSCI group was stronger. In terms of the edge weight, the Ising Model provided the largest overall edge weight, followed by the MGM and then the GGM.




**Orange nodes:** Secondary health conditions (SHC); **Blue nodes**: Health outcomes.

FIGURE 1
Network analysis of the 2011–2012 Canadian SCI Community Survey dataset using the Gaussian Graphical Model, Ising Model, and Mixed Graphical Model in persons with traumatic spinal cord injury (TSCI: **A,C,E**) and non-traumatic spinal cord injury (NTSCI: **B,D,F**). Nodes represent the 30 secondary health conditions (SHCs, orange dots) and health outcome measures (blue dots). Edges (lines) represent a temporal/contemporaneous relationship between another variable at the next measurement. Blue edges have positive associations and red edges have negative associations; edge intensity represents the strength of the relationship; stronger associations are more saturated. For the Ising Model independent non-binary variables PCS-12, MCS-12, and age were removed. SHCs consisted of AD, Autonomic dysreflexia; BI, Bowel incontinence; Can, Cancer; Cons, Constipation; DA, Osteoarthritis/degenerative arthritis; Depre, Depression/mood problem; Dia, Diabetes; DVT, Deep vein thrombosis/pulmonary embolism; EP, Elbow/wrist problems; Fati, Fatigue; HBP, High blood pressure; HD, Heart disease; Head, Light headedness/dizziness; Inj, Injuries caused by loss of sensation; JC, Joint contractures; KS, Kidney stones; LD, Liver disease; ND, Neurological deterioration; NP, Neuropathic pain; Oste, Osteoporosis; PU, Pressure ulcers; RI, Respiratory infections; SD, Sexual dysfunction; SP, Shoulder problems; Spas, Spasticity; TS, Trouble sleeping; Ulcer, Ulcer/gastric esophageal reflux disease; UI, Urinary incontinence; UTI, Urinary tract infection; WP, Weight problem. Health outcome measures included Care: felt needed care not received (Y/N); PCS-12, Physical Component Summary score; MCS-12, Mental Component Summary score; QoL, Quality of Life; Satis, Life Satisfaction-11.

For TSCI data, the three network structures showed similarities in terms of which nodes were connected and/or isolated. In general, the edge weights of the QoL score and LiSAT-11, MCS-12 and depression, and elbow/wrist problems and shoulder problems were strong in all models. Cancer, DVT, liver disease, and heart disease were isolated in all models. The estimation of strength was stable for all models. For AD, the magnitude of strength was slightly different among the methods, where MGM gave the highest value and GGM gave the lowest value. For EI, the estimation was stable under the Ising Model and MGM, but the CS-coefficient was 0.361 under the GGM. The estimation of EI for the QoL score was quite different between the Ising Model and the others. Betweenness indicated instability in all models, and the Ising Model had the lowest CS-coefficient. Moreover, edge weight was stable under all models.

For NTSCI data, all three network models were sparse. Only one-third of the nodes were connected, and the associations were generally weak. In all models, the connection between elbow/wrist and shoulder problems had the strongest edge. The QoL score and LiSAT-11, cancer and heart disease, MCS-12 and depression were also closely related. The Ising Model and MGM had zero CS-coefficients for all centrality indices (Figure 2B). Furthermore, the GGM presented an unstable strength, EI [CS (cor = 0.7) = 0.438], and betweenness [CS (cor = 0.7) = 0]. Meanwhile, the edge weight estimation was unstable under all three models. The estimation of strength was quite different among models. The differences among the models were larger than that for TSCI data, and GGM provided a larger magnitude compared with the others. For strength, the estimation of kidney stones was quite different among the models where the Ising Model gave the largest estimation. For EI, the estimated value of the QoL score was very different between the Ising Model and the other two where the Ising Model gave a much smaller number. The differences also existed for kidney stones where the Ising Model had a much bigger value. The estimation of

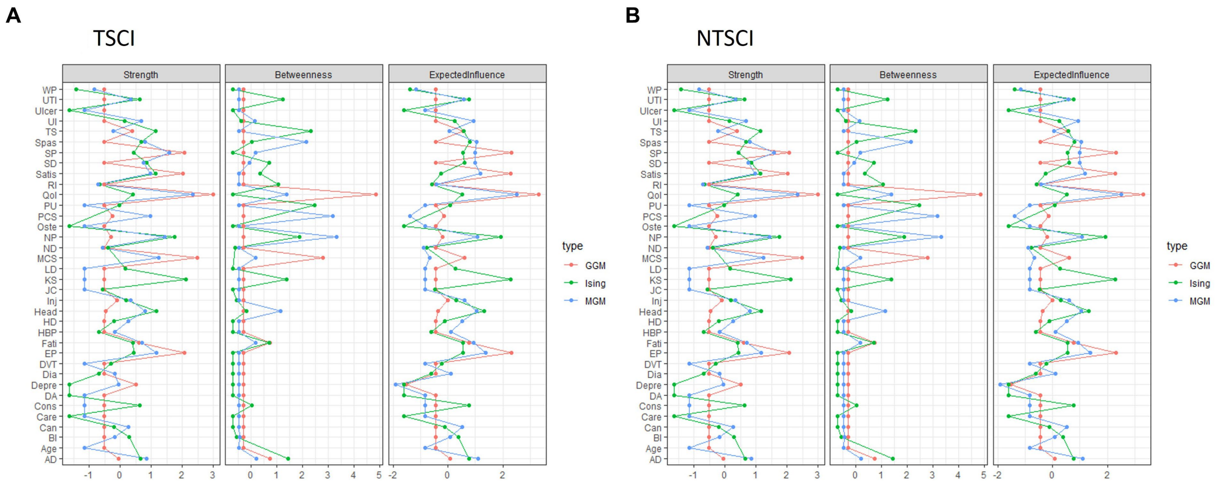



FIGURE 2
The centrality indices: strength, betweenness, and expected influence for each network model: Gaussian Graphical Model (GGM), Ising Model (Ising), and Mixed Graphical Model (MGM) in person with **(A)** traumatic spinal cord injury (TSCI) and **(B)** non-traumatic spinal cord injury (NTSCI). Nodes represent the 30 secondary health conditions (SHCs, i.e., multimorbidity) and health outcome measures. SHCs consisted of AD, Autonomic dysreflexia; BI, Bowel incontinence; Can, Cancer; Cons, Constipation; DA, Osteoarthritis/degenerative arthritis; Depre, Depression/mood problem; Dia, Diabetes; DVT, Deep vein thrombosis/pulmonary embolism; EP, Elbow/wrist problems; Fati, Fatigue; HBP, High blood pressure; HD, Heart disease; Head, Light headedness/dizziness; Inj, Injuries caused by loss of sensation; JC, Joint contractures; KS, Kidney stones; LD, Liver disease; ND, Neurological deterioration; NP, Neuropathic pain; Oste, Osteoporosis; PU, Pressure ulcers; RI, Respiratory infections; SD, Sexual dysfunction; SP, Shoulder problems; Spas, Spasticity; TS, Trouble sleeping; Ulcer, Ulcer/gastric esophageal reflux disease; UI, Urinary incontinence; UTI, Urinary tract infection; WP, Weight problem. Health outcome measures included Care: healthcare utilization-felt needed care not received (coded as Y/N); health status: PCS Physical Component Summary (PCS-12) score and MCS Mental Component Summary (MCS-12) score; QoL, Quality of Life; Satis, Life Satisfaction-11.

betweenness was similar, however GGM gave a larger estimation for the QoL and MCS-12 scores, while Ising had a larger estimation for urinary tract infections and trouble sleeping.

Thus, by comparing the three network results and combining the bivariate analysis, cancer, DVT, diabetes, high blood pressure and liver disease were removed from the MMI-30, and the remaining 25 SHCs formed the network-derived MMI-25.

## Comparison of MMI-30 vs. MMI-25 using the TSCI dataset

To test the efficiency of the network-derived MMI-25 using the TSCI dataset, the MMI-30 and MMI-25 logistic regression model outcomes were compared for HCU-FNCNR, PCS-12, MCS-12, LiSAT-11, and the QoL score (Table 2). Both the MMI-30 and the MMI-25 significantly correlated with each of the health outcome measures ($p < 0.0001$), suggesting that the MMI-25 was as effective as the MMI-30.

## Comparison of MMI-30 vs. MMI-25 using the NTSCI dataset

Logistic regression model outcomes were compared between the MMI-30 and MMI-25 using the NTSCI dataset (Table 3). The MMI-30 significantly correlated with HCU-FNCNR, PCS-12, MCS-12, LiSAT-11, and the QoL scores ($p < 0.0001$ in all models). Similarly, the MMI-25 achieved the same significance in all models ($p < 0.0001$). The MMI-25 correlation coefficient was larger than the MMI-30 and the odds ratio was slightly stronger than the MMI-30, suggesting that the MMI-25 was as effective as the MMI-30.

# Discussion

Previously, we reported that multimorbidity using the MMI-30 was associated with higher HCU and lower physical and mental health and QoL in persons with TSCI (11) and NTSCI (13). In this study, we applied three network models: GGM, Ising Model, and MGM to the 2011–2012 Canadian SCI Community Survey dataset (24) and created the MMI-25, a short form of the MMI-30.

Within the TSCI dataset (n = 1,137), the three network models showed medium-dense connections, with most of the associations being positive. Overall results of centrality, correlation stability, and significance testing in all three models indicated stable network structures. Notably, several SHCs were isolated from the networks, which included cancer, diabetes, DVT, heart disease, liver disease, kidney stones, and/or injuries caused by loss of sensation. Strong connections were evident between the QoL score, LiSAT-11, MCS-12, depression, elbow/wrist, and shoulder problems; of which the most significant edge weights were between the QoL score and LiSAT-11, depression and MCS-12, and elbow/wrist and shoulder problems. In alignment with published literature regarding QoL and life satisfaction (5–7) as well as depression and MCS-12 (26, 28, 34) we found strong connections between the QoL score and LiSAT-11 and depression and MCS-12 in the network models. Several factors have high associations with the QoL score and LiSAT-11, including both modifiable and non-modifiable ones, such as pain, contractures, sleep problems, bowel and sexual dysfunction (34). Surprisingly, in our study, these

TABLE 2 Comparison of MMI-30 vs. MMI-25 regression models and the health outcome measures in persons with traumatic spinal cord injury (TSCI).

A) Analysis of "Healthcare Utilization-Felt that Needed Care was Not Received" using logistic regression.

| Variables | MMI-30 | | | | MMI-25 | | | |
|---|---|---|---|---|---|---|---|---|
| | β | value of p | OR | 95% CI | β | value of p | OR | 95% CI |
| Live in own home | -0.107 | 0.169 | 0.81 | 0.60, 1.10 | −0.111 | 0.154 | 0.80 | 0.59, 1.09 |
| Incomplete SCI | −0.006 | 0.931 | 0.99 | 0.74, 1.32 | −0.007 | 0.924 | 0.99 | 0.74, 1.32 |
| Sex, male | −0.257 | **0.001** | 0.60 | 0.44, 0.81 | −0.256 | **0.001** | 0.60 | 0.45, 0.81 |
| Age | −0.002 | 0.775 | 1 | 0.99, 1.01 | 0.000 | 1.000 | 1 | 0.99, 1.01 |
| Days since injury | 0.000 | **0.021** | 1 | 1, 1 | 0.000 | **0.024** | 1 | 1, 1 |
| MMI | 0.174 | **<0.0001** | 1.19 | 1.15, 1.24 | 0.182 | **<0.0001** | 1.20 | 1.15, 1.25 |

B) Analysis of "PCS-12" using multiple linear regression.

| Variables | MMI-30 | | | MMI-25 | | |
|---|---|---|---|---|---|---|
| | *β* | Value of *p* | 95% CI | *β* | Value of *p* | 95% CI |
| Age | −0.080 | **<0.0001** | −0.12, −0.05 | −0.090 | **<0.0001** | −0.13, −0.05 |
| Sex, male | −0.989 | 0.057 | −2.01, 0.03 | −0.996 | 0.055 | −2.01, 0.02 |
| Incomplete SCI | 0.273 | 0.571 | −0.67, 1.22 | 0.284 | 0.556 | −0.66, 1.23 |
| Area of residence* | | | | | | |
| Large cities | 1.830 | **0.010** | 0.44, 3.22 | 1.854 | **0.009** | 0.47, 3.24 |
| Pop >100k | 1.961 | **0.002** | 0.74, 3.19 | 1.977 | **0.002** | 0.75, 3.20 |
| Pop 10k-100k | −0.460 | 0.540 | −1.93, 1.01 | −0.420 | 0.575 | −1.89, 1.05 |
| Not married | −1.078 | **0.024** | −2.01, −0.14 | −1.117 | **0.019** | −2.05, −0.18 |
| MMI | −0.858 | **<0.0001** | −0.97, −0.75 | −0.892 | **<0.0001** | −1.00, −0.78 |

C) Analysis of "MCS-12" using multiple linear regression.

| Variables | MMI-30 | | | MMI-25 | | |
|---|---|---|---|---|---|---|
| | *β* | Value of *p* | 95% CI | *β* | Value of *p* | 95% CI |
| Age | 0.039 | 0.119 | −0.01, 0.09 | 0.031 | 0.224 | −0.02, 0.08 |
| Sex, male | 0.874 | 0.225 | −0.54, 2.29 | 0.887 | 0.220 | −0.53, 2.30 |
| Incomplete SCI | −1.067 | 0.111 | −2.38, 0.25 | −1.036 | 0.123 | −2.35, 0.28 |
| Area of residence* | | | | | | |
| Large cities | −0.012 | 0.990 | −1.94, 1.92 | −0.001 | 0.999 | −1.93, 1.93 |
| Pop >100k | 0.423 | 0.625 | −1.28, 2.12 | 0.426 | 0.624 | −1.28, 2.13 |
| Pop 10k-100k | −0.623 | 0.549 | −2.67, 1.42 | −0.597 | 0.567 | −2.65, 1.45 |
| Not married | −2.238 | **0.001** | −3.54, −0.94 | −2.271 | **0.001** | −3.57, −0.97 |
| MMI | −0.851 | **<0.0001** | −1.00, −0.70 | −0.859 | **<0.0001** | −1.02, −0.70 |

D) Analysis of "Life Satisfaction-11" using logistic regression.

| Variables | MMI-30 | | | | MMI-25 | | | |
|---|---|---|---|---|---|---|---|---|
| | *β* | Value of *p* | OR | 95% CI | *β* | Value of *p* | OR | 95% CI |
| Ethnicity, white | 0.120 | 0.333 | 1.27 | 0.78, 2.07 | 0.127 | 0.308 | 1.29 | 0.79, 2.09 |
| Age | 0.004 | 0.440 | 1.00 | 0.99, 1.01 | 0.003 | 0.602 | 1.00 | 0.99, 1.01 |
| Sex, male | −0.140 | **0.047** | 0.76 | 0.57, 1.00 | −0.139 | **0.048** | 0.76 | 0.57, 1.00 |
| Education, high school or greater | 0.416 | **<0.0001** | 2.30 | 1.58, 3.34 | 0.419 | **<0.0001** | 2.31 | 1.59, 3.36 |
| Married | 0.338 | **<0.0001** | 1.97 | 1.53, 2.53 | 0.340 | **<0.0001** | 1.97 | 1.53, 2.54 |
| MMI | −0.115 | **<0.0001** | 0.89 | 0.87, 0.92 | −0.117 | **<0.0001** | 0.89 | 0.86, 0.92 |

*(Continued)*

TABLE 2 (Continued)

| E) Analysis of "Quality of Life Score" using logistic regression. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | MMI-30 | | | | MMI-25 | | | |
| | *β* | Value of *p* | OR | 95% CI | *β* | Value of *p* | OR | 95% CI |
| Ethnicity, white | 0.347 | **0.006** | 2.00 | 1.22, 3.28 | 0.357 | **0.005** | 2.04 | 1.25, 3.34 |
| Age | −0.009 | 0.081 | 0.99 | 0.98, 1.00 | −0.011 | **0.040** | 0.99 | 0.98, 1.00 |
| Sex, male | −0.173 | **0.025** | 0.71 | 0.52, 0.96 | −0.173 | **0.025** | 0.71 | 0.52, 0.96 |
| Education, high school or greater | 0.194 | **0.041** | 1.47 | 1.02, 2.14 | 0.197 | **0.039** | 1.48 | 1.02, 2.15 |
| Married | 0.355 | **<0.0001** | 2.04 | 1.559, 2.67 | 0.357 | **<0.0001** | 2.04 | 1.55, 2.68 |
| MMI | −0.147 | **<0.0001** | 0.86 | 0.84, 0.89 | −0.153 | **<0.0001** | 0.86 | 0.83, 0.89 |

*Baseline is population < 10,000 individuals. Bold font indicates statistical significance.

conditions were not found to be strongly connected to the QoL score and LiSAT-11 in the TSCI networks. This could be due to the design of the 2011–2012 Canadian SCI Community Survey (24), the way in which the QoL score was measured (5-point question rating overall QoL and 6-point question asking about overall life satisfaction), or the fact that QoL was self-reported and based on the participants' account of the past 2 weeks preceding the survey. Future studies should consider using longitudinal domain-specific measures to provide more concrete information on areas of dissatisfaction and guidance for clinical care.

In terms of the strong connection between elbow/wrist problems and shoulder problems and its significant edge weight in both the TSCI and NTSCI networks, this was an unexpected finding when considering all the other possible connections within the 35 nodes. However, as persons with SCI are highly dependent on their arms and hands for mobility and several activities of daily living, they are at high risk for shoulder, elbow, wrist, and hand injuries, including neuromusculoskeletal pathologies and nociceptive pain (35). Shoulder problems can be caused by acute injury or chronic pathology, but are most often related to overuse injuries of the rotator cuff (36–38). Whereas for elbow/wrist problems, the elbow joint is often overused particularly during push-up manoeuvres required for both weight shifts and transfers (39). Both elbow/wrist and shoulder problems can significantly negatively affect a person's health and function; thus, this significant association between elbow/wrist problems and shoulder problems can enable clinicians to identify these injuries earlier, and employ treatment and/or preventive strategies to preserve shoulder and elbow function after SCI.

Another important observation within the three TSCI network structures and the node centrality measures was the role of AD. The high centrality scores for AD suggested that it plays an important role in connecting several nodes within each network. AD is characterized by the acute elevation of arterial blood pressure and bradycardia in response to stimuli such as urinary retention, constipation, or infection (40, 41). Persons with an SCI above T6 are at high risk of developing AD; moreover, those with complete injuries have a greater likelihood of AD episodes than those with an incomplete injury (42). Left untreated AD may have serious consequences such as stroke, seizures, and cardiac arrest. Our findings here indicate that AD is central to many other SHCs and suggests that if AD can be effectively managed, treated or prevented, then other SHCs such as light headedness, spasticity, and health outcomes such as PCS-12 and MCS-12 may also be improved.

When comparing the network differences between TSCI and NTSCI, the small NTSCI sample size ($n = 412$) resulted in sparse network structures. However, the key associations identified in the TSCI networks were also observed in the NTSCI networks, for example the connections between the QoL score and LiSAT-11 and elbow/wrist problems and shoulder problems. Thus, rather than creating two network-derived MMIs, one for TSCI and one for NTSCI, we chose to create one generalized MMI for both types of SCI. To do this, we reviewed the bivariate and network results, and removed five SHCs (cancer, diabetes, DVT, high blood pressure and liver disease) from the MMI-30, creating the network-derived MMI-25.

Logistic regression models were constructed to examine the MMI-25's influence on each health outcome measure, then both the MMI-25 and the original MMI-30 were compared. Our findings indicated that the MMI-25 was as effective as the MMI-30, as it demonstrated the same significance and a larger correlation coefficient. Accordingly, the MMI-25 would be easier for clinicians to incorporate into their routine work to determine patients' risk for poorer health outcomes (as evident in the regression models no information was lost).

Several limitations of this study should be considered. First, the data in the 2011–2012 Canadian SCI Community Survey is self-reported, which may be subject to recall bias. Second, cross-sectional data cannot be used to infer causality, it is not clear to determine if the most central symptom caused other symptoms/outcomes, the other way around, or both. Thus, future research should consider conducting a longitudinal SCI survey. Third, the NTSCI sample size of 412 participants, while relatively large compared to other NTSCI studies, resulted in sparse and unstable network structures, limiting the ability to detect differences between centrality estimates and estimation accuracy. Fourth, for the Ising Model, the two continuous independent variables (PCS-12 and MCS-12 scores) were not included; therefore, some of the information related to the connections between the 30 SHCs and these two continuous outcomes may not be measured. Fifth, the GGM requires variables to have multivariate Gaussian distribution, which is not the case for most variables in our study,

TABLE 3 Comparison of MMI-30 vs. MMI-25 and the health outcome measures in participants with non-traumatic spinal cord injury (NTSCI).

A) Analysis of "Healthcare Utilization-Felt that Needed Care was Not Received" using logistic regression.

| Variables | MMI-30 | | | | MMI-25 | | | |
|---|---|---|---|---|---|---|---|---|
| | *β* | Value of *p* | OR | 95% CI | *β* | Value of *p* | OR | 95% CI |
| Live in own home | −0.054 | 0.686 | 0.90 | 0.53, 1.52 | −0.057 | 0.673 | 0.89 | 0.53, 1.51 |
| Incomplete SCI | −0.065 | 0.704 | 0.88 | 0.45, 1.71 | −0.062 | 0.716 | 0.88 | 0.45, 1.72 |
| Sex, male | −0.431 | **0.001** | 0.42 | 0.25, 0.71 | −0.419 | **0.001** | 0.43 | 0.26, 0.72 |
| Age | −0.006 | 0.512 | 0.99 | 0.98, 1.01 | −0.005 | 0.547 | 1.00 | 0.98, 1.01 |
| Days since injury | −0.000 | 0.483 | 1.00 | 1, 1 | −0.000 | 0.492 | 1.00 | 1, 1 |
| MMI | 0.129 | **<0.0001** | 1.14 | 1.08, 1.20 | 0.135 | **<0.0001** | 1.14 | 1.08, 1.21 |

B) Analysis of "PCS-12" using multiple linear regression.

| Variables | MMI-30 | | | MMI-25 | | |
|---|---|---|---|---|---|---|
| | *β* | Value of *p* | 95% CI | *β* | Value of *p* | 95% CI |
| Age | −0.103 | **<0.001** | −0.16, −0.05 | −0.108 | **<0.0001** | −0.16, −0.05 |
| Sex, male | 0.221 | 0.782 | −1.35, 1.79 | 0.096 | 0.904 | −1.47, 1.66 |
| Incomplete SCI | −0.683 | 0.526 | −2.80, 1.43 | −0.724 | 0.500 | −2.83, 1.38 |
| Area of residence* | | | | | | |
| Large cities | 0.925 | 0.449 | −1.48, 3.35 | 0.960 | 0.430 | −1.43, 3.35 |
| Pop >100 k | −0.528 | 0.617 | −2.60, 1.55 | −0.472 | 0.654 | −2.54, 1.60 |
| Pop 10 k-100 k | −0.024 | 0.986 | −2.73, 2.68 | 0.043 | 0.975 | −2.66, 2.74 |
| Not married | −0.314 | 0.710 | −1.97, 1.35 | −0.333 | 0.693 | −1.99, 1.32 |
| MMI | −0.744 | **<0.0001** | −0.91, −0.58 | −0.779 | **<0.0001** | −0.95, −0.61 |

C) Analysis of "MCS-12" using multiple linear regression.

| Variables | MMI-30 | | | MMI-25 | | |
|---|---|---|---|---|---|---|
| | *β* | value of p | 95% CI | β | value of p | 95% CI |
| Age | 0.024 | 0.533 | −0.05, 0.10 | 0.018 | 0.642 | −0.06, 0.09 |
| Sex, male | −0.509 | 0.645 | −2.68, 1.66 | −0.675 | 0.542 | −2.85, 1.50 |
| Incomplete SCI | −2.347 | 0.117 | −5.28, 0.59 | −2.389 | 0.110 | −5.32, 0.54 |
| Area of residence* | | | | | | |
| Large cities | 1.987 | 0.241 | −1.34, 5.31 | 2.032 | 0.230 | −1.29, 5.36 |
| Pop >100 k | 0.859 | 0.558 | −2.02, 3.74 | 0.925 | 0.528 | −1.95, 3.80 |
| Pop 10 k-100 k | 2.533 | 0.186 | −1.22, 6.29 | 2.620 | 0.171 | −1.13, 6.37 |
| Not married | −1.467 | 0.211 | −3.77, 0.83 | −1.481 | 0.206 | −3.78, 0.82 |
| MMI | −1.036 | **<0.0001** | −1.26, −0.81 | −1.069 | **<0.0001** | −1.30, −0.83 |

D) Analysis of "Life Satisfaction-11" using logistic regression.

| Variables | MMI-30 | | | | MMI-25 | | | |
|---|---|---|---|---|---|---|---|---|
| | *β* | Value of *p* | OR | 95% CI | *β* | Value of *p* | OR | 95% CI |
| Ethnicity, white | 0.081 | 0.700 | 1.18 | 0.52, 2.67 | 0.088 | 0.672 | 1.19 | 0.53, 2.69 |
| Age | −0.005 | 0.496 | 1.00 | 0.98, 1.01 | −0.006 | 0.421 | 0.99 | 0.98, 1.01 |
| Sex, male | −0.130 | 0.245 | 0.77 | 0.50, 1.20 | −0.139 | 0.214 | 0.76 | 0.49, 1.17 |
| Education, high school or greater | 0.018 | 0.906 | 1.04 | 0.58, 1.87 | 0.025 | 0.867 | 1.05 | 0.58, 1.89 |
| Married | 0.307 | **0.009** | 1.85 | 1.16, 2.93 | 0.306 | **0.009** | 1.84 | 1.16, 2.92 |
| MMI | −0.159 | **<0.0001** | 0.85 | 0.81, 0.90 | −0.159 | **<0.0001** | 0.85 | 0.81, 0.90 |

*(Continued)*

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TABLE 3 (Continued)

| E) Analysis of "Quality of Life score" using logistic regression. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | MMI-30 | | | | MMI-25 | | | |
| | $\beta$ | Value of *p* | OR | 95% CI | $\beta$ | Value of *p* | OR | 95% CI |
| Ethnicity, white | 0.374 | 0.075 | 2.11 | 0.93, 4.80 | 0.381 | 0.067 | 2.14 | 0.95, 4.83 |
| Age | −0.020 | **0.015** | 0.98 | 0.97, 1.00 | −0.021 | **0.011** | 0.98 | 0.96, 1.00 |
| Sex, male | 0.026 | 0.820 | 1.05 | 0.68, 1.64 | 0.017 | 0.884 | 1.03 | 0.66, 1.61 |
| Education, high school or greater | −0.028 | 0.856 | 0.95 | 0.52, 1.73 | −0.022 | 0.888 | 0.96 | 0.52, 1.75 |
| Married | 0.300 | **0.011** | 1.82 | 1.15, 2.89 | 0.297 | **0.012** | 1.81 | 1.14, 2.87 |
| MMI | −0.169 | **<0.0001** | 0.85 | 0.80, 0.89 | −0.170 | **<0.0001** | 0.84 | 0.80, 0.89 |

*Baseline is population < 10,000 individuals. Bold font indicates statistical significance.

and the efficiency of GGM may be affected by including binary variables. However, this limitation was not a problem for MGM which used both continuous and discrete variables. Nevertheless, these study results illustrate the value of network analysis in SCI outcome research.

To our knowledge, this is the first study to perform network analysis on SHCs and health outcomes in persons with SCI. Network analysis provided another way to examine the relationship between multimorbidity and health outcomes compared with the traditional statistical methods. The results demonstrated strong connections between (1) the QoL score and LiSAT-11, (2) MCS-12 and depression, and (3) elbow/wrist problems and shoulder problems, within the network structures. Furthermore, cancer, DVT, diabetes, high blood pressure and liver disease were isolated. Thus, the network-derived MMI consisted of 25 SHCs, and was shown to be as powerful as the previously published MMI-30 (11, 13). This study used cross-sectional data, but network analysis can also be applied to longitudinal data and may be a topic for future analysis. Future directions include piloting the MMI-25 as a screening tool to identify patients at risk of having poor health outcomes during routine community follow-up and conducting additional psychometric analyses using longitudinal data.

## Data availability statement

The datasets presented in this article are not readily available because participants did not provide consent to share the data. Requests to access the datasets should be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by an independent Canadian Independent Review Board (IRB), the Research Ethics Board of Université Laval and local IRBs. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

NF: Conceptualization, Formal analysis, Writing – original draft. HH: Formal analysis, Conceptualization, Writing – review & editing. DW: Formal analysis, Writing – original draft. SH: Writing – review & editing. JP: Writing – review & editing. KW: Writing – review & editing. JS: Writing – review & editing. RC-M: Writing – review & editing. CLC: Writing – review & editing. CJC: Writing – review & editing. VN: Funding acquisition, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1286143/full#supplementary-material

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# Convergent validity and responsiveness of The Standing and Walking Assessment Tool (SWAT) among individuals with non-traumatic spinal cord injury

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**Aim:** This study aimed to (1) describe the use of the Standing and Walking Assessment Tool (SWAT) among individuals with non-traumatic spinal cord injury or disease (NT-SCI/D); (2) evaluate the convergent validity of SWAT for use among inpatients with NT-SCI/D; (3) describe SWAT responsiveness; and (4) explore the relationship between hours of walking therapy and SWAT change.

**Methods:** A quality improvement project was conducted at the University Health Network between 2019 and 2022. Participants' demographics and impairments data, rehabilitation length of stay, and FIM scores were obtained from the National Rehabilitation Reporting System. The walking measure data were collected by therapists as part of routine practice. Hours of part- or whole-gait practice were abstracted from medical records. To determine convergent validity, Spearman's correlation coefficients were calculated between SWAT stages (admission and discharge) and the walking measures. The change in SWAT levels was calculated to determine responsiveness. Spearman's correlation coefficient was calculated between SWAT change and hours of walking therapy.

**Results:** Among adult NT-SCI/D participants with potential walking capacity (SWAT≥1B), the majority were classified as American Spinal Injury Association (ASIA) Impairment Scale D (AIS D) at admission. The SWAT category of 1C ($N = 100$, 18%) was the most frequent at admission. The most frequent SWAT stage at discharge was 3C among participants with NT-SCI/D, with positive conversions in SWAT stages from admission to discharge ($N = 276$, 33%). The mean change in SWAT score was 3 for participants with T-SCI and NT-SCI/D. Moderate correlations between SWAT stages and walking measures were observed. The correlation of hours of gait therapy with the SWAT change (admission to discharge) was 0.44 ($p < 0001$).

**Conclusion:** The SWAT has sufficient convergent validity and responsiveness for describing standing and walking recovery and communicating/monitoring rehabilitation progress among patients with NT-SCI/D.

KEYWORDS

spinal cord injuries, walking, psychometric properties, outcome assessment, walking speed

## 1 Introduction

Spinal cord injury/D (SCI/D) refers to damage or trauma (motor vehicle accident, fall, and gunshot wound) to the spinal cord resulting in combined or isolated loss or alteration of motor, sensory, and autonomic function at or below the level of cord injury. Non-traumatic spinal cord injury or disease (NT-SCI/D) refers to disease, inflammation, or injury of the spinal cord sufficient to produce motor, sensory, bowel, and bladder impairments, in addition to a plausible non-traumatic etiology of injury (1). The extent of impairment and the specific deficits experienced can vary widely, depending on the location of the injury and the severity of the injury/pathology. The tool most commonly used to predict neurological outcomes after traumatic spinal cord injury (T-SCI) is the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), together with the American Spinal Injury Association (ASIA) Impairment Scale (AIS) (2). The ASIA Impairment Scale is a standardized neurological classification system developed by the American Spinal Injury Association (ASIA) for assessing and categorizing the severity of SCI/D. The scale is based on sensory and motor function, comprehensively describing the extent of impairment following an SCI. The scale ranges from AIS A (complete injury, no motor or sensory function preserved below the level of injury) to AIS E (normal neurological function) (3). Following NT-SCI/D, clinicians seek to predict the functional outcome of patients, help patients understand their anticipated recovery, and ensure the appropriate allocation of rehabilitation resources (4). Among patients with incomplete injuries, walking has been reported as a primary therapeutic goal (5).

The demographic characteristics of individuals admitted for tertiary rehabilitation services in Ontario are changing, with a higher proportion of individuals with NT-SCI/D vs. T-SCI (6). These individuals are more likely to be over the age of 60, female, and have a reasonable prognosis for ambulation based on their admission neurological level, AIS, and lower extremity motor score (LEMS). Many predict that by 2032, individuals aged over 60 will account for 46% of all new injuries, resulting in increases in care costs and rest-of-life costs of 54 and 37%, respectively (7). Therefore, it is critical to consider changes in demographics, etiology, and management of NT-SCI/D when planning for current and future healthcare delivery needs.

Up to 75% of individuals with incomplete SCI/D will experience some gains in walking capacity within the first year following injury (8). Historically, the severity of the injury predicts the amount of recovery in walking following a spinal cord injury (9). Returning to walking is a realistic goal for those with motor incomplete SCI/D or AIS grades C and D and LEMS greater than 20 (9). When a clinical examination is not feasible, such as when a patient is unresponsive, sedated, or uncooperative due to pain, somatosensory evoked potentials can be used to predict motor recovery and walking outcomes (10). Timed measures of walking, such as the 6-min walk test (6MWT) and 10-meter walk test (10MWT), have been the focus of walking assessment in SCI/D rehabilitation and related research settings (11).

The Standing and Walking Assessment Tool (SWAT) is a standardized and objective staging tool used in Canada to evaluate lower limb function in individuals with SCI/D (12), which allows healthcare professionals to track progress, evaluate treatment outcomes, and make informed decisions regarding the choice of appropriate interventions and therapies for each patient. This staging assessment tool allows a therapist to describe a patient's stage of walking recovery and then guide the choice of walking measures to characterize and evaluate walking abilities during inpatient rehabilitation. The SWAT is usually performed upon rehabilitation admission and discharge or when a patient's walking ability improves from one state to another. The SWAT includes the 6MWT and 10MWT as two walking measures. The Rick Hansen SCI/D Registry (RHSCIR) introduced the SWAT as a best practice for walking evaluation during inpatient rehabilitation nationally among patients with T-SCI in 2015 (13).

Although the SWAT was implemented as part of the registry for T-SCI, additional efforts were needed to encourage routine walking evaluation of patients with NT-SCI/D during inpatient rehabilitation for all patients admitted among member sites of the Spinal Cord Injury-Implementation and Evaluation Quality Care Consortium (SCI-IEQCC). This included routine implementation of structure, process, and outcome indicators for individuals admitted for tertiary rehabilitation.

The validity, reliability (14), and responsiveness of SWAT among T-SCI have been confirmed in previous studies (15). Convergent validity is the degree to which different measures of the same construct are correlated with each other and refers to the degree to which a measurement tool or instrument accurately measures the theoretical construct or trait it is intended to measure (16). On the other hand, responsiveness was defined as the capacity of the measurement tool of interest to detect changes in a health domain over time (17), specifically changes in standing and walking capacity among inpatients with motor incomplete spinal cord injury.

Despite the higher incidence of NT-SCI/D in Ontario, no studies have described the functional capacity of individuals with NT-SCI/D using SWAT. Given the differences in age, etiology of injury, impairment, and treatment goals among individuals with traumatic and non-traumatic SCI/D and the routine use of SWAT during inpatient rehabilitation in Canada, we sought to: (1) describe the neurological impairments and changes in SWAT staging of patients with NT-SCI/D and T-SCI/D between admission and discharge; (2) evaluate the convergent validity; (3) determine the responsiveness of the SWAT among inpatients with NT-SCI/D; and (4) explore the association between changes in SWAT and hours of evidence-based physiotherapist-delivered whole or partial practice of gait. We hypothesized that the SWAT has sufficient convergent validity and responsiveness for describing standing and walking recovery among patients with NT-SCI/D.

# 2 Materials and methods

## 2.1 Project scope

The data to support the stated objectives were obtained as part of the Spinal Cord Injury Implementation and Evaluation Quality Care Consortium (SCI-IEQCC), an ongoing quality improvement project at the University Health Network (UHN) between January 2019 and December 2022. Descriptions of the procedures for selecting walking as a priority domain for implementation within the SCI-IEQCC (18), and the Spinal Cord Injury Rehabilitation Care High-Performance Indicators (SCI-HIGH) project methods (19), the development of the SCI-HIGH walking indicators (20), the process of concurrent implementation of best practices, and the collection of structure, process, and outcome indicators within the SCI-IEQCC (21) are provided in the referenced manuscripts. Although SWAT was implemented as part of the Rick Hansen Spinal Cord Injury Registry for T-SCI, additional efforts were needed to encourage routine walking evaluation of inpatients with NT-SCI/D using SWAT among member sites of the SCI-IEQCC. This included routine implementation of the walking structure, process, and outcome indicators for all individuals admitted for tertiary rehabilitation. The SCI-IEQCC provided a decision tree depicting when the focus of therapy should be on walking vs. advancing wheelchair skills as the primary goal for functional mobility (22). During the process of routine implementation of the walking indicators, including SWAT as a process indicator, we identified the need to evaluate if the SWAT validity and responsiveness are similar among individuals with NT-SCI/D to those observed among patients with T-SCI (6). As SWAT has been implemented at UHN since 2015 and remains a sustained practice, we chose to conduct this evaluation using UHN data. A Research Ethics Board waiver for the project was obtained (UHN QI # 20-0111).

## 2.2 National rehabilitation reporting system

All adults with NT-SCI/D and T-SCI over 18 years of age admitted for inpatient tertiary SCI rehabilitation at UHN's Lyndhurst Center were eligible for participation. Participants with Guillain–Barré syndrome ($n = 1$) and multiple sclerosis ($n = 5$) were excluded from the analysis as they did not have a primary cord impairment. Participants were assigned a unique Consortium ID, which was used to de-identify their clinical program SWAT data. This unique ID allowed us to link clinical data with data from the National Rehabilitation Reporting System (NRS) (23) within the central SCI-IEQCC data repository housed at UHN for analysis.

Demographic and impairment data ($n = 842$) for adult inpatients with SCI of traumatic and non-traumatic etiology at the UHN were obtained from the NRS. The NRS collects data from participating adult inpatient rehabilitation facilities and programs across Canada. The following variables were obtained from the local NRS data set: participant's age, sex, neurological impairment at admission (paraplegia vs. tetraplegia, incomplete vs. complete), rehabilitation client grouping, AIS, admission date, discharge date, length of stay (LOS), and Functional Independence Measure (FIM) scores.

The FIM is an 18-item ordinal scale, scored from 0 to 7, which measures the burden of care and changes in performance throughout a comprehensive inpatient rehabilitation and measures independence in self-care, including sphincter control, transfers, walking, communication, and social cognition (24). This instrument has been used to assess disability among individuals with T-SCI (25). LOS was calculated by subtracting the discharge from the admission date and then subtracting the days the patient was out of the rehabilitation center for any reason (medical assessment and/or emergency room visit). Each participant's FIM scores at admission and discharge were abstracted. The FIM change and FIM efficiency were calculated. The FIM efficiency score was calculated by subtracting the admission FIM score from the discharge FIM score divided by LOS.

## 2.3 SWAT data collection and analysis

SWAT data were collected for all individuals with T-SCI and NT-SCI/D by therapists as part of routine care within 1 week following inpatient admission and within 1 week before or after discharge. The SWAT stages at admission and discharge were recorded from stages 0 to 4 (Figure 1) (15). The SWAT alphanumeric stage at admission and discharge was recorded and later translated during the analysis into a score from 0 to 11 (creating 12 scores). Thus, SWAT Stage 0 corresponds to a score of 0, and SWAT Stage 4 corresponds to a score of 11 (Table 1). The change in the SWAT stage from admission to discharge was calculated for each participant. Therefore, each unit increase or decrease in SWAT score from admission to discharge was considered a one-category change in SWAT (Figure 1) (15).

In T-SCI patients, Musselman et al. reported that individuals with AIS A or B improved by a median of 1 stage (range: 0–11), while those with AIS C and D improved by a median of 3 stages. The responsiveness of SWAT correlated strongly with the Berg Balance Scores and the lower extremity motor scores ($\rho = 0.778$ and 0.836) and moderately with the mTUG (s), 10MWT, and 6MWT scores (15). The 10MWT, which measures walking speed over 10 m at both preferred and maximum speeds, was reported in meters per second (26).

The timed up and go (TUG) is a frequently used outcome measure that evaluates a patient's ambulatory and transfer skills to determine activity limitations. It has been established that the test's main objective is to provide an evaluation of overall mobility in patients with a range of disabilities over the lifespan (27). The modified timed up and go (mTUG) test is a variation of the TUG test that accounts for the level of physical assistance required by an individual to complete the test (28). The mTUG, a general measure of mobility, consists of transferring between sitting and standing, walking a short distance, and turning. The time taken to complete the task and the required level of assistance per the procedure specified in the RHSCIR Standing and Walking Toolkit are reported in seconds (13). As we had missing data regarding the assistive device used on the mTUG, only the time in seconds was reported. The mTUG was collected once the patient met the specified threshold for mTUG collection and again at discharge, where appropriate.

## 2.4 Hours of intervention

The ability to move forward over the ground using voluntary lower limb movement while controlling one's balance in an upright posture (with or without assistance from others or aids) was

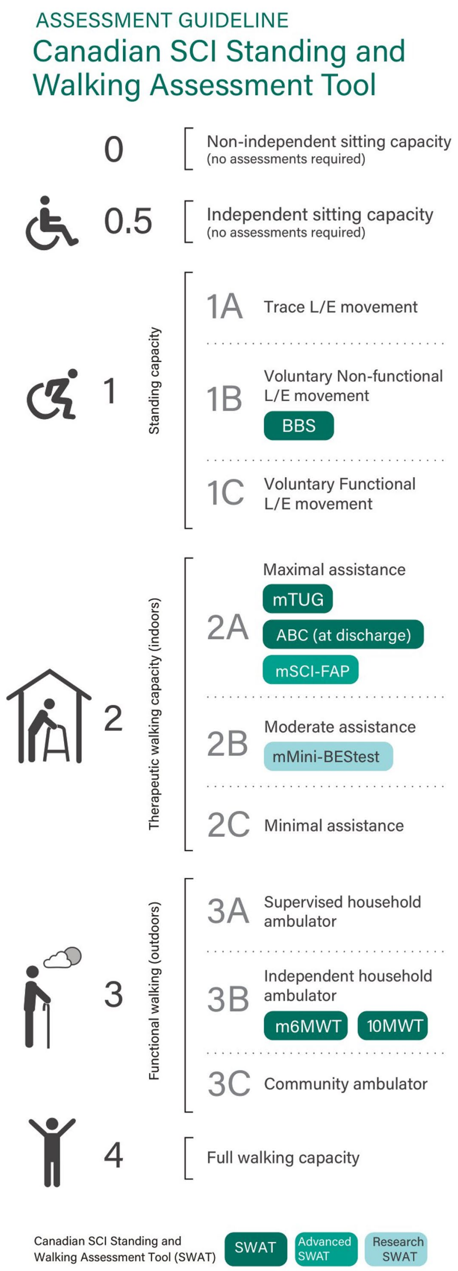


FIGURE 1
Canadian SCI standing and walking assessment tool (15).

characterized as walking. The whole or part practice of gait was defined as the below interventions:

- Sit-to-stand training and standing pivot transfers,
- Partial-gait activities, including standing weight-shifting, forced-use exercises, single-leg stance, and stepping,
- Standing balance activities, such as standing in parallel bars without support, perturbations, and walking on soft surfaces,
- Walking activities, including indoor over-ground ambulation, treadmill training with or without body weight support, and outdoor ambulation
- Hydrotherapy activities related to walking goals, gait initiation in water, and walking in waist-height water.

The time for any interventions mentioned above completed with physiotherapists or physiotherapist assistants was recorded for each patient.

## 2.5 Statistical analysis

A thorough visual examination of raw data and graphical representations were performed for the quality control of the extracted data ($n = 842$). The walking domain analyses were performed for participants with standing (1B standing with assistance) or walking (2A or above) capacity [i.e., SWAT stage 1B and higher ($n = 442$)], and a spinal cord impairment of non-traumatic ($n = 329$) or traumatic etiology ($n = 113$). Participants with a SWAT admission score of 0, 0.5, and 1A ($n = 391$) were excluded from the responsiveness analysis as no change in the SWAT stage was anticipated. All participants with recorded SWAT stages at admission or discharge and etiology for the SCI/D ($n = 833$) were used to calculate the change in SWAT scores. Therefore, if a participant's stage was 2B upon admission and 3B at discharge, this indicated a three-stage progression. Any negative change from admission to discharge indicates a worsening of the SWAT stage, while a positive number is associated with increments in the SWAT stage.

The appropriate parametric statistical test and independent sample t-tests were used to test the difference between continuous and normally distributed variables, such as age and FIM efficiency score, of the participants with T-SCI and NT-SCI/D. Non-parametric statistics, such as the Spearman correlation coefficient and the chi-square test of independence, were used for hypothesis testing of the severity of injury and level of injury among T-SCI and NT-SCI, as well as SWAT stage at admission and discharge and their walking performance (10MWT PS, 10MWT MS, and mTUG), and compared these two groups. As hypotheses testing for validity assessments should contain an indication of the predicted direction and magnitude of correlations or differences (17), and based on the results from a previous study (15), we expected to detect a positive, moderate correlation between SWAT stage and clinical walking measures (17).

The correlation coefficient measures the strength and direction of the relationship between two variables, with values ranging from −1 to 1. The significant value of ps and bigger correlation coefficients suggest a reliable relationship between the variables. To evaluate responsiveness, the conversion of SWAT from admission to discharge was calculated by the standardized mean difference (Cohen's *d*). All statistical analyses were performed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria), considering an alpha error of 0.05. The "effsize Package" in R was used to calculate Cohen's d and 95% confidence interval.

# 3 Results

## 3.1 Population

We identified a total of 842 participants with SCI/D, including 559 (66%) with NT-SCI/D and 274 (33%) with T-SCI. Nine participants had a missing etiology of injury and were excluded from the analysis; hence, a total of 833 participants were included in the analysis.

TABLE 1 Conversion of the SWAT alphanumeric stage to a SWAT score from 0 to 11.

| SWAT stage | 0 | 0.5 | 1A | 1B | 1C | 2A | 2B | 2C | 3A | 3B | 3C | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SWAT score | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |

TABLE 2 Characteristics of 833 individuals with SCI/D categorized based on the mechanism of injury.

| Variable | Total | Traumatic | Non-traumatic | *p*-value |
|---|---|---|---|---|
| | (*N* = 833) | (*N* = 274) | (*N* = 559) | |
| Age – mean ± SD | 58.48 ± 16.88 | 53.93 ± 18.73 | 60.64 ± 15.43 | <0.001 |
| Female – *N* (%) | 296 (35.2) | 64 (23.4) | 230 (41.1) | <0.001 |
| LOS – mean ± SD | 63.11 ± 34.80 | 71.81 ± 36.05 | 59.61 ± 32.98 | <0.001 |
| Severity incomplete | 743 (89.2) | 219 (79.9) | 524 (93.7) | <0.001 |
| FIM efficiency score – Mean ± SD | 0.66 ± 1.22 | 0.60 ± 0.70 | 0.75 ± 0.83 | 0.008 |
| *Injury severity – N (%) | | | | |
| AIS A – Complete | 71 (11.8) | 53 (19.4) | 18 (5.6) | <0.001 |
| AIS B – Incomplete | 38 (6) | 24 (8.8) | 14 (4.3) | |
| AIS C – Incomplete | 102 (17) | 48 (17.6) | 52 (16.1) | |
| AIS D – Incomplete | 389 (64.7) | 148 (54.2) | 238 (73.7) | |
| AIS E – Normal | 1 (0.2) | 0 (0) | 1 (0.3) | |
| Level of injury – N (%) | | | | |
| Paraplegia | 423 (53) | 101 (37) | 322 (52) | 0.00009 |
| Tetraplegia | 378(47) | 169 (63) | 299 (48) | |

*For 236 participants with non-traumatic spinal cord injury or disease (NT-SCI/D) and 1 participant with traumatic spinal cord injury, AIS data were not available.

## 3.2 Demographic and injury characteristics

The demographic and impairment characteristics of the participants categorized by the etiology of injury are shown in Table 2. Participants with NT-SCI/D were significantly older ($p < 0.001$), with a significantly higher proportion of female participants ($p < 0.001$) compared to those with T-SCI. Data regarding the level of injury were available for 801 participants; among them, 423 (53%) were paraplegic, and 378 (47%) were categorized as tetraplegia. The majority of participants with T-SCI and NT-SCI/D were categorized as AIS D at admission ($n = 176$).

## 3.3 SWAT analysis

Forty-eight percent ($N = 366$) of participants with NT-SCI/D or T-SCI had a SWAT stage of 0, 0.5, and 1A at admission, indicating no standing and/or walking capacity, and were excluded from the subsequent analyses. The remaining participants with NT-SCI/D with SWAT data ($n = 329$) vs. T-SCI ($n = 113$) were included in the analysis of the relationship between the SWAT stage and walking performance (Figure 2). The mean changes in SWAT score from admission to discharge for NT-SCI/D and T-SCI were 2.94 (SD = 2.09) and 3.22 (SD = 2.06), respectively. Cohen's d effect size was −1.38 (95% CI: −1.54, −1.23) among NT-SCI/D with walking capacity, suggesting a large practical significance and highlighting the magnitude of the observed difference between the SWAT at admission and SWAT at discharge. The negative Cohen's *d* suggests that the mean of the SWAT at admission is lower than the mean of the SWAT at discharge. The mean change for each SWAT stage was slightly lower in participants with NT-SCI/D vs. T-SCI; however, the differences were not statistically significant ($p = 0.47$). Figure 3 depicts the median SWAT scores categorized by SWAT at admission.

Among participants with NT-SCI/D with potential capacity to stand or walk (SWAT 1B and higher), the majority were classified as AIS D at admission ($N = 176$), with the highest percentage belonging to the SWAT category of 1C ($N = 53$, 28% of NT-SCI with potential capacity to stand or walk) (Figure 4). The most frequent SWAT stage at discharge was 3C among participants with NT-SCI/D ($N = 93$, 52% of NT-SCI with potential capacity to stand or walk), with positive conversions in SWAT stages from admission to discharge observed among most participants ($N = 252$, 82%) (Figure 5). A similar frequency of SWAT category 3C at discharge was observed among participants with T-SCI (shown = 48, 46%). A total of 69 participants (both NT-SCI/D and T-SCI) had no observed change in SWAT. One participant had a one-level deterioration in the staging score (SWAT score change = −1) throughout rehabilitation (admission SWAT = 2A). The mean (SD) of the SWAT change among participants with paraplegia and tetraplegia of non-traumatic etiology in terms of walking capacity was 2.91 (2.06) and 3.06 (2.93), respectively.

## 3.4 Correlation between walking measures and SWAT

Table 3 presents the frequency of the SWAT stage at admission and discharge. The distribution of 10 MWT Preferred Speed (10MWT PS), 10 MWT Maximum Speed (10MWT MS), and mTUG scores (all

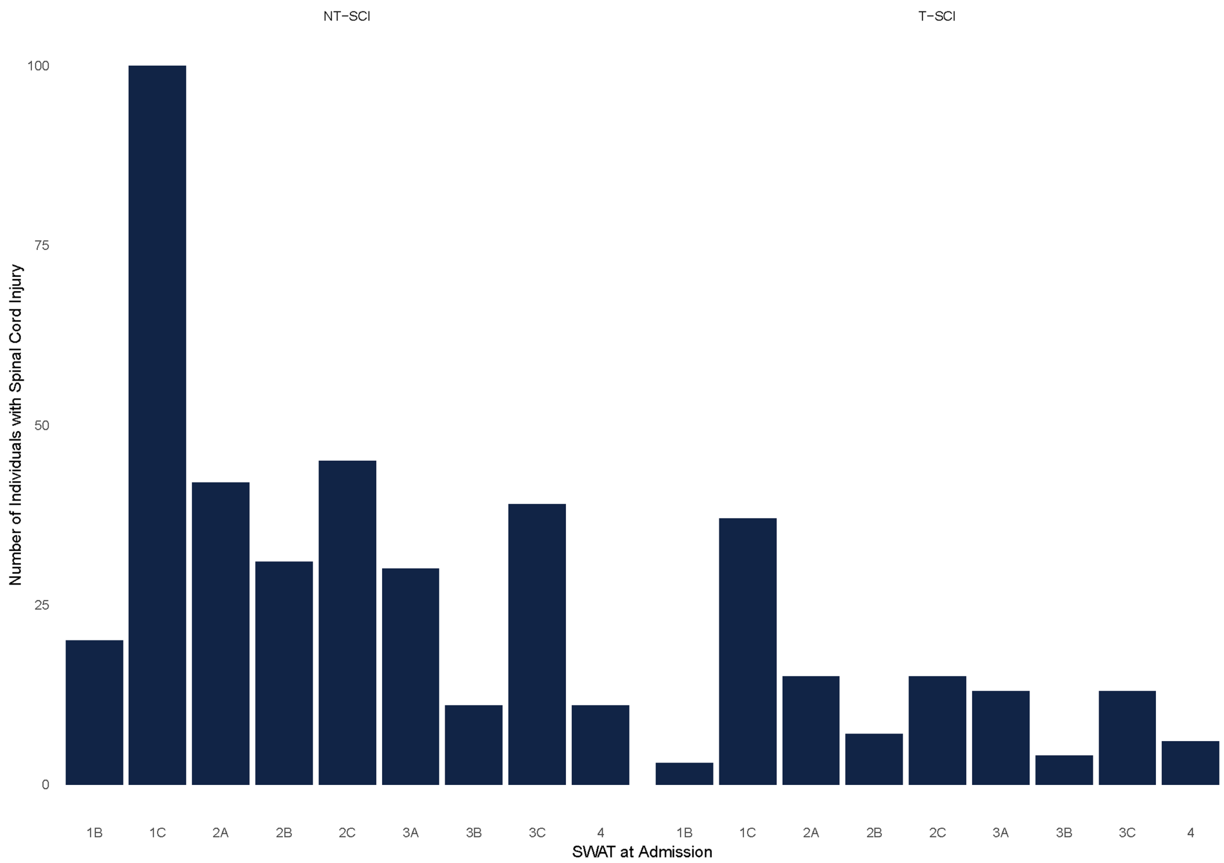


FIGURE 2
SWAT at admission by the mechanism of injury (trauma vs. non-trauma).

in seconds) show a distribution slightly skewed to the right at admission and discharge for participants with NT-SCI/D. However, these scores for different SWAT stages improved from admission to discharge (Table 4). The mean of 10MWT PS (Meter/Sec) was slightly higher in tetraplegic participants (0.70 ± 0.25) compared to participants with paraplegia (0.62 ± 0.30).

The findings in Table 5 display the Spearman's Rho correlation coefficients and corresponding value of ps for various measures, including the 10MWT PS, 10MWT MS, mTUG time, total FIM at admission, FIM efficiency score, LOS, and hours of walking service intervention, and the SWAT scores at admission and discharge among participants with NT-SCI/D. The SWAT admission scores positively correlated with the 10MWT PS and the 10MWT MS and negatively correlated with the mTUG test. These correlation coefficients suggest that higher SWAT admission scores are associated with better performance (lower time or higher speed) on these measures. The same directionality for the correlation, with a slightly weaker correlation, was observed at discharge. The FIM efficiency scores also revealed a positive correlation with the SWAT admission scores, suggesting that higher efficiency in completing activities of daily living is associated with higher SWAT admission scores (Spearman's Rho = 0.43, $p < 0.0000$). The mean total hours of gait practice with physiotherapists or physiotherapist assistants were 10.44 (SD ± 8.05) in participants with NT-SCI/D, with the highest hours devoted to participants with SWAT stages 1C and 2A (13.04 and 13.92 h, respectively). The correlation of hours of gait intervention with the SWAT change from admission to discharge (not shown) was 0.44 ($p < 0.0001$). The hours of gait practice showed a negative correlation with the SWAT admission scores, suggesting that higher hours of gait intervention from physiotherapists are devoted to the participants with potential walking capacity and lower SWAT stages (1B, 1C, and 2A) (Spearman's Rho = −0.44, $p < 0.00001$).

## 4 Discussion

As hypothesized, the convergent validity and responsiveness of SWAT among participants with NT-SCI/D were moderate and similar to those previously observed in the Canadian T-SCI population (15). Therefore, in addition to the participants with T-SCI, SWAT stages are appropriate to describe walking recovery among individuals with NT-SCI/D. The study results revealed a moderate correlation between SWAT stages and walking measures, including 10MWT PS, 10MWT MS, mTUG, and FIM, among participants with NT-SCI/D. The correlation coefficients between SWAT and 10MWT PS and 10MWT MS were slightly higher than those reported for SWAT stages and walking measures in T-SCI (15). These findings and Cohen's d statistics support the convergent validity and responsiveness of the SWAT as a measure of standing and walking ability in individuals with NT-SCI/D.

This study's strength is the substantial and diverse sample of participants with NT-SCI/D. This enables the authors to draw

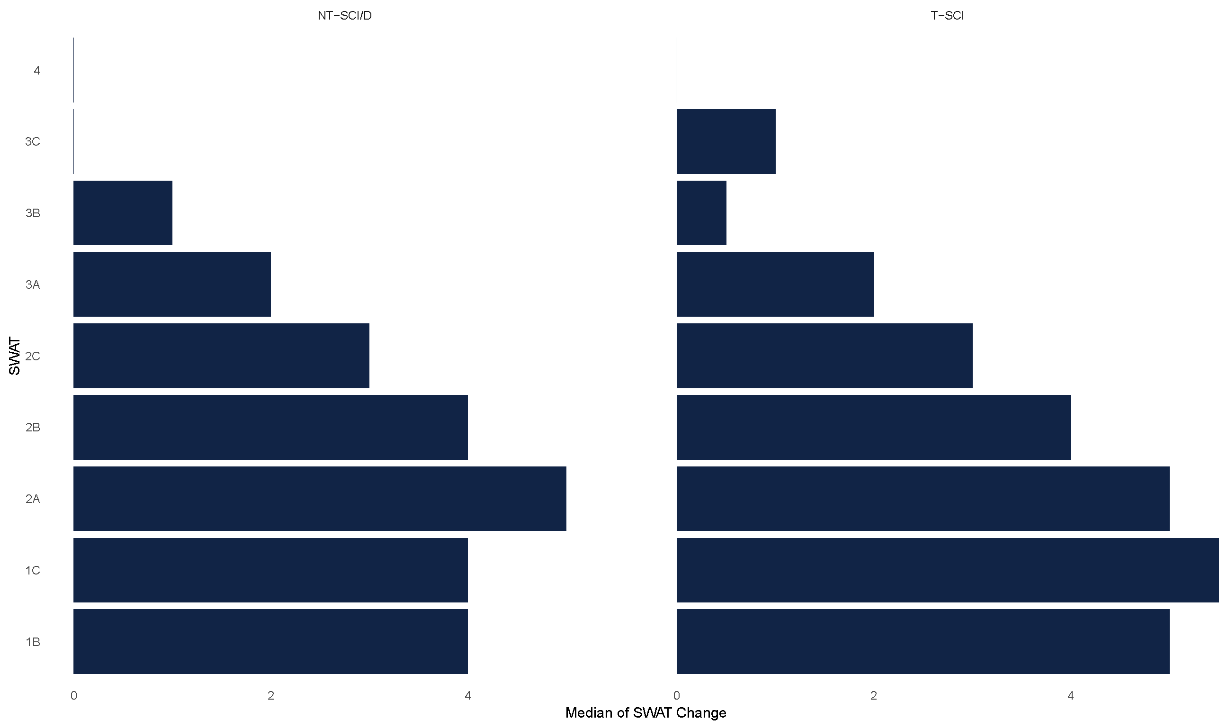


FIGURE 3
Median of SWAT change from admission to discharge by injury etiology.

meaningful and generalizable conclusions, enhancing the reliability and validity of the findings. Furthermore, the quality improvement work verifies the relationship between the SWAT stage and walking performance, 10MWT MS (m/s), 10MWT PS (m/s), and mTUG (s).

We acknowledge that LOS and hours of service provision are driven by many variables. For example, among participants whose admission SWAT stage is 1B-2A, there tend to be more global mobility needs, including equipment and housing. Therefore, a longer LOS is required, and more hours of gait practice are provided. Despite these provisos, the assessment of hours of gait practice showed a moderate and positive correlation with SWAT change, indicating a longer duration of intervention during rehabilitation results in a greater change in SWAT staging. The data exploring the relationship between SWAT change and hours of walking intervention reveal that physiotherapists and physiotherapy assistants are appropriately spending more time with participants (spent on transfers, pre-gait activities, and aquatic therapy with the lower functioning participants) with walking potential and lower SWAT stages at admission.

Categorizing individuals with SCI/D using SWAT is a standardized and comprehensive walking assessment (12). The 10MWT is a valid and reliable outcome measure to assess walking speed over a short distance in participants with SCI/D (29). Among the three measurements, mTUG had the lowest correlation with the SWAT scores at admission, likely due to the heterogeneity in trunk control. However, all walking measures showed a moderate correlation with SWAT at admission and discharge. The correlation coefficient for 10MWT MS was 0.61 at admission and 0.56 at discharge, slightly higher than the moderately positive correlation between 10MWT PS and the SWAT scores. The SWAT has the potential to more accurately reflect the capacity for performing activities of daily living (e.g., supervised household ambulator and community ambulator) (12). Similar to the findings of this study, among T-SCI participants, Musselman et al. (15) found that SWAT stages are moderately correlated with mTUG, 10MWT, and 6MWT.

The Spinal Cord Independence Measure III (SCIM) and FIM are two essential assessment tools used in SCI/D rehabilitation to evaluate functional abilities and describe the burden of care among individuals with SCI/D, respectively. The SCIM is a specialized instrument explicitly designed to assess various aspects of functional independence related to activities of daily living in individuals with spinal cord lesions. SCIM takes into account tasks such as self-care, mobility, and respiration. The SCIM and FIM play crucial roles in guiding treatment plans, tracking progress, and determining the level of assistance and support needed by individuals with spinal cord injuries to achieve optimal functional outcomes and improve their overall quality of life. The FIM is a multi-dimensional scale with a motor subscale that includes two locomotor-related items: walking or wheelchair propulsion and stair climbing. FIM is intended to assess the burden of care and functional impairment and is not a pure ambulation measure (30). For assessing patients' functional independence with SCI/D, SCIM III is likely a better measure (31). However, in this quality improvement project, only FIM total scores were available for analysis. Therefore, finding a moderate correlation between SWAT and FIM at admission and discharge is not surprising.

The study results verify that the etiology of SCI (NT-SCI/D vs. T-SCI/D) is not a predictor of AIS improvement during rehabilitation (32). However, other authors have proposed that patients with T-SCI suffer from more severe neurologic impairments compared to patients with NT-SCI/D (33). Although age is not associated with functional recovery after rehabilitation for SCI/D (34), individuals with

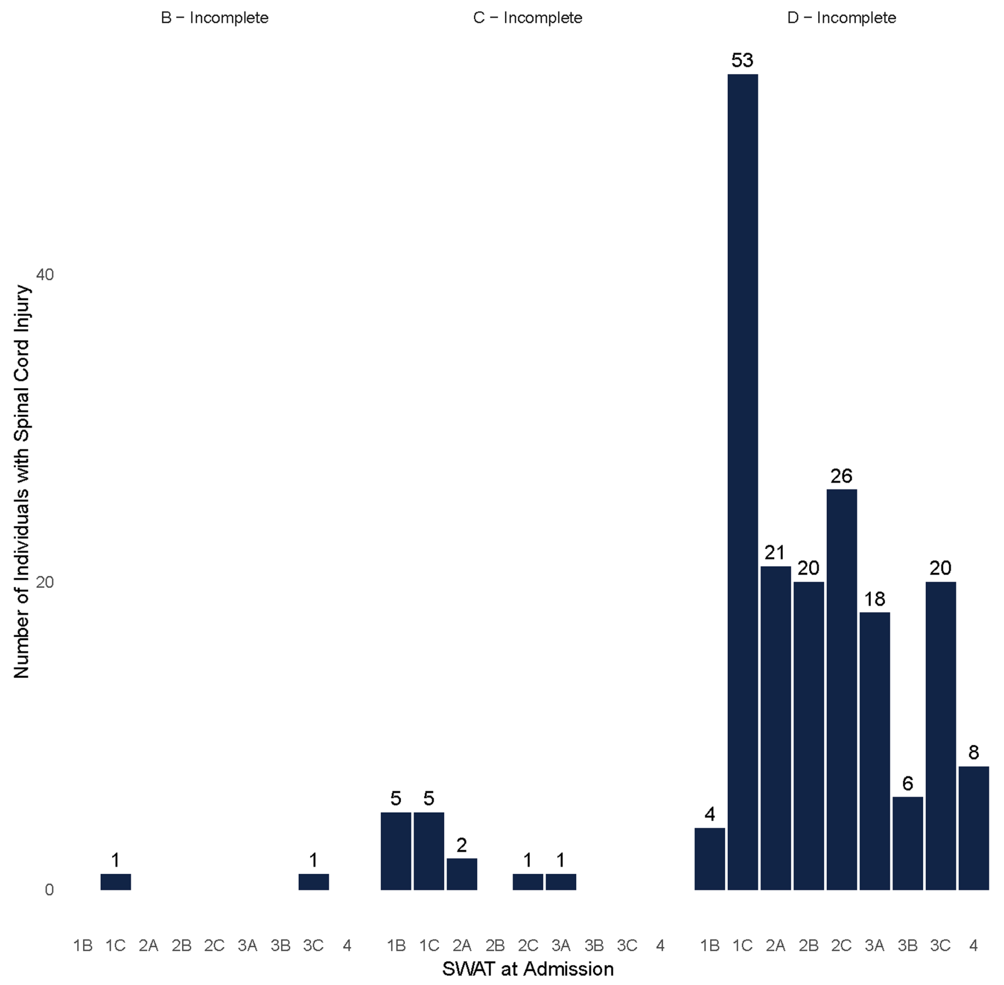


FIGURE 4
SWAT at admission by AIS among non-traumatic individuals with SCI/D who had the capacity to walk (SWAT≥1B).

NT-SCI/D tend to be older, and their recovery takes longer compared to younger individuals. Future studies developing recovery profiles for patients with NT-SCI/D should adjust for age at injury, cord pathology, and duration of injury. Most participants with a walking capacity based on SWAT stages were in the AIS D group with NT-SCI/D. The distribution of SWAT at admission and discharge was not different between participants with T-SCI and NT-SCI/D who converted to SWAT stage 3C prior to discharge. Considering most participants were at stage 1C at admission, the conversion to stage 3C represents a 6-level improvement in the SWAT stage at discharge. Although the SWAT stages showed a floor effect among individuals with T-SCI (12), this was not evident among NT-SCI/D participants in this quality improvement project, as we removed those at stages 0, 0.5, and 1A.

Some limitations should be considered when interpreting the results of this quality improvement project. We used data from the clinical practice of local healthcare providers in a tertiary rehabilitation center. The project plan and analysis were not developed *a priori*. Second, the subscales of FIM were not available in our admin data set and thus were not included in the data analysis, which would have been a preferable strategy. However, the correlations of SWAT with the FIM total score and FIM efficiency score were measured. Third, the number of missing values for AIS was high among participants with NT-SCI/D patients, reflecting the complexity of ISCNSCI reporting in this group. This might have influenced the distribution of the SWAT stages across AIS groups. However, the assessment of the missing values did not reveal important differences or a systematic bias with the available data, as the missing values were likely random. Fourth, we did not calculate mTUG scores; rather, we reported the mTUG time in seconds. Fifth, information about the lower extremity motor score was not available, making it impossible to describe changes in motor scores with concurrent changes in SWAT stages. Finally, the absence of the 6-min walk test and Berg Balance Scale score data is also a limitation of this study. However, these measures are best used among those with established walking ability and may not be most appropriate during inpatient rehabilitation when the focus of care is on pre-gait or early gait interventions. On the other hand, the Berg Balance Scale does not consider dynamic balance and only assesses postural changes, transfers, static balance, and activities not strictly related to walking (35).

In conclusion, the SWAT has sufficient convergent validity and responsiveness for describing standing and walking recovery among patients with NT-SCI/D. The findings suggest that higher SWAT scores at admission and discharge are associated with better performance on measures of walking ability (10MWT and mTUG)

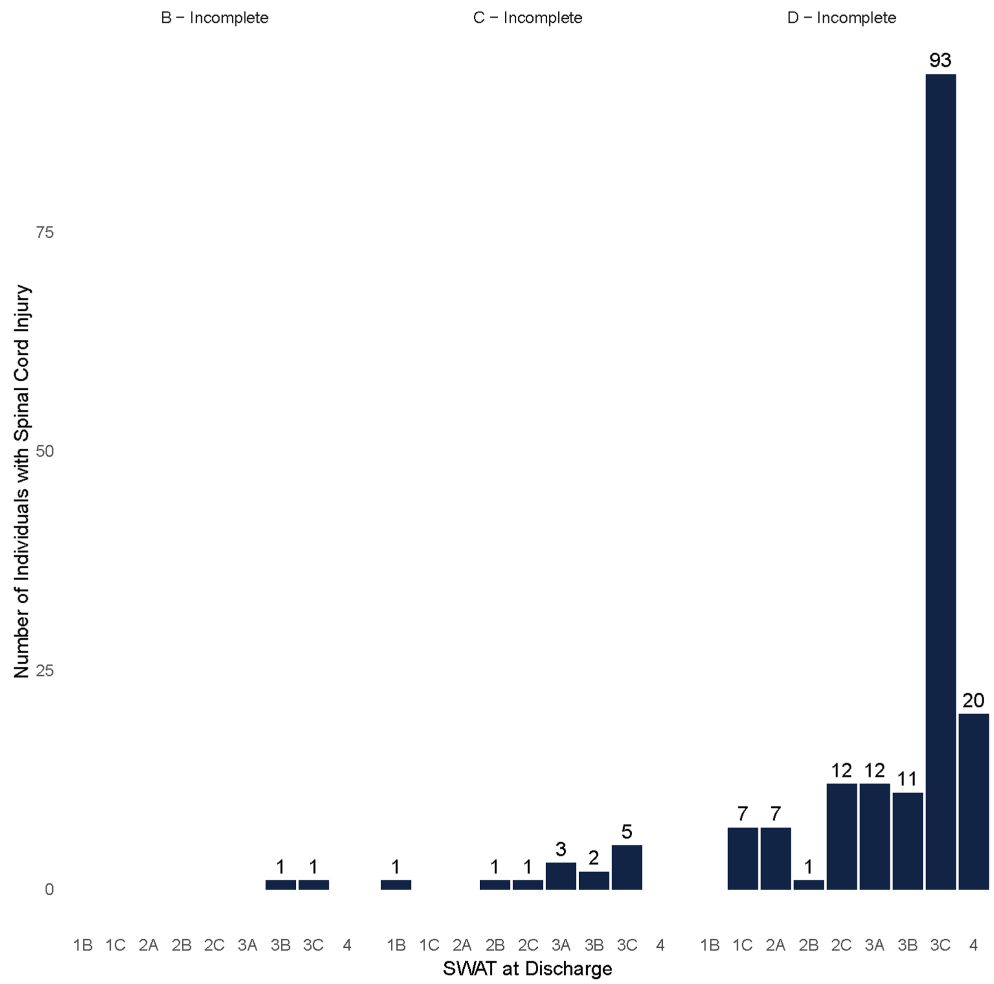


FIGURE 5
SWAT at discharge by AIS among non-traumatic individuals with SCI/D who had the capacity to walk (SWAT≥1B).

**TABLE 3 SWAT at admission and discharge for the total cohort of participants categorized by injury etiology, prior to the exclusion of those without walking potential (less than 1B) – N (%).**

| SWAT | Admission – N (%) | | | Discharge – N (%) | | |
|---|---|---|---|---|---|---|
| | Total | Traumatic | Non-traumatic | Total | Traumatic | Non-traumatic |
| | (*N* = 809) | (*N* = 272) | (*N* = 533) | (*N* = 763) | (*N* = 252) | (*N* = 507) |
| 0* | 202 (25) | 100 (37) | 100 (19) | 67 (9) | 38 (15) | 28 (5) |
| 0.5* | 114 (14) | 43 (16) | 71 (13) | 57 (8) | 28 (11) | 29 (6) |
| 1A* | 50 (6) | 16 (6) | 33 (6) | 59 (8) | 21 (8) | 38 (7) |
| 1B | 23 (3) | 3 (1) | 20 (4) | 18 (2) | 7 (3) | 11 (2) |
| 1C | 137 (17) | 37 (14) | 100 (19) | 37 (5) | 8 (3) | 29 (6) |
| 2A | 57 (7) | 15 (5) | 42 (8) | 26 (3) | 8 (3) | 18 (4) |
| 2B | 38 (5) | 7 (3) | 31 (6) | 15 (2) | 4 (2) | 11 (2) |
| 2C | 60 (8) | 15 (5) | 45 (8) | 57 (8) | 14 (6) | 42 (8) |
| 3A | 44 (5) | 13 (5) | 30 (6) | 48 (6) | 11 (4) | 35 (7) |
| 3B | 15 (2) | 4 (1) | 11 (2) | 40 (5) | 15 (6) | 25 (5) |
| 3C | 52 (6) | 13 (5) | 39 (7) | 276 (36) | 74 (29) | 202 (40) |
| 4 | 17 (2) | 6 (2) | 11 (2) | 63 (8) | 24 (10) | 39 (8) |

TABLE 4 Mean and SD categorized by SWAT stage at admission and discharge for 10MWT PS, 10 MWT MS, and mTUG among NTSCI/D Participants.

| SWAT stage | 10MWT PS (Sec) | | 10MWT MS (Sec) | | mTUG (Sec) | |
|---|---|---|---|---|---|---|
| | Admission | Discharge | Admission | Discharge | Admission | Discharge |
| 1B | 31.95 ± 24.11 | 26.37 ± 20.73 | 28.95 ± 21.28 | 23.40 ± 18.76 | 30.92 ± 26.95 | 18.25 ± 8.38 |
| 1C | 32.62 ± 23.08 | 23.48 ± 12.49 | 21.18 ± 13.25 | 17.06 ± 7.59 | 31.35 ± 24.05 | 25.51 ± 16.14 |
| 2A | 21.07 ± 9.31 | 17.65 ± 10.55 | 17.04 ± 10.25 | 13.01 ± 7.63 | 21.93 ± 10.44 | 19.81 ± 18.24 |
| 2B | 17.10 ± 3.40 | 17.39 ± 6.40 | 12.08 ± 2.22 | 13.13 ± 5.31 | 21.52 ± 8.06 | 18.82 ± 13.05 |
| 2C | 17.85 ± 7.04 | 19.19 ± 10.07 | 12.77 ± 3.96 | 13.57 ± 6.61 | 25.70 ± 14.61 | 18.72 ± 10.90 |
| 3A | 20.62 ± 15.38 | 26.44 ± 40.83 | 15.16 ± 11.58 | 13.51 ± 10.20 | 20.72 ± 18.74 | 13.06 ± 13.85 |
| 3B | 17.30 ± 5.99 | 12.49 ± 4.59 | 12.53 ± 3.87 | 9.22 ± 3.01 | 18.41 ± 12.77 | 9.07 ± 5.28 |
| 3C | 12.95 ± 5.04 | 10.60 ± 3.12 | 9.91 ± 4.06 | 7.87 ± 2.33 | 13.15 ± 5.85 | 9.65 ± 5.45 |
| 4 | 10.44 ± 2.10 | 8.69 ± 1.64 | 7.18 ± 1.76 | 6.13 ± 0.88 | 10.74 ± 3.23 | 4.59 ± 5.75 |

TABLE 5 Correlation coefficients (Spearman's Rho) and corresponding value of ps for various measures and SWAT scores at admission and discharge among individuals with non-traumatic SCI.

| | | Spearman's Rho | *p*-value |
|---|---|---|---|
| SWAT admission | Admission | | |
| | 10MWT PS | 0.57 | <0.0001 |
| | 10MWT MS | 0.61 | <0.0001 |
| | mTUG | −0.52 | <0.0001 |
| | Total FIM – Admission | 0.65 | <0.0001 |
| | FIM efficiency score | 0.59 | <0.0001 |
| | LOS | −0.63 | <0.0001 |
| | Hours of walking service intervention | −0.44 | <0.0001 |
| SWAT discharge | Discharge | | |
| | 10MWT PS | 0.37 | <0.0001 |
| | 10MWT MS | 0.56 | <0.0001 |
| | mTUG | −0.43 | <0.0001 |
| | Total FIM – discharge | 0.77 | <0.0001 |
| | FIM efficiency score | 0.69 | <0.0001 |
| | LOS | −0.6 | <0.0001 |
| | Hours of walking service intervention | −0.23 | 0.004 |

and higher functional independence. These results support the use of the SWAT as a tool for assessing and tracking walking capacity and functional outcomes in participants undergoing inpatient rehabilitation with NT-SCI/D. SWAT staging brings together commonly used measures of walking and balance and may, in the future, provide some guidance regarding the optimal timing and intensity of rehabilitation and be a valuable tool for describing recovery during rehabilitation among clinicians. SWAT addresses the requirement for a uniform method of evaluating the lower extremities appropriate for all individuals with SCI by demonstrating the validity of this categorization system among participants with NT-SCI/D. By implementing the SWAT, clinicians can gather valuable data to monitor changes in walking ability over time, inform minimum service requirements, and contribute to efforts to improve our therapeutic interventions to augment walking outcomes and limit related impairments in individuals with SCI.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: access to the dataset is restricted to authorized individuals or groups. Users are required to obtain permission or credentials to access and use the dataset. Requests to access these datasets should be directed to BC at cathy.craven@uhn.ca.

## Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

## Author contributions

MA: Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. FF: Project administration, Writing – review & editing. KM: Writing – review & editing. KP: Data curation, Writing – review & editing. MO: Data curation, Writing – review & editing. MV: Writing – review & editing. SA: Formal analysis, Writing – review & editing. BC: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.


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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Effect of body mass index on survival after spinal cord injury

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**Introduction:** Increased mortality after acute and chronic spinal cord injury (SCI) remains a challenge and mandates a better understanding of the factors contributing to survival in these patients. This study investigated whether body mass index (BMI) measured after acute traumatic SCI is associated with a change in mortality.

**Methods:** A prospective longitudinal cohort study was conducted with 742 patients who were admitted to the Acute Spine Unit of the Vancouver General Hospital between 2004 and 2016 with a traumatic SCI. An investigation of the association between BMI on admission and long-term mortality was conducted using classification and regression tree (CART) and generalized additive models (spline curves) from acute care up to 7.7 years after SCI (chronic phase). Multivariable models were adjusted for (i) demographic factors (e.g., age, sex, and Charlson Comorbidity Index) and (ii) injury characteristics (e.g., neurological level and severity and Injury Severity Score).

**Results:** After the exclusion of incomplete datasets ($n = 602$), 643 patients were analyzed, of whom 102 (18.5%) died during a period up to 7.7 years after SCI. CART identified three distinct mortality risk groups: (i) BMI: > 30.5 kg/m$^2$, (ii) 17.5–30.5 kg/m$^2$, and (iii) < 17.5 kg/m$^2$. Mortality was lowest in the high BMI group (BMI > 30.5 kg/m$^2$), followed by the middle-weight group (17.5–30.5 kg/m$^2$), and was highest in the underweight group (BMI < 17.5 kg/m$^2$). High BMI had a mild protective effect against mortality after SCI (hazard ratio 0.28, 95% CI: 0.09–0.88, $p = 0.029$), concordant with a modest "obesity paradox". Moreover, being underweight at admission was a significant risk factor for mortality up to 7.7 years after SCI (hazard ratio 5.5, 95% CI: 2.34–13.17, $p < 0.001$).

**Discussion:** Mortality risk (1 month to 7.7 years after SCI) was associated with differences in BMI at admission. Further research is needed to better understand the underlying mechanisms. Given an established association of BMI with metabolic determinants, these results may suggest unknown neuro-metabolic pathways that are crucial for patient survival.

KEYWORDS

**acute spinal cord injury, body mass index, mortality risk, Charlson comorbidity index, injury severity score**

## Introduction

Mortality after spinal cord injury (SCI) remains a substantial challenge (1). While infections and septic conversions remain the main causes, so far unknown reasons may drive mortality risk. Obesity is a well-characterized modifiable risk factor for vascular disease, which warrants control for primary and secondary prevention of stroke (2, 3) and represents a substantial challenge. Obesity and cardiometabolic risk markers are frequently pre-existent in patients with acute SCI (4).

In contrast to the deleterious chronic effects of obesity, ischemic brain injury studies have demonstrated that obese patients may have a lower acute mortality rate compared to their underweight counterparts (5, 6). This has been confirmed by *post-hoc* analysis of large trials (7), including the randomized, multicenter Field Administration of Stroke Therapy–Magnesium Study (8). The paradoxical phenomenon of lower mortality despite a higher risk of recurrent vascular insults in patients with obesity is referred to as the "obesity paradox" (9, 10). One explanatory reason is a catabolic state early after CNS injury being aggravated further by additional energy resources that are required for mounting a stress response and temperature rise in case of prevalent fever. The impaired ability to respond to these challenges due to a dysregulated, decentralized autonomic nervous system suggests the presence of non-homeostatic compensation strategies. In addition to cancer (11) and stroke, an obesity paradox has also been described in amyotrophic lateral sclerosis, where a lowered risk for disease progression or death has been observed in individuals with a high body mass index (BMI) (12, 13).

Acute SCI represents a life-threatening event triggering a profound stress response mirrored by hypercortisolism (14–16). Hypercortisolism indicates a stress response capable of mobilizing the body's energy, which can decrease lean body and muscle mass. Applying a bed-to-benchside approach to understand causality, a recent study verified lesion-level-dependent hypercortisolism as a catabolic and systemic driver of muscle wasting/sarcopenia, contributing to early weight loss after SCI affecting the entire body, including non-denervated muscles above the lesion site (17). It appears that the acute time window after SCI is different from the chronic SCI phase. During the first 6–10 weeks post-injury, early weight loss and body fat reduction have been reported (18), verifying a prevailing catabolic state. Recent studies have determined the association of body mass with mortality occurring after this first catabolic phase. This includes data from the US-National SCI Model System Database examining mortality from 3 months to 1 year after SCI (19). A putative obesity-related protective effect, however, would be expected during the first 3 months after SCI, with concurrent weight loss and body fat reduction (18). In addition to this putative "protective" effect of high BMI, an entirely different pathophysiological response may be in effect in cases of low BMI or being "underweight," which may also impact mortality.

To provide an integrative and comprehensive assessment of the role of nutritional status/body mass index 'on admission' after a traumatic SCI, we analyzed mortality over time from acute to chronic phases of SCI. Specifically, to test the hypothesis regarding the influence of BMI on mortality at different time points following SCI, we examined the association between admission BMI and mortality data at 1 month, 3 months, 1 year, and a long-term endpoint extending up to 7.7 years after SCI to analyze the dynamic association of admission BMI with mortality.

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; ASIA, American Spinal Injury Association; BMI, Body mass index; CART, Classification and regression tree; CCI, Charlson Comorbidity Index; CNS, Central nervous system; GAM, Generalized additive model; ISNCSCI, International Standards for the Neurological Classification of Spinal Cord Injury; ISS, Injury Severity Scale; ML, Machine learning; RHSCIR, Rick Hansen Spinal Cord Injury Registry; SCI, Spinal cord injury; WHO, World Health Organization.

## Materials and methods

### Study and ethical approval

The study was approved by both the Vancouver Coastal Health Research Institute and the University of British Columbia Clinical Research Ethics Board. Data were collected from interviews and medical chart abstraction for individuals who consented to participate in the Rick Hansen Spinal Cord Injury Registry (expanded dataset) (20). In addition, data were collected via additional medical chart abstraction for individuals enrolled in RHSCIR under a consent waiver (minimal dataset).

### Study population, design, setting, and data variables

This is a prospective longitudinal cohort study consisting of 1,245 acute SCI patients admitted to the Acute Spine Unit of the Vancouver General Hospital between 2004 and 2016 who were enrolled in the Rick Hansen Spinal Cord Injury Registry (RHSCIR) (20). Individuals with missing weight and/or height data at admission and mortality data were not included in this study ($n = 503$). Cases without complete data for model adjustment were excluded ($n = 99$) from the analysis. The sample used for the analysis was 643 (Figure 1A).

Age, sex, American Spinal Injury Association Impairment Scale (AIS), neurological level, Charlson Comorbidity Index (CCI), Injury Severity Score (ISS), body weight, and height were collected at admission to the Acute Spine Unit (21, 22). Pre-injury/admission body weight and height data were gathered by questioning the patients or their relatives. The BMI was calculated by dividing a person's weight in kilograms by the square of a person's height in meters ($BMI = weight_{kg}/height^2_m$). The conventional BMI categories are underweight BMI < 18.5 kg/m$^2$; normal weight BMI 18.5–24.9 kg/m$^2$; overweight BMI 25.0–29.9 kg/m$^2$; and obese, BMI ≥30.0 kg/m$^2$ (2, 3). The outcome (mortality) was collected up to 7.7 years post-injury.

### Statistical modeling

Demographic and injury data were compared for the outcome (survival vs. mortality). Continuous variables including age, BMI, ISS, and CCI were analyzed using t-tests, and categorical variables such as sex, AIS, and neurological level groupings (i.e., Cl 1 to T1 vs. T2 to S5)

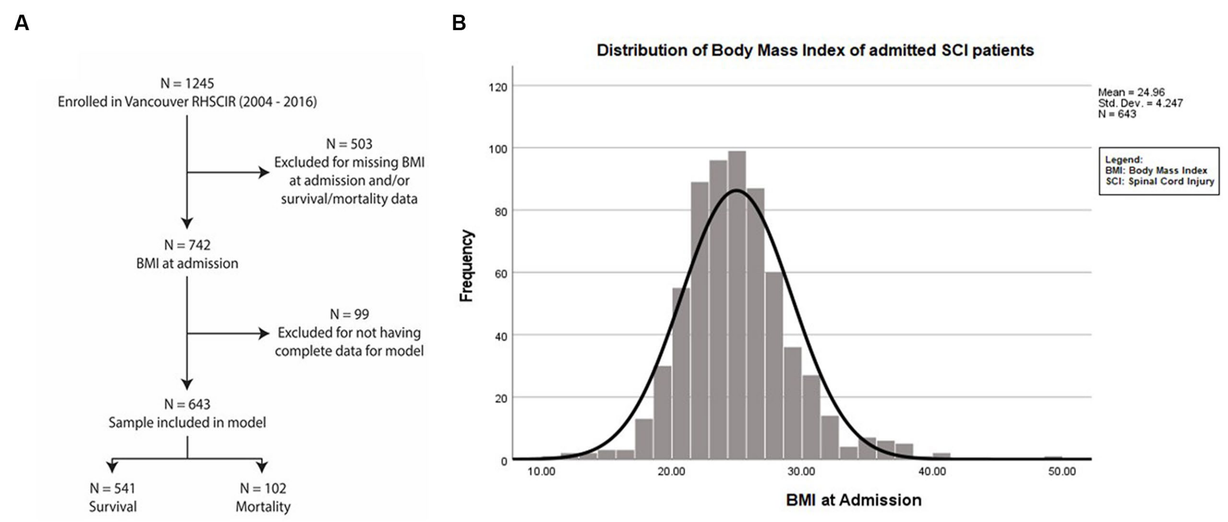


FIGURE 1
Dataset selection and enrolment. **(A)** Flowchart of patients admitted with traumatic SCI from 2004 to 2016 at the Acute Spine Unit. Among the 1,245 SCI participant datasets, 602 were excluded due to being incomplete. Of the remaining 643 participants, 102 died and 541 individuals survived up to 7.7 years after SCI. **(B)** Mean BMI at admission of the entire study population was 24.92 kg/m$^2$ + 4.25 (SD).

were analyzed using chi-square tests. In a missing data analysis, demographic and injury characteristics were compared between groups that were defined based on the availability of BMI data.

To determine if BMI at admission was associated with mortality from acute care up to 7 years after SCI, predictive models were created using classification and regression tree (CART) analysis. This approach was chosen because the World Health Organization (WHO) obesity criteria (3) may be non-informative in patients with SCI (23, 24). CART accounted for the binomial distributions in the response variable and identified 'nodes', or subgroups that were most homogeneous with regards to the probability of mortality. These BMI subgroups were then applied to Kaplan–Meier curves and Cox regression. For comparability with other studies, we used BMI categories based on the WHO obesity criteria. In addition, Cox regression was conducted, categorizing BMI by the 10th, 11th–89th, and 90th percentiles in a sensitivity analysis. To determine the survival for each BMI category relative to the WHO normal or medium range for BMI, unadjusted and adjusted Kaplan–Meier curves and log-rank tests were calculated. All variables and stratified BMI categories were tested for proportionality assumptions (Schoenfeld residuals) before applying them to the Cox regression data in order to calculate mortality hazard ratios (MHRs). In this analysis, there was no evidence of time-varying effects. The model was adjusted for age, sex, AIS, neurological level (C1 to T1 vs. T2 to S5), and ISS (25–27). In total, two models were calculated [(i) using all variables and (ii) applying BMI only] for the analyses using the WHO BMI categories and the CART BMI categories.

To further elucidate the association between BMI and survival, we applied the generalized additive model (GAM) with cubic splines using the BMI continuous data instead of the BMI categories in a sensitivity analysis. Assessments were made over time at 1 month, 3 months, 1 year, and the long-term endpoint (7.7 years). A value of $p$ of <0.05 was considered statistically significant, along with the 95% CI. All statistical analyses were performed using SPSS (version 26) and R × 64 (version 3.1).

## Results

We investigated mortality in patients admitted to the Acute Spine Unit of the Vancouver General Hospital (Figure 1A) with traumatic spinal cord injuries. An analysis comparing the cohort that was included vs. those excluded due to missing data revealed no relevant differences in sex or age. The included patients comprised slightly fewer cervical injuries and more individuals with AIS A injuries. Both groups had similar mortality rates (Supplementary Table S1).

The mean ± SD value of BMI for the patients during their acute admission was 24.96 ± 4.25 kg/m$^2$ (Figure 1B). The distribution of (i) demographic factors (age, sex) and (ii) SCI characteristics [injury severity (AIS), neurological level (C1 to T1 vs. T2 to T12 vs. L1 to S5)], accompanying severity of ISS, and premorbid comorbidities using the CCI is described in Table 1.

There were 446 individuals (69.3%) who were admitted directly to the center, while 197 (30%) were admitted indirectly. The time to admission was less than 24 h for 366 individuals (82%) in the direct admission group and 175 individuals (88.8%) in the indirect group. Rates of surgery were similar (88.8 and 91.4%) for the direct and indirect admitted patients, respectively.

During the follow-up period, 102 patients (15.8%) were deceased as of 2016, and the mean time to death post-injury was 25.85 ± 26.04 months. Mortality rates were 2.2% at 1 month, 5% at 6 months, 6.5% at 1 year, 12.1% at 3 years, and 15.9% at 7.7 years following SCI. The mortality group was characterized by being older, comprising more men, having more injuries to the cervical cord, and having a higher CCI and ISS.

### CART identified three distinct mortality-hazard ("risk") groups

Comparing the survival of the 10th with the 90th BMI percentile of the study population, the mortality rate was higher. The survival time was

TABLE 1 Demographic and injury data for the survival and mortality groups.

| | Survival $n = 541$ | Mortality $n = 102$ | $p$-value |
|---|---|---|---|
| Age, mean ± SD | 42.5 ± 17.9 | 63.0 ± 17.9 | < 0.001 |
| Sex, % male ($n$) | 72.5% (407) | 83.3% (85) | 0.047 |
| BMI kg/m² at admission, mean ± SD | 25.1 ± 4.2 | 24.2 ± 4.3 | 0.055 |
| AIS at admission, % ($n$) | | | 0.412 |
| A | 46% (251) | 53% (54) | |
| B | 13% (68) | 15% (15) | |
| C | 21% (112) | 18% (18) | |
| D | 20% (110) | 15% (15) | |
| Neurological level of injury, % ($n$) | | | < 0.001 |
| C1-T1 | 59% (318) | 89% (91) | |
| T2-T12 | 28.5% (154) | 8.8% (9) | |
| L1-S5 | 12.8% (69) | 2% (2) | |
| CCI, mean ± SD | 0.35 ± 0.83 | 0.83 ± 1.14 | < 0.001 |
| ISS, mean ± SD | 27.1 ± 11.5 | 30.7 ± 16.9 | 0.044 |

Of the 643 patients, 102 (15.9%) died, and 541 survived up to 7.7 years post-SCI. The two groups were statistically different with regard to age, sex, neurological level, Charlson Comorbidity Index (CCI), and Injury Severity Score (ISS). The mortality group had a higher age, a higher number of men, a higher number of cervical injuries, and a higher CCI and ISS. A predictive model was used to adjust for: (i) demographic factors (age and sex) and (ii) SCI characteristics [level and completeness of injury (AIS; ASIA Impairment Scale)] as well as for comorbidities (CCI) and severity of polytrauma (ISS) associated with SCI. AIS, American Spinal Injury Association Impairment Scale; CCI, Charlson Comorbidity Index; ISS, Injury Severity Score; BMI, body mass index.

shorter in the 10th percentile, where 15 of 64 patients died (24.4%) at a mean time of 81.4 (95% CI: 72.8–90.0) months after injury. In contrast, in the 90th percentile, 6 deaths occurred in 65 patients (9.2%) after 94.5 (95% CI: 89.9–99.1) months. In the 11th–89th percentile, 81 of 514 patients (15.8%) died at 88.3 (95% CI: 85.8–90.8) months after injury.

To classify BMI categories based on the survival/mortality outcome, we applied CART to identify cohorts with different survival rates according to BMI. CART analysis identified three distinct subgroups (Figure 2A). Individuals with a BMI > 30.5 kg/m² (blue, $n$ = 53) demonstrated the lowest mortality, followed by patients with a BMI of 17.5–30.5 kg/m² (green, $n$ = 578), and the highest mortality was in patients with a BMI < 17.5 kg/m² (red, $n$ = 12) (Figure 2B). Survival analysis over time illustrated that the protective effects of higher BMI against mortality: (i) occurred in a dose-dependent manner, (ii) started early, and (iii) were long-lasting (Figure 2B). BMI groups are illustrated as Kaplan–Meyer curves after the Cox regression in Figure 2B. Comparison with WHO BMI categories confirmed the dose-dependent effect of BMI at admission on mortality (Supplementary Figure S2).

## The two effects on mortality: obesity and underweight

For the most accurate interpretation of the association between BMI and mortality (mortality hazard ratios) and to distinguish obesity/overweight from underweight-associated effects, Cox regression models were conducted, examining: (i) BMI bins as identified by recursive partitioning (Table 2) and (ii) BMI groups defined according to the WHO obesity criteria (Supplementary Table S2). Next, we examined whether the hazard ratios were different compared to the middle CART group (BMI 17.5–30.5 kg/m², $n$ = 578) or the WHO normal weight definition group (BMI 18.5–24.9 kg/m², $n$ = 325), respectively. The middle CART group (BMI 17.5–30.5 kg/m², $n$ = 578) and the WHO normal weight group (BMI 18.5–24.9 kg/m², $n$ = 325) were defined as the reference categories.

Compared to the reference category (middle weight), the high-range BMI group identified by CART (BMI > 30.5 kg/m², $n$ = 53) displayed a significant decrease in mortality risk by 28% (HR 0.28, 95% CI 0.09–0.88, $p$ = 0.029). In the obese WHO group (BMI ≥ 30.0 kg/m², $n$ = 67), the mortality risk was also significantly reduced to 32% (HR 0.32, 95% CI 0.14–0.76, $p$ = 0.009) compared to the normal weight WHO group. In the overweight WHO group (BMI 25.0–29.9 kg/m², $n$ = 227), the effect on mortality was much weaker (HR 0.65, 95% CI 0.42–1.01, $p$ = 0.053) compared to the medium/normal range BMI group.

By contrast, the low-range BMI group identified by the CART (BMI < 17.5 kg/m², $n$ = 12) likewise demonstrated a significantly elevated risk of mortality (HR 5.55, 95% CI 2.34–13.17, $p$ < 0.001) compared to the CART-based mid-range BMI group (BMI 17.5–30.5 kg/m²). The underweight group, defined by the WHO criteria (BMI < 18.5 kg/m², $n$ = 24) was characterized by a significantly increased risk of mortality (HR 2.43, 95% CI 1.17–5.03, $p$ = 0.017) compared to the WHO medium/normal weight group.

The three CART-defined BMI groups revealed a differing distribution based on the neurological impairment on admission (baseline), where there were more incomplete patients with SCI in the low-range BMI group and more cases with cervical SCI present in the middle BMI group. Other baseline characteristics that were slightly different between the groups were the CCI and ISS (Table 3). However, the differences in the neurological level distribution across the BMI groups had no effect on BMI-associated mortality (Supplementary Table S3).

## Dynamics of BMI association with mortality spanning from subacute to chronic SCI

Next, we applied an additional non-linear model (generalized additive model [GAM]) to investigate the association between BMI at admission and long-term mortality. In order to explore if there was a shift over time, we assessed the association between linear BMI and mortality at various time points after SCI in an unadjusted and adjusted GAM. For the outcome of mortality, a restricted cubic spline curve analysis demonstrated a non-linear association of BMI with mortality. This association was visible throughout the time points in the adjusted models (Supplementary Figure S1), whereas, in the unadjusted models, a similar pattern was also detected at 1 and 3 months after SCI. For BMI values less than 17.5 kg/m², the slope was inclined, indicating a higher mortality (Supplementary Figure S1). With a higher BMI >30.5 kg/m², a declined slope at all time points indicates a progressively reduced risk (Supplementary Figure S1).

Further spline curve analysis revealed a non-linear association between mortality and age, where there was increased mortality with higher age and an inclined slope indicating a progressively increased risk (Supplementary Figure S1J).

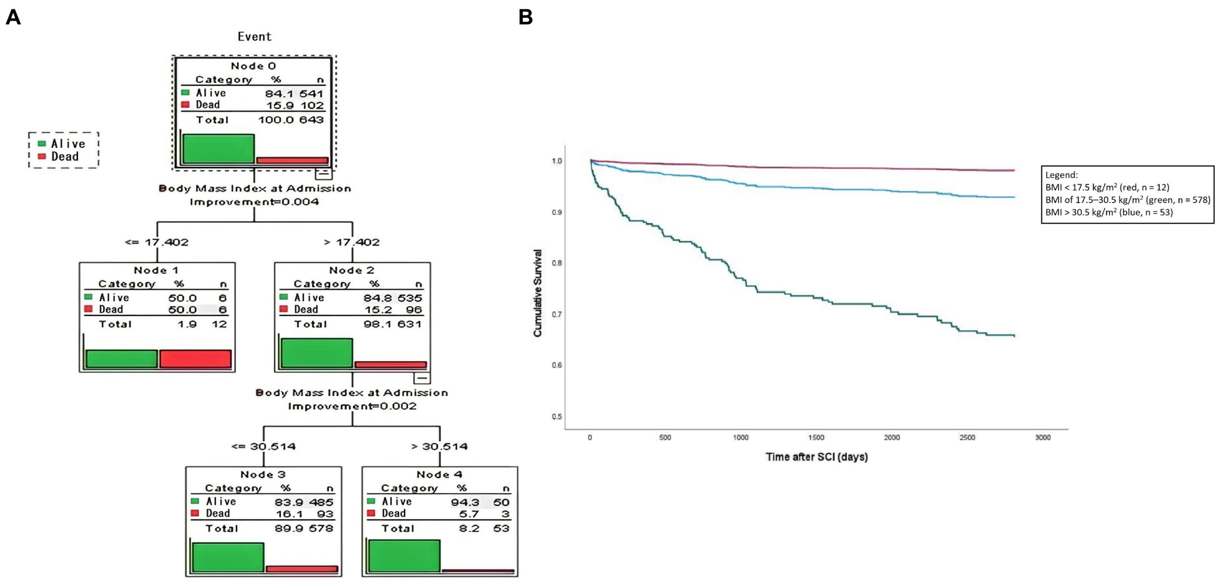


FIGURE 2
Analysis identified three distinct BMI groups using unbiased recursive partitioning (CART BMI categories). **(A)** A predictive model was developed by applying a classification and regression tree (CART) analysis. Survival was analyzed as an event following a binominal distribution [1 = mortality/event (red), vs. 0 = survival (green)]. Decision trees identified three cohorts that were most homogenous with regard to the probability of mortality. Survival was significantly lower in patients with a BMI < 17.5 kg/m$^2$ (red) compared with patients with a BMI = 17.5 kg/m$^2$ (Node 1 and 2). In the BMI cohort >17.5 kg/m$^2$, patients with a BMI > 30.5 kg/m$^2$ demonstrated lower mortality compared with patients with a BMI > 17.5–30.5 kg/m$^2$ (Nodes 2 and 3). The overall number and percentage of deaths per group are listed and graphically illustrated in red vs. green (survival). **(B)** Linearized cumulative survival over time illustrated a protective effect of a higher BMI in a class (dose) dependent manner which occurs early and is long-lasting. Whereas, elevated mortality was observed in patients who were severely underweight (< 17.5 kg/m$^2$, red, *n* = 12), patients with a BMI of 17.5–30.5 kg/m$^2$ (green, *n* = 578) or > 30.5 kg/m$^2$ (blue, *n* = 53); where there is a less negative slope that nearly plateaus after 3 years.

## Discussion

Mortality risk during acute and chronic phases following SCI (ranging from 1 month to 94 months or 7.7 years) was associated with BMI at admission. Data-driven CART analysis was applied to determine which BMI categories were associated with mortality. Multivariable Cox regression models adjusting for effects of confounders such as age, sex, CCI, ISS, AIS, and neurological level were applied. Finally, spline curve analyses were calculated, depicting the association of BMI at admission with mortality over time after SCI.

The results based on the CART analysis indicated two different effects. There was an overarching strong effect of being underweight (BMI < 17.5 kg/m$^2$), which was positively associated with mortality (HR 5.5), and a milder effect of an inverse association of being overweight (BMI > 30.5 kg/m$^2$) with mortality (HR 0.28). While being underweight (BMI <17.5 kg/m$^2$) was associated with an increased mortality risk, a higher BMI (>30.5 kg/m$^2$) may be considered protective. This study suggests a putative 'obesity paradox' pronounced during the first months after SCI and diminishing thereafter. Deciphering the mechanisms underlying these protective effects may provide new leads for improving the survival of normal and underweight SCI patients.

Adjusted Cox regression and spline curve analysis confirmed the robustness of the survival analysis. Additionally, the comparison of baseline characteristics among the BMI groups defined by CART did not provide evidence of obvious differences in the composition of the BMI groups that might otherwise explain the differential mortality risk. For example, despite having a slightly higher ISS, which is a predictor of mortality during acute care, the low-range BMI group comprised fewer cases of complete (AIS A) and cervical SCI compared with the mid-range group, both of which are associated with long-term mortality (1). Together, the observed BMI effects were observed independently of either applying predefined BMI or CART categories and emphasized their relevance.

Other recent evidence analyzing multi-center data confirmed that mortality risk is altered in individuals with deviations from "normal" weight, both for patients being overweight and underweight (19). However, the studies have a fundamentally different design and thus are not directly comparable. While Wen et al. focused on a time window ranging from 3 months to 1 year after SCI, this analysis also included an early time window (before 3 months) as well as a long-term endpoint (up to 7.7 years). In addition, Wen et al. measured body weight and height during initial rehabilitation in patients up to 90 days post-injury, and our study used pre-injury or admission body weight and height. Thus, post-injury changes in body weight in the Wen et al. study could explain these divergent results. Furthermore, the analytical strategy was considerably different. Our study did not rely on the WHO criteria developed for able-bodied individuals as it may not be appropriate for individuals with SCI (23), but instead, we used a data-driven, unsupervised approach to identify BMI ranges associated with mortality risk. Notably, the BMI effects were stronger for the recursive partitioning-based categories compared with those based on the WHO definitions, both for underweight (HR 5.5 vs. 2.4) as well as for obese (HR 0.28 vs. 0.32) BMI categories. Moreover, the effects observed in the CART BMI categories were confirmed by the

TABLE 2 Differential mortality risk for BMI groups identified by unbiased recursive partitioning (CART BMI groups).

| Model | Variables | Hazard ratio (95% CI) | *p*-value |
|---|---|---|---|
| Univariable | BMI kg/m² 17.5–30.5 (ref) | | |
| | BMI kg/m² < 17.5 | 4.18 (1.83–9.57) | < 0.001 |
| | BMI kg/m² > 30.5 | 0.33 (0.10–1.03) | 0.056 |
| Multivariable | Age (per 1 year increase) | 1.07 (1.06–1.08) | < 0.001 |
| | Sex (male) | 3.12 (1.82–5.36) | < 0.001 |
| | Neurological level (C1 to T1) | 4.84 (2.52–9.28) | < 0.001 |
| | AIS A | 3.496 (1.83–6.68) | < 0.001 |
| | AIS B | 2.30 (1.11–4.77) | 0.024 |
| | AIS C | 1.68 (0.84–3.35) | 0.145 |
| | AIS D | Ref | |
| | ISS (per 1 unit increase) | 1.02 (1.01–1.03) | 0.003 |
| | BMI 17.5–30.5 kg/m² (ref) | Ref | |
| | BMI <17.5 kg/m² | 5.55 (2.34–13.17) | < 0.001 |
| | BMI >30.5 kg/m² | 0.28 (0.09–0.88) | 0.029 |

Three groups of different body composition (BMI) were associated with a distinct mortality risk: (1) BMI 17.5–30.5 kg/m² (reference), (2) BMI < 17.5 kg/m², (3) BMI > 30.5 kg/m². BMI group 2 had a 5.5-fold mortality risk compared to BMI group 1. By contrast, BMI group 3 had a 28% lower mortality risk compared to BMI group 1. AIS, American Spinal Injury Association Impairment Scale; ISS, Injury Severity Score; BMI, Body Mass Index. CART Categories: BMI < 17.5 (*N* = 12); BMI 17.5–30.5 (*N* = 578); BMI > 30.5 (*N* = 53).

TABLE 3 Baseline characteristics stratified for the CART BMI groups.

| | BMI < 17.5 kg/m² *n* = 12 | BMI 17.5–30.5 kg/m² *n* = 578 | BMI > 30.5 kg/m² *n* = 53 |
|---|---|---|---|
| Age (years), mean ± SD | 47.25 ± 21.97 | 45.58 ± 19.68 | 47.11 ± 15.38 |
| Sex, % male (*n*) | 75% (9) | 76.5% (442) | 77.4% (41) |
| BMI kg/m²at admission, mean ± SD | 14.47 ± 2.21 | 24.34 ± 2.91 | 34.1 ± 3.59 |
| AIS at admission, % (*n*) | | | |
| A | 33.3% (4) | 47.8% (276) | 47.2% (25) |
| B | 25% (3) | 11.4% (66) | 26.4% (14) |
| C | 25% (3) | 20.4% (118) | 17% (9) |
| D | 16.7% (2) | 20.4% (118) | 9.4% (5) |
| Cervical injury (C1 to T1), % (*n*) | 50% (6) | 64.9% (375) | 52.8% (28) |
| CCI, mean ± SD | 0.67 ± 1.23 | 0.41 ± 0.86 | 0.60 ± 1.17 |
| ISS, mean ± SD | 31.67 ± 17.7 | 27.67 ± 12.61 | 27.13 ± 10.72 |

Three body composition (BMI) groups were calculated based on CART: (1) BMI < 17.5 kg/m²; (2) BMI 17.5–30.5 kg/m², and (3) BMI > 30.5 kg/m². The three groups differed by ASIA Impairment Scale (AIS), neurological level (C1-T1), Charlson Comorbidity Index (CCI), and Injury Severity Score (ISS). AIS, American Spinal Injury Association Impairment Scale; BMI, body mass index; CCI, Charlson Comorbidity Index; ISS, Injury Severity Score.

cubic splines within the GAMs. In the unadjusted models, a significant association developed after 1 year to the final data point (7.7 years). In the adjusted models, the association between being underweight and having a greater risk for mortality as well as the protective effects of obesity were visible early on, from 1 month throughout the follow-up period of 7.7. years. Together, these results suggest that being underweight at admission is an extra risk factor compared to what would be expected by a later reduction of BMI only.

Aligned with the subtle protective effect of a higher BMI, its detection may be more difficult and dependent on the array of biostatistical methods being applied. This is supported by ongoing debates in other acute central nervous system (CNS) injury areas such as stroke (28) while more recent high-quality multi-center studies identified an obesity paradox (8). After traumatic brain injury, an obesity-associated decrease in overall complications was observed; however, this did not result in reduced mortality (29). In chronic neurodegenerative disease, a high BMI demonstrated a protective effect regarding disease prevalence (12) and mortality (13). Patients who are malnourished have been considered at higher risk given their lowered metabolic reserve necessary to survive the complications they encounter after injuries such as SCI. For example, even mounting a fever to combat infection poses profound metabolic needs. Future studies using novel techniques are needed to link mortality with better measures of energy expenditure (30). In addition to energy expenditure in underweight individuals, skewed neuroendocrine profiles can trigger muscle wasting and sarcopenia after acute CNS injury (31) pointing to a multifaceted and so far poorly understood area regarding which elements are contributing to systemic pathophysiology that emerges following SCI.

In considering these results, it is important to acknowledge the limitations. This study is not population-based, and as a result, there is a potential bias with regard to the catchment area and the representation of different ethnic minorities or rural populations. We acknowledge that the missing data and use of self-reported data (e.g., height and weight) inherent to using registries may also introduce bias. Nevertheless, relevant differences between included and excluded patients were only observed for AIS. As the included patients comprised more AIS A patients, we do not expect a bias toward an underrepresentation of seriously injured patients in the analysis. Moreover, assessing BMI at admission only is a possible limitation, as BMI is likely to change over time (32). BMI may underestimate the amount of body fat, especially in populations experiencing changes in their body composition, and future studies should explore changes in fat, lean tissue, and bone mineral content. It is also important to acknowledge the small sample size ($n = 12$) for the BMI < 17.5 kg/m$^2$ group, and the reported effect estimates should be interpreted cautiously. Future studies are needed with larger samples to validate our results.

While the limitations are inherent, studies investigating acute or neurodegenerative diseases had similar limitations, and the presented data represent the 'best evidence available' to substantiate the need for prospective multi-center studies to validate these findings. Systematic studies on changes in body composition after SCI and on treatment options are warranted to establish the pathophysiology and evidence-driven management of nutritional status in these patients, particularly to determine what specific nutritional support might mitigate the risk of mortality in those who are 'underweight' when injured. While our article primarily addresses survival during the acute phase and the potentially protective effects of a high BMI, it is important to acknowledge the challenges with weight management and the serious health impacts of chronic SCI.

In conclusion, high BMI imposes a mild protective factor associated with lower mortality in individuals sustaining SCI, concordant with a modest "obesity paradox." Moreover, being underweight is a highly significant risk factor for death during acute care and up to 7.7 years after SCI. The results suggest unknown neuro-metabolic pathways crucial for survival that are impaired in patients who are underweight. Identifying protective mechanisms and factors underlying the protective effectiveness of adiposity may lead to increased survival in low- to normal-weight patients early after SCI.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: access to deidentified data used for this study is available via the RHSCIR Data Use and Disclosure Policy which is administered by the Praxis Spinal Cord Institute. Requests to access these datasets should be directed to dataservices@praxisinstitute.org.

## Ethics statement

The studies involving humans were approved by Vancouver Coastal Health Research Institute and the University of British Columbia Clinical Research Ethics Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

NF: Conceptualization, Formal analysis, Writing – review & editing. VN: Conceptualization, Funding acquisition, Writing – review & editing. NT: Writing – review & editing. BK: Conceptualization, Writing – review & editing. MK: Conceptualization, Writing – original draft. JS: Conceptualization, Funding acquisition, Writing – original draft.

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## Conflict of interest

NF, VN, and NT are employees of the Praxis Spinal Cord Institute.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1269030/full#supplementary-material

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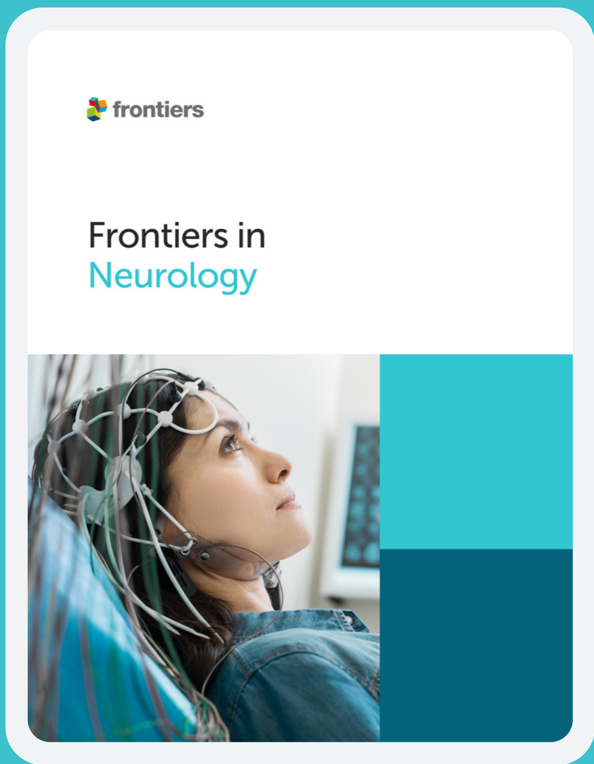


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