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FUNCTIONAL OUTCOMES AFTER SPINAL CORD INJURY: A MULTIDISCIPLINARY APPROACH

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List of contents

Introduction

Spinal cord injury

A lesion of the spinal cord produces a partial or complete interruption of afferences and efferences at the level of damage.[1] This results in alteration or loss of somatic and autonomic functions below the level of injury, with possible lifelong disability and deterioration of quality of life.[2] This condition causes an increase of morbidity and hospitalization, with considerable burden on the health care system.[3] Moreover, subjects with spinal cord injury (SCI) have a higher mortality risk compared to the general population.[4]

Etiology and epidemiology

Traumatic SCI affects each year 15–53 new individuals per million in Western countries and is the most represented etiology, accounting for about 90% of cases. [2,5,6]

On the other hand, there is paucity of high-quality studies concerning incidence of non-traumatic SCI: the estimated incidence ranges from 6 to 76 cases per million individuals/year.[7] The commonest cause of non-traumatic spinal cord injury in developed country is represented by degenerative myelopathy.[7,8] Other etiologies of SCI include tumors, infections, vascular causes, inflammatory/autoimmune diseases, and neural tube disorders.[7] It is expected that with the aging of the global population the incidence of non-traumatic SCI will substantially increase.[7]

In Italy the incidence of traumatic SCI is 14.7 cases per million per year, with a mean age of 54 years and a male to female ratio of 4:1.[9,10] The leading cause of traumatic SCI is fall, especially for patients over 55, followed by road traffic accidents, especially for patients under 55. [9,10]

Clinical presentation and syndromes

The clinical presentation is mainly determined by the level and grade of spinal cord damage.[1] As a consequence of injury, a complete or partial loss of motor function and sensitivity below the level of injury is observed, with a condition of tetraplegia/paresis if the lesions affects the cervical or the first thoracic metamer or paraplegia/paresis in case of a lower lesion.[1] Muscle tone and reflexes usually appear reduced immediately after injury, while a progressive augmentation up to hypertonia and hyperreflexia in the following days, after the resolution of the so called "spinal shock phase".[1] The damage of somatic and autonomic pathways contributes to the onset of neurogenic bladder and bowel dysfunction, two complexes and disabling syndromes characterized by the loss of control of spontaneous micturition and bowel movement, with consequent urinary/fecal retention and/or incontinence.[11,12] Other possible sequelae include respiratory failure, dysphagia, autonomic dysreflexia, sexual dysfunctions, pressure ulcers, thrombosis, neurogenic heterotopic ossifications and psychological problems, chronic pain. [13]

In case of anatomically defined lesions, the clinical presentation assumes peculiar characteristics, configuring the so-called spinal syndromes, such as the central cord syndrome, the Brown-Séquard syndrome, the conus medullaris syndrome, the cauda equine syndrome, the anterior cord syndrome and the posterior cord syndrome.

In particular, the central cord syndrome is assuming a growing epidemiological relevance due to the increasing incidence of low-energy hyperextension neck injury (for example, secondary to a fall forward) in the context of preexisting cervical degenerative disease, usually in the elderly population.[8] This mechanism is responsible for sudden impingement of the spinal cord in the anteroposterior plane, with consequent elective damage of the neural fibers located in the central

region, which are directed to the innervation of upper limbs.[8] As a consequence, patients display upper limb weakness disproportionately greater than lower limb weakness. [8]

Diagnosis and evaluation systems

The diagnosis is based on clinical neurological examination and confirmed by radiological and neurophysiological exams.[1,14] After traumatic injury, the radiological examination commonly performed if a spinal cord damage is suspected include plan and dynamic radiographic study, computed tomography (CT) for revealing fracture and vertebral subluxation and MRI for detecting ligamentous damage, disk herniation, and edema or hemorrhage in the spinal cord.[1,14] Neurophysiological examinations (including motor evoked potentials, sensory evoked potentials, nerve conduction study) are commonly employed to study the function of specific spinal tracts and of the peripheral nervous system.[14] The neurophysiological evaluation constitutes an objective assessment which is feasible even when the patient is unable to cooperate, allowing a distinction of gray and white matter injury at different spinal levels and for distinct anatomic regions.[14]

The assessment of a patient with SCI is based on the evaluation of neurological impairment using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) and on the evaluation of disability through the Spinal Cord Independence Measure. [15-17]

The ISNCSCI is an established grading system developed and published by American Spinal Injury Association (ASIA) to determine the level and classify the severity of SCI.[15] This grading system rates with a six-point scale (from 0 = total paralysis to 5 = active movement with full range of motion against gravity and full resistance) the strength of ten key muscle groups of each limb, evaluates the light-touch and pinprick sensation for each dermatome of the body (0 = absent, 1 = impaired, 2 =

normal) and assesses the presence of voluntary anal contraction and sensation of deep anal pressure.[15] The ISNCSCI provides a few cumulative scores, i.e., upper extremity motor score (UEMS), lower extremity motor score (LEMS), and light-touch and pinprick scores, and allows the identification of neurological level, motor level, and sensory level and the classification with the ASIA Impairment Scale (AIS) in five different grades of severity (from A = complete lesion, B, C, D = incomplete lesions with progressive lower impairment, to E = normal sensation and motor function in all body districts). [15]

Since the grading system was introduced in clinical practice, the ISNCSCI have been regularly refined and updated and their measurement properties have been widely validated in patients with traumatic SCI. [15]

The SCIM is a validated tool specifically designed for the evaluation of functional capacity of subjects with SCI and investigates the ability to perform SCI-relevant tasks of daily living, clustered into three subscales: the self-care domain (with a score range of 0–20), including feeding, bathing, dressing, and grooming; respiration and sphincter management (score range 0–40), including respiration, bladder, and bowel management and use of toilet; and mobility (score range 0–40), including mobility in bed, transfers, mobility indoors and outdoors, and stair management. The total SCIM score ranges from 0 to 100, with higher scores indicating higher levels of independence. Over the last years, two revisions of this evaluation system have been proposed, SCIM version II and III, respectively.[16,17]

Clinical evolution

The medical or surgical treatment of SCI in the acute phase is highly variable on the basis of the clinical characteristics and of the etiology.[1,8]

Most of studies reporting data on clinical evolution are derived from data of patients with traumatic SCI, indicating a possible predictive value of the ISNCSCI and of the neurophysiological examination.[18-22]

Neurological recovery after traumatic SCI depends on severity, level, and mechanism of injury.[18] Neurological recovery is greater in incomplete lesions and in lumbar injuries, while the thoracic ones show the lowest grade of recovery. [18] Thoracic SCI and penetrating SCI were significantly more likely to result in complete injury.[18]

The natural history of spinal syndromes and secondary SCI is less known, due to the paucity of studies focused on these cohorts of patients.

Rehabilitation and functional recovery

The rehabilitation phase is directed to the achievement of the higher possible neurological and functional recovery, to the treatment of concurrent medical problems, to the prevention of mid-long term complications, to the instruction of patient and caregivers for the care after discharge, to the preparation of a home and work environment suitable to receive the subject with SCI and to the promotion of social reintegration.[23]

In this context, the prediction of functional outcomes is essential for counselling and to establish realistic objectives shared among the rehabilitative team, the patient and the caregiver. [23]

The main functional outcomes for individuals with SCI include arm/hand function (for individuals with tetraplegia), ambulation, bowel, bladder, and sexual function.[24]

For the prediction of ambulation and upper limb function after traumatic SCI, two models have been derived and validated.[25,26] These models may be applied in clinical practice to counsel patients and to fix the rehabilitative aims.

Recovery of bladder and bowel functions represents an absolute priority for individuals affected by SCI, and the recovery of independence in sphincter management is indicated by patients to be more important than recovery of walking or reduction of chronic pain. [24] In this context, our group has recently derived and validated two models to predict the recovery of independent and reliable bladder management one year after traumatic SCI, which can be applied in clinical and research practice.[27]

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Aim of the project

The aim of the project is to deepen the knowledge of spontaneous evolution and the prediction of functional outcomes after SCI. The research is focused on:

- the study of the role of neurophysiological parameters in the prediction of global functional outcome after traumatic cervical SCI;
- the evaluation of the validity of our prediction models for bladder outcome in patients affected by ischemic SCI;
- the development of a valid model to predict bowel outcome after traumatic SCI;
- the validation of the bowel outcome prediction model in an independent sample of patients with traumatic SCI;
- the evaluation of the validity of the bowel outcome prediction model in a sample of patients with ischemic SCI;
- the evaluation of functional outcomes after central cord syndrome;
- the study of the measurement properties of the International Standards for Neurological Classification of Spinal Cord Injury in the evaluation of patients with non-traumatic SCI.

Role of neurophysiology in the prediction of global functional outcome after traumatic cervical spinal cord injury

This chapter is derived from the study:

Hupp M*, Pavese C*, Bachmann LM, Koller R, Schubert M; EMSCI Study Group.

Electrophysiological Multimodal Assessments Improve Outcome Prediction in Traumatic Cervical Spinal Cord Injury.

J Neurotrauma. 2018 Dec 15;35(24):2916-2923. *Authors with equal contribution

Introduction

Prognostication of outcome following spinal cord injury (SCI) is as important to patients and their families as it is to the medical staff and to caregivers when planning rehabilitation.[1]

Correct prognostication of outcome is also crucial to achieving meaningful early stratification when conceiving clinical trials.[2]

However, because of the heterogeneity of lesion characteristics, the disability secondary to traumatic SCI is highly variable. Functional independence after rehabilitation typically depends on spinal lesion levels and severity. It also varies with the focal distribution of segmental spinal lesion pattern, resulting in a variable combination of central and peripheral neural lesion burden at any affected spinal segment.[3] Further, a multitude of secondary injury mechanisms with variable degrees of subsequent demyelination and axonal damage result from spinal trauma.[4] In this context, neurophysiological techniques have been suggested for prognostication because they are objective and available early after injury even if a patient is unable to cooperate.[5,6] In addition to clinical examination according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), neurophysiological evaluation allows for quantitative differentiation of gray and white matter injury at different spinal levels and for testing of distinct anatomic regions of the spinal cord.[4] A demyelination will typically result in slowing of conduction velocity and axonal damage results in amplitude reduction of evoked potentials or compound muscle action potentials.

We have shown in the past that neurophysiological evaluation can serve as an independent stratification tool in describing typical homogeneous cohorts among SCI patients, and that these cohorts can be used for prediction of functional outcome in paraplegic and tetraplegic patients.[3,7–10]

Neurophysiological evaluation can, therefore, provide an objective and quantitative measure of underlying spinal pathology. Although these aspects speak to a systematic use of neurophysiological

evaluation in SCI, the significance for outcome prediction and relationship with function have not been systematically established. More specifically, given the high prognostic value of standardized clinical testing according to ISNCSCI examination, the additional cost and effort to obtain neurophysiological evaluation requires justification.[11–13] Hence, it remains unclear what neurophysiological evaluation can add to improve prediction of functional outcome in traumatic SCI.

It was assumed that the complexity and extent of damage within the spinal cord would be reflected in the alteration pattern of combined sensory and motor evoked potential and nerve conduction study testing. Assuming that neural repair in the human central nervous system is minimal, we expected that permanent lesion burden would be reflected in the readout from neurophysiological evaluation very early after spinal injury, thus relating to, and anticipating, functional outcome. We hypothesized that early neurophysiological evaluation could enhance the predictive power of clinical examination for any severity and lesion level of cervical SCI in the assessment of functional prognosis.

Methods

Data were derived from the European Multicenter Study about Spinal Cord Injury (EMSCI) (www.emsci.org), ClinicalTrials.gov Identifier NCT01571531, which provides a database containing prospective data on neurological, neurophysiological, and functional status from 18 SCI centers in Europe. Patients are tested according to a strictly standardized protocol within the following time schedule: stage 1 (0–15 days post-injury), stage 2 (16–40 days post-injury), stage 3 (70–98 days post-injury), stage 4 (150– 186 days post-injury), and stage 5 (300–400 days post-injury). Individuals with a single traumatic event resulting in paraplegia or tetraplegia for whom an assessment within the first 6 weeks is possible are included in the database. Exclusion criteria are: dementia or severe

reduction of intelligence leading to reduced capabilities of cooperation or giving consent, peripheral nerve lesions above the level of the lesion (i.e., plexus brachialis impairment), pre-existing polyneuropathy, polytrauma, or severe traumatic brain injury. Data of all participating centers are centrally monitored by independent and blinded raters. All patients gave their written informed consent before they were included in the database. The study is in accordance with the Declaration of Helsinki and was approved by the regional institutional review board (EK-03/2004; PB_2016-00293). For the present study, we extracted from EMSCI database the data of all patients with traumatic SCI included between July 2001 and October 2015 (with 1-year follow-up data at latest in December 2015).

Clinical and functional assessments

Neurological examinations were performed according to the ISNCSCI. The scale provides a total motor score which ranges from 0 to 100, and a total light touch and pin prick score from 0 to 112 points, respectively. Severity of SCI was classified following the American Association of Spinal Cord Injury (ASIA)/ISNCSCI impairment scale (AIS) as A (motor–sensory complete), B (motor complete, sensory incomplete), C (motor–sensory incomplete), and D (motor–sensory incomplete, average of key muscles below the lesion show movement against gravity).[14,15] Examinations were performed by trained rehabilitation specialists with several years of experience in the field of SCI rehabilitation. The functional assessments were scored by the team of physical and occupational therapists and nurses with several years of experience in the field of SCI and according to the validated Spinal Cord Independence Measure (SCIM) II/III protocol.[16,17] Both SCIM versions comprise different subscores relating to body function in self-care (20 points) and mobility (40 points), as well as bladder, bowel and breathing function (40 points). Different versions consist of minor adaptions in single scores, but no difference in subscores or total score (100 points).

Neurophysiological examination

Neurophysiological examinations were independently performed by trained technicians and experienced physicians according to common clinical standards.18 All neurophysiological measurements were obtained on conventional clinically certified electromyography machines, and these examinations followed a strict measurement protocol throughout the EMSCI network. Recordings were obtained bilaterally for somatosensory evoked potentials (SEP) following stimulation of the ulnar and tibial nerves. For technical details of neurophysiological recordings see previous publications. [3,7,9,10] Motor evoked potentials (MEP) were obtained bilaterally following transcranial magnetic stimulation of the corresponding cortical motor area from anterior tibial and abductor digiti minimi muscles. For technical details of neurophysiological recordings see previous publications.[3,6,8] Nerve conduction studies were obtained from the ulnar and tibial nerves bilaterally. Distal latency, minimal F-wave latency, and amplitude of the compound muscle action potential from tibial anterior and abductor digiti minimi muscles were obtained. Readouts were transferred to the database and monitored by blinded raters before further evaluation.

Neurophysiological abnormalities from both sides were rated according to cutoff criteria in order to transform individual data into an ordinal scale.

Transformation to a score guided by clinical normative data was done for several reasons according to an earlier publication:[19] reduction of the number of variables (amplitude and latency of both SEP and MEP recordings, amplitude and F-wave persistence of nerve conduction studies each derived from four extremities allowed reduction from 24 to 3 variables), definition of robust pathological values to allow application in a clinical setting, reduction of variance, and an increased power (assuming that much larger numbers of patients would have to be included with an increasing number of variables). Criteria included amplitude, latency, and F-wave persistence. This resulted in

an electrophysiological score. Within this score all neurophysiological examinations were rated as normal, impaired, or abolished, and scores were implemented as explained subsequently (Table 1). MEPs and SEPs were rated according to latency and amplitude of the collected potentials, respectively. Latency was normalized for body height. Limits were determined according to laboratory determined reference values as follows.

Amplitude of MEP were scored with 2 points if they reached at least 0.1 mV, 1 point if clearly present but <0.1 mV, and no points if the potential was missing. Body height corrected latency for upper extremities and for lower extremities was scored with 1 point if it was <25 ms and <34 ms, respectively, otherwise it was scored with no points. A maximum score of 3 was achieved if latency and amplitude were within these defined normal limits, a score of 2 was achieved if either latency was delayed or amplitude was reduced, a score of 1 was achieved if both latency and amplitude were beyond limits, and a score of 0 was achieved if no potential could be obtained.

Amplitude of SEP was scored with 2 points if it reached at least 0.5 lV, 1 point if it was clearly present but <0.5 lV, and no points if the potential was abolished. Body height corrected latency <21.7 ms for upper extremities respectively <44.3 ms for lower extremities was scored with 1 point, otherwise it was scored with no points. A maximum score of 3 was achieved if latency and amplitude were within normal limits. A score of 2 indicated that either latency was delayed or amplitude was reduced, whereas a score value of 1 indicated that both latency and amplitude were beyond limits. A score value of 0 was attributed if no potential could be obtained.

The nerve conduction studies were scored according to compound motor action potential (cMAP) amplitude and F wave persistence. Amplitude was scored with 2 points if cMAP reached at least 5/4mV in tibial/ulnar neurography, respectively, 1 point when it was below these limits, and no points when abolished. F-wave persistence was scored with 1 point if >50% in both studies, otherwise it was scored with no points. Therefore, a maximum score of 3 was achieved if all

parameters were above limits, a score of 2 was achieved if cMAP amplitude or Fwave persistence was below limits, a score of 1 was achieved if cMAP and F wave persistence were below limits, and a score of no points if no cMAP, and therefore also no F-waves, could be collected.

Sum scores were calculated per modality (motor evoked potentials respectively sensory evoked potentials resp. nerve conduction study) with a maximum score of 12 each.

Patient selection

A whole database query was made on February 8, 2016, resulting in 3568 data sets of all included paraplegic and tetraplegic patients. Tetraplegic patients were identified according to the neurological level of injury (segments C1 to T1) in stage 2, if data were missing in stage 1. Patients who could not be classified at these time points because of missing clinical data or who were classified as paraplegic were excluded from the analysis. All AIS grades were included in the evaluation. For the analysis, we considered the baseline data collected between 16 and 40 days after SCI (stage 2) when available. When those data were missing, the stage 1 assessment (within 15 days from injury) was used for analysis. Measurements 6 months after SCI (stage 4) were used as outcome measures and if not available, the 12-month outcome (stage 5) was used.

Functional outcome The functional outcome at 6 months (or at 12 months, if no data were available at 6 months) after SCI was assessed through SCIM II/III total score. A score of 100 (full score) was considered as a positive outcome. SCIM versions II and III within the EMSCI database were combined in the present evaluation, as total scores (maximum 100 points) do not differ between the two versions.

Statistical analysis

Candidate parameters for the prediction of a total SCIM score of 100 points, were identified using a stepwise augmentation procedure from the initial data set including age, sex, neurological level of injury, ISNCSCI total motor score, ISNCSCI total pin prick score, ISNCSCI total light touch score, MEP, SEP and nerve conduction study score. SCIM score was not included in the procedure as it was used as the outcome variable. The procedure was performed separately for the clinical and the electrophysiological parameters. We bootstrapped the stepwise augmentation procedure 100 times and counted how often each of the candidate variates remained in the final model. Parameters that were selected at least 60 out of 100 times were used in the analysis.20 Using multivariate logistical regression models, where a presence of a SCIM score of 100 at 6/12 months was the dependent and the clinical or electrophysiological parameters within 40 days from injury were the independent variates, we estimated the probabilities for various combinations of predictors. Additionally, to test the discrimination capacity of each prediction model in the complete sample of 224 patients, a comparison of the prediction in both models was calculated in respect to a ‘‘rule in’’ threshold of >95% probability respectively ‘‘rule out’’ threshold of <5% probability reaching the outcome SCIM 100. We tested the predictions of the models with the v2 test implemented in Stata’s ‘‘roccomp’’ routine. We summarized continuous variates with means and standard deviations and dichotomous variates with percentages. A p value <5% was considered statistically significant. All statistical analyses were conducted using the Stata 14.2 statistics software package (Stata- Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Study population

From a total of 3568 patients in the database, 317 could not be classified at stage 1 or 2 assessments because of lacking clinical data, and 1509 were classified as paraplegic and therefore excluded from further analysis. A total of 1742 data sets of tetraplegic patients were used for further analysis.

Although 1518 data sets were missing one or more baseline or outcome parameters, 224 data sets contained complete clinical and electrophysiological baseline data within 40 days after SCI and outcome data after 6 or 12 months (Figure 1). Study population descriptive parameters are shown in Table 2. Thirty-one patients reached outcome SCIM 100 after 6–12 months after spinal cord injury.

Identification of relevant baseline parameters for outcome prediction The clinical parameters selected were patients' age at study entry and the total motor score. Performing 100 repeated prediction calculations with clinical parameters, ISNCSCI total motor score was included 100 times in the prediction model as the most important predictor and age was included 99 times. Sensory scores (total pin prick score, included 16 times, total light touch score, included 30 times), sex (included 8 times), and neurological level of injury (included 29 times) were by far less important in calculations.

The electrophysiological variables chosen were MEP, SEP, and nerve conduction study score, included to the same extent (MEP 97 times, SEP 86 times, nerve conduction study 99 times) in the prediction model.

Therefore, ISNCSCI total motor score, age, SEP, MEP, and nerve conduction study score could be identified as the most important baseline parameters and were therefore used for further receiver operating characteristic (ROC) analyses and multivariate logistical regression models.

Outcome prediction value of a single modality ROC analysis revealed total motor score as the best single prediction parameter for the chosen outcome (total SCIM score 100) with an excellent AUC (0.909; 95% CI: 0.871–0.947). SEP score (AUC 0.829; 95% CI: 0.758–0.900) as well as MEP (AUC 0.868; 95% CI: 0.799–0.936) and nerve conduction study score (AUC 0.832; 95%CI: 0.770–0.895) alone also showed reasonable outcome prediction. Repeated analysis considering the 6-month outcome (available in 199 of 224 patients) and the 12-month outcome (available in 176 of 224 patients) showed corresponding results.

Electrophysiological examinations improve outcome prediction

To evaluate the additional benefit of electrophysiological examinations, multivariate logistics regression models for outcome SCIM score 100 were calculated. The first prediction model was derived from clinical predictors only, and is based on age and ISNCSCI total motor score: this model showed an AUC of 0.936 (95% CI: 0.904–0.968). The addition of the three neurophysiological parameters showed a significant increase of the AUC (0.956 (95% CI: 0.930–0.982; p = 0.019) (Figure 2). Corresponding results could be observed in repeated analysis when considering 6-month outcome (available in 199 of 224 patients) and 12-month outcome (available in 176 of 224 patients). Repeated analysis with respect to baseline SCIM, excluding patients with baseline SCIM 100, showed no significant differences in the results.

The effect of the increased discrimination capacity of the model with electrophysiology can be translated into additional patients correctly classified given specific rule-in or rule-out probability thresholds. The significant improvement translates into more cases of correct prediction within the complete sample of 224 subjects Comparing the two models within the group reaching SCIM 100 outcome, one more patient was classified correctly (‘‘rule in’’) when using the full rather than the simple model. On the other hand, when comparing the two models within the group not reaching

SCIM 100 outcome, seven more patients were classified correctly (‘‘rule out’’) when using the full rather than the simple model. Only one false positive prediction was found when applying the simple model.

Discussion

In this analysis, we could show that early prediction of functional outcome can be achieved with high accuracy based on clinical assessment of ISNCSCI total motor score alone, as well as by neurophysiological examinations. However, accuracy could significantly be increased when combining both clinical examination and neurophysiology. The number of patients for whom a correct functional prediction could be achieved was increased in the full model with respect to neurophysiological information. This is highly relevant, given the potential reduction of numbers to treat when powering clinical trials and for the individual benefit of each additional correctly predicted patient, as accurate outcome prediction at an early stage after SCI is crucial for planning the rehabilitation course and long-term living modalities. Further, at an early stage, clinical examination can be less reliable because of the impaired ability of a patient to cooperate and, therefore, electrophysiological examinations could provide standardized additional predictive power early after injury. We will further discuss these results and why prediction precision remains difficult and why improving the accuracy of outcome prediction is essential.

The SCIM score provides reliable functional information on activities of daily living and is a routine assessment during SCI rehabilitation and treatment.[17] Moreover, the Spinal Cord Outcomes Partnership Endeavor (SCOPE) suggested SCIM III as primary outcome measure for pivotal phase III clinical trials.[21] SCIM score at 6/12 months has been chosen for outcome, as most clinical improvement is achieved at this time and rehabilitation in tetraplegic patients is usually accomplished after 9 months.[22] Predicting functional status at that time, therefore, is crucial for

organizing assistance and devices after hospitalization. In previous studies,[11,23] the functional recovery assessed by SCIM at 6 months and 1 year has commonly been used for the derivation of clinical prediction rules of functional recovery after SCI. In this study, we intended to show the relevance of adding neurophysiological assessments to improve a prediction model in principal. We dichotomized patients' outcome based on SCIM II and III total score 6 months after SCI in I; ''optimal functional recovery'' when the SCIM total score was 100 and II. We coded ''incomplete functional recovery'' when the SCIM total score was <100, because we considered that the distinction of ''optimal'' versus ''incomplete'' recovery could be regarded as unambiguous.

SCIM total score is a global score, derived from the sum of different subscores of functional domains. For that reason, any other cutoff value of SCIM total score would have been problematic, as values <100 can correspond to very different clinical conditions, with possible limitations in different domains (e.g., arm function, transfers, bladder and bowel management, respiration). By choosing 100 as cutoff, we could distinguish two distinct populations: those with a full functional recovery as assessed by SCIM and those with a variable degree of functional impairment. This is instrumental to our study, which was conceived as a proof of principle to evaluate the additional predictive value added from neurophysiological examinations to clinical predictors. This finding prepares the field for further studies assessing the potential contribution of neurophysiological examinations to the prediction of a particular functional outcome in SCIM domains.

ISNCSCI examination is a standardized, reliable clinical examination of SCI patients used commonly in the SCI community.

Assessment of motor, as well as sensory, function by light touch and pinprick testing is implemented in the protocol and, therefore, provides information about motor and sensory system integrity.

Therefore, it is not surprising to find the high predictive value of total motor score. However, neurophysiological examination can provide additional independent and objective information

about spinal cord function. SEP reflects the dorsal column, MEP reflects the corticospinal tract and nerve conduction study reflects the anterior horn and peripheral nervous system function. Thus, additional anatomical and somatotopic information about the extent and localization of nervous system damage is reflected in neurophysiological data. A reliable quantification of the extent of the impairment of spinal cord function is available from these recordings.

Neurophysiological techniques have been suggested for prognostication because they are objective and available early after injury, even if a patient is unable to cooperate.[5,6] The obtained potentials can be rated according to robust cutoffs for latency and amplitude as normal, impaired, and abolished. To simplify the use of electrophysiological examinations, a scoring was introduced in this study as mentioned (Table 1). Thereby the abundance of neurophysiological data can be reduced and scaled for use in the simplification of a prediction model.

Although 1742 of 3568 patients could be identified as tetraplegic, only 224 complete data sets could be used for our statistical analysis, because of missing baseline data or outcome assessments.

In most cases, electrophysiological data were missing (Figure 1). One reason is that not all SCI centers participating in the EMSCI network have implemented the complete electrophysiological protocol in the clinical workup within the rehabilitation course and, therefore, not all patients were tested with neurophysiological examinations.

On the other hand, at baseline (up to 40 days after SCI), because of complications, some patients' status might have been such that some of the results of the clinical examinations could not be performed. Further, because of implementation of all electrophysiological modalities in our model, we observed a relatively high dropout rate of patients for whom incomplete neurophysiological examinations were performed. However, 224 data sets with >30 patients reaching the predicted outcome (SCIM score of 100) represent a reasonable sample for statistical analysis. Descriptive

parameters (Table 2) of our tetraplegic study population were comparable with those of populations published before and, therefore, the evaluation of prediction can be assumed to be representative.[3] In a prediction model published earlier, age, motor score, and light touch sensation in the segment L3 and S1 had been identified as crucial parameters for prediction of walking ability.[11] The Lower Extremity Motor Score of ISNCSCI was identified as main predictor of bladder function recovery after SCI.[12,13] SEP, MEP, and nerve conduction study have been shown to provide important information for prediction of the outcome of walking ability as well as hand function.[3,5,6,9,10] So far, no combination of these modalities has been evaluated for prediction, and the additional value of electrophysiological examinations has not been shown.

In this study, total motor score and age, as well as SEP, MEP, and nerve conduction study score, but not sensory scores, were identified as useful parameters for outcome prediction using the bootstrapping procedure. A possible reason for this may be the fact that dermatomal sensory testing has little meaning for total function in activities of daily life as assessed by SCIM. Another reason may be the comparatively coarse scale of sensory rating distinguishing only the levels of impaired and loss of sensation, whereas motor rating is more elaborate. Further, inconsistencies of sensory scoring might be a reason for poor relevance for prediction in our analysis.

On the other hand, SEP scores did show good reliability for outcome prediction, although both light touch sensory testing and SEP examinations reflect dorsal column function. This might be attributed to a variety of causes. SEPs objectively measure dorsal column conductivity and may, therefore, be more representative of the likelihood of preserved spinal integrity. This was shown earlier, as the initial presence of tibial SEPs after SCI was highly related to positive functional outcome in terms of the regaining of walking ability.[5] Similarly, presence and quality of ulnar SEPs were shown to indicate good hand function outcome.10 Given the fact that SEPs are only preserved when a significant number of dorsal column fibers are excitable in a synchronized volley, it is conceivable that tibial or

ulnar SEP represent a benchmark for preserved spinal conductivity, indicating good likelihood for preserved spinal transmission. This may be a better criterion than arbitrary sensory scores, which are dependent on patients' and raters' subjective judgment.

It should be pointed out as a limitation that subgroup analysis of AIS categories could not be performed because a full functional recovery as indicated by a total SCIM score of 100 was only found in patients who were SCI incomplete and initial AIS D. For technical reasons, we decided to use this unambiguous total SCIM value as target outcome in this proof of principle study to test the additional prediction value of electrophysiological examinations. From a clinical standpoint, the use of a variety of SCIM dichotomization limits and/or subscores would likely be more meaningful, and could provide analysis within AIS subgroups. However, given the notion that SCIM is a composite score, any other dichotomization limit would mean widely varying individual outcomes with respect to possible combinations of the sums of SCIM subscores for self-care, respiratory/bladder function, and mobility. Further, any analysis within SCIM subscores would not have allowed a general statement about the additional benefit of electrophysiological assessment for the prediction of global function in SCI recovery. As a consequence, the results of this analysis may not be generalized to all AIS grades. More detailed outcome analyses with respect to SCIM domains such as self-care and hand function are required, including electrophysiological data. This will allow clinically more meaningful dichotomizations and, therefore, will likely include all AIS groups. The overarching goal is clinically meaningful prediction of detailed function with best precision. According to the present analysis, neurophysiological examinations are good candidates to contribute significantly to prediction precision.

Conclusions

In a population of 224 tetraplegic patients, our study has shown excellent prediction of full functional recovery 6–12 months after traumatic SCI by use of ISNCSCI, age, SEP, MEP, and nerve conduction examinations.

The prediction model based on clinical variables could be significantly improved by combining it with electrophysiological multimodal parameters, reflecting better prediction precision because of the addition of neurophysiological data. Our analysis suggests the use of neurophysiology in the workup of patients with SCI, in order to provide the best possible outcome prediction for adequate patient information and future planning.

Table 1: Scoring of electrophysiological examinations

		Scoring		
Modality	**Parameter**	**2**	**1**	**0**
MEP	**latency UE**	-	< 25 ms	≥ 25 ms or abolished
	latency LE	-	< 34 ms	≥ 34 ms or abolished
	amplitude	≥ 0.1 mV	> 0.05 mV	abolished
SEP	**latency UE**	-	< 21.7 ms	≥ 21.7 ms or abolished
	latency LE	-	< 44.3 ms	≥ 44.3 ms or abolished
	amplitude	≥ 0.05 µV	< 0.05 µV	abolished
NCS	**amplitude UE**	≥ 4 mV	< 5 mV	abolished
	amplitude LE	≥ 5 mV	< 4 mV	abolished
	F-wave persistence	-	> 50 %	≤ 50 %

Electrophysiological examinations were scored according to the latency and amplitude in motor evoked potentials and sensory evoked potentials respectively to amplitude and F-wave persistence in nerve conduction studies as displayed above.

(MEP = motor evoked potentials, SEP = sensory evoked potentials, NCS = nerve conduction study, UE = upper extremities, LE = lower extremities, ms = milliseconds, mV = milli Volt, µV = micro Volt)

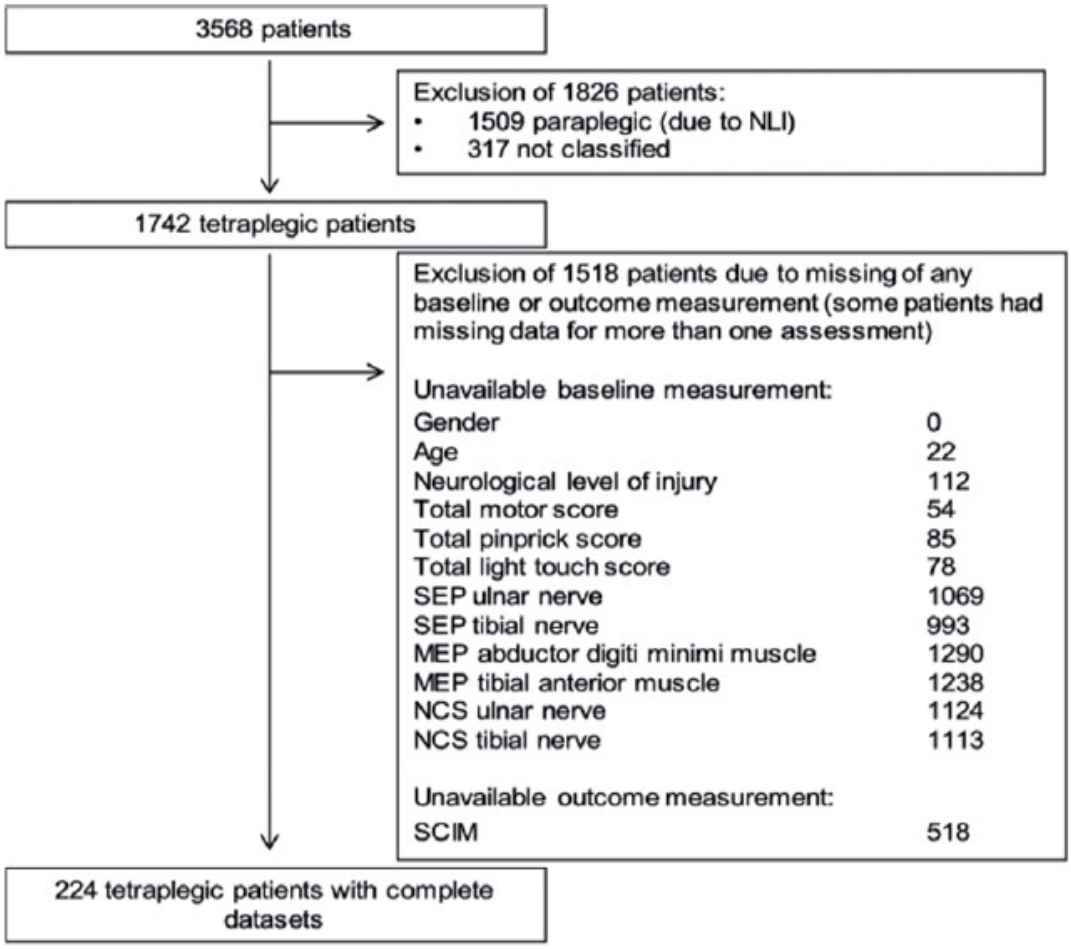
Table 2: Distribution of baseline and outcome parameters

Clinical parameters						
	Complete sample (n=224)		**Patients with 6-month outcome (n=199)**		**Patients with 1-year outcome (n=25)**	
	N	**%**	**N**	**%**	**N**	**%**
Baseline						
Female gender	42	18.8	34	17.1	8	32
Lesion level						
C1	6	2.7	6	3	0	
C2	9	4.0	8	4	1	4
C3	26	11.6	23	11.6	3	12
C4	80	35.7	74	37.2	6	24
C5	56	25.0	50	25.1	6	24
C6	29	13.0	24	12.1	5	20
C7	14	6.3	11	5.5	3	12
C8	1	0.5	1	0.5	0	
T1	1	0.5	1	0.5	0	
NT	2	0.9	1	0.5	1	4
AIS grade						
A	53	23.7	50	25.1	3	12
B	29	13.0	28	14.1	1	4
C	41	18.3	38	19.1	3	12
D	98	43.8	81	40.7	17	68
NT	3	1.3	2	1	1	4
	Mean	***Std. Dev.***				

ISNCSCI Total motor score (max. 100)	45.3	30.4	43	30	64.1	26.3
ISNCSCI Total pinprick score (max. 112)	54.1	31.7	52	30.8	70.5	34.6
ISNCSCI Total light touch score (max 112)	65.7	28.6	63.9	28.3	79.4	28.2
Age	46.0	19.1	45.3	19	50.1	20.1
Electrophysiological parameters						
MEP Score (max. 12)	4.3	4.2	4.1	4.1	5.4	4.7
SEP Score (max. 12)	4.7	3.9	4.6	4	5.7	3.4
NCS Score (max. 12)	9.0	2.5	8.9	2.5	9.4	2.3
Outcome						
SCIM score (max. 100)	57.5	31.4	55	30.7	77.6	30.2
Patients with maximum SCIM score (%)	31 (13.8)		23 (11.6)		8 (32)	

NT = not testable, MEP = motor evoked potentials, SEP = sensory evoked potentials, NCS = nerve conduction study, SCIM = spinal cord independence measure

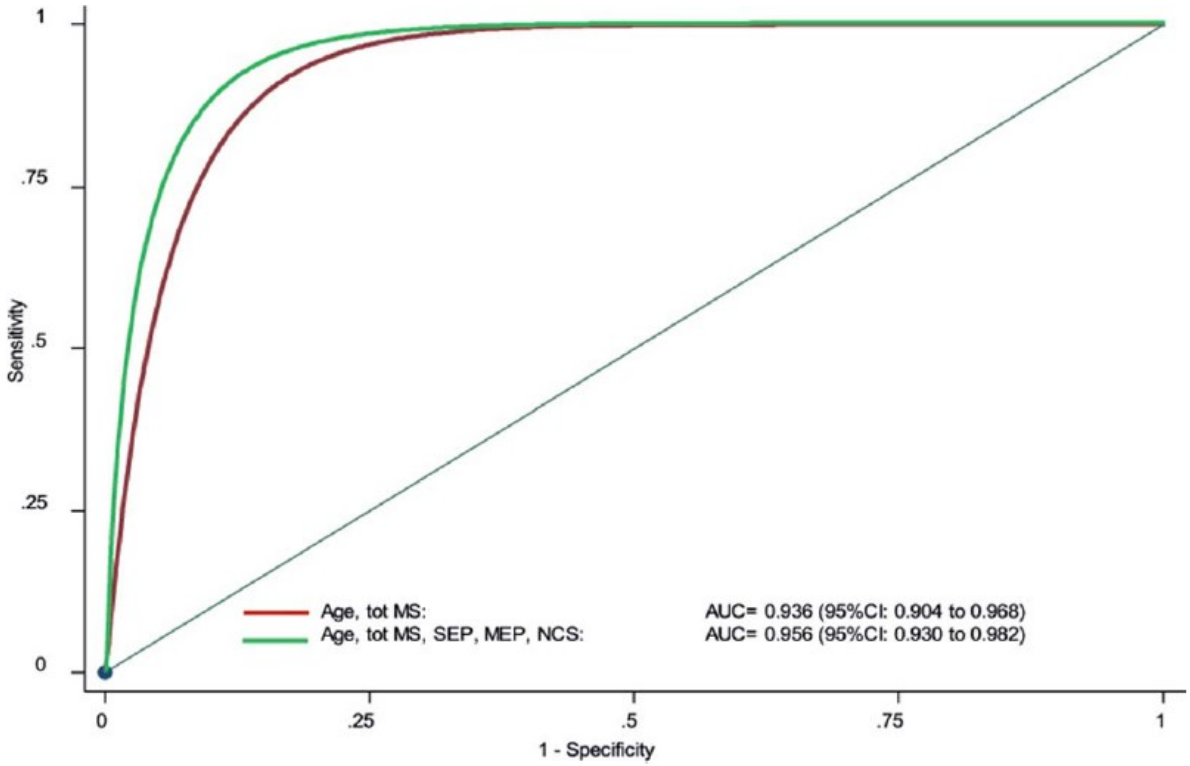
Figure 1: Identification of complete datasets of tetraplegic patients for statistical analysis



NLI = neurological level of injury, MEP = motor evoked potentials, SEP = sensory evoked potentials,

NCS = nerve conduction study, SCIM = spinal cord independence measure

Figure 2: Electrophysiological examinations improve outcome prediction



Prediction of model 1 (red line) including only age and total motor score could be significantly improved from an AUC of 0.936 (95%CI: 0.904 to 0.968) to 0.956 (95%CI: 0.930 to 0.982) with additional electrophysiological information in model 2 (green line, p=0.019) including age, total motor score and all neurophysiological variables. (MEP = motor evoked potentials, SEP = sensory evoked potentials, NCS = nerve conduction study, AUC = area under curve)

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Prediction of bladder outcome after ischemic spinal cord injury

This chapter is derived from the study:

Scivoletto G, Pavese C, Bachmann LM, Schubert M, Curt A, Finazzi Agro E, Kessels AG, Kessler TM.

Prediction of bladder outcomes after ischemic spinal cord injury: A longitudinal cohort study from the European multicenter study about spinal cord injury.

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Introduction

The incidence of traumatic spinal cord injury (SCI) is estimated at 23 new cases per million/year.[1] However, statistics for non-traumatic SCI are scarce, but the rate is described to be between 6 and 76 new cases per million/year, depending on the different regions of the world.[2] Although infrequent, the social and economic burden of these lesions is remarkable. SCI can interrupt the neural connections between the pontine and sacral centers devote to bladder control, compromising the parasympathetic as well the sympathetic supply to the bladder and sphincters.[3] This may lead to one of the most disabling consequence of SCI, the deficit of bladder control.

The management of bladder dysfunction in SCI subjects is crucial to prevent urinary infections and harms to the upper tract, thus preserving kidney function.[4,5] However, despite the advances made in the last decades in the management of urinary control dysfunction of SCI subjects, upper and lower urinary tract complications are still common and represent one of the leading cause of re-hospitalization after SCI.[6,7] Furthermore, although the rate of mortality due to renal failure progressively decreased along time, urogenital complications still represent the cause of death in about 11% of subjects with SCI.[8] Therefore, the major effort of the research is concentrated on the treatment of neurogenic bladder dysfunction, aiming at avoiding urinary tract problems.

However, there is much less research on bladder recovery after SCI, despite the importance of this issue to SCI patients and their families.[9] In fact, Lloyd[10] reported that good bladder control (the capacity to store urines and avoid the bladder volitionally have a high impact on the social independence of SCI subjects (eg, the ability to frequent a workplace or classroom). The recovery of micturition and evacuation control is placed at the first choice by subjects with complete SCI[11] and is considered as important as ambulation improvement by subjects with incomplete SCI.[12] Early

prediction of bladder function recovery would play a key role to orient a patient-tailored rehabilitative program and to counsel patients and their families.[13]

Using the European multicenter study about spinal cord injury (EMSCI) database, we recently developed two valid models that allow physicians to predict 1-year bladder outcome based on acute phase characteristics.[14]

Up to date, most of the studies assessing bladder function recovery focus on patients with traumatic SCI and no rule to predict bladder outcome after non-traumatic SCI is available.

We therefore explored if our prediction models developed from patients with traumatic SCI are also valid in patients with ischemic SCI.

Methods

Sample

Data were derived from the EMSCI database (www.emsci.org).[15] In brief, EMSCI is a prospective longitudinal database started in July 2001, recording the neurological and functional data of subjects with SCI due to trauma or ischemia. As per protocol, data were prospectively acquired within the first 15 days after the lesion, between 16 and 40 days, and 3 months, 6 months, and 12 months after the lesion. From the EMSCI database, we derived the data of all subjects with ischemic SCI, aged 18 or older, who suffered a SCI between July 2001 and April 2015, and had their first neurological and functional evaluation within 40 days from date of injury (baseline or T0), and the final evaluation at 1 year (T2). The following data were registered: gender, age, and clinical features, the neurological status according to ISNCSCI[16] (with evaluation of lesion level and severity, of motor scores (total, upper extremity, and lower extremity) and of light touch and pin-prick sensation in 56 dermatomes).

Their functional status was evaluated by the SCIM version II or III (SCIM II/III). The SCIM is a tool specifically developed to assess the independence of SCI subjects in performing daily life activities.[17] The SCIM assess 17 functional activities divided into three subscales: the self-care domain, respiration and sphincter management, and mobility. The total SCIM score ranges between 0 and 100, with higher scores reflecting higher levels of independence.

One-year bladder outcome

The outcome was good bladder control at 1 year after SCI defined according to our previous work[14] as follows: “urinary continence (assessed by bladder diary) and complete bladder emptying (ie, postvoid residual <100 mL assessed by ultrasound or “in-out” catheterization).” The outcome was assessed through item 6 (sphincter management—bladder) of SCIM II/III dichotomized into 1 (item 6 scored 15 points) or 0 (item 6 score <15 points).

Prediction models

The two prediction models rely on data derived from the ISNCSCI and SCIM II/III. According to our previous work[14] “the full model relies on three predictors: lower extremity motor score (LEMS) of ISNCSCI, light-touch sensation in the S3 dermatome of ISNCSCI, and the subscale respiration and sphincter management of SCIM. The simplified model is based on LEMS of ISNCSCI only.”

Statistical evaluation

Data are reported as means and standard deviation. Statistical analysis was carried out by means of Mann-Whitney U test to compare continuous data and chi square test to assess contingencies

differences. In order to assess the prediction power of the two models in the cohort of patients with ischemic SCI, we calculated the area under the receiver operating characteristic curves (aROC).[18]

Results

Demographics

The sample consisted of 85 patients (29 females and 56 males); mean age was 55.2 ± 15 years (range 18-82) (Table 1). At admission, 18 (21.2%) patients had an American Spinal Injury Association (ASIA) Impairment Scale (AIS) A, 12 (14.1%) AIS B, 17 (20%) AIS C, 33 (38.8%) AIS D (38.8%) and one AIS E (1.2%), respectively. The impairment was not testable in four patients. The lesion was at cervical level in 26 (30.6%) subjects, at dorsal level in 42 (49.4%), and at lumbar level in 11 (12.9%). The AIS E patient (1.2%) had no lesion level and the level was not testable in five subjects.

Bladder outcome

At baseline, 7 of the 85 (8%) showed complete bladder control. At 1-year examination, 23 (27%) patients (including those with complete bladder control at baseline) had good bladder control, and 62 (73%) had an incomplete recovery. Comparing the two groups, the patients with complete bladder function recovery had significantly better total and lower extremity motor scores, light touch S3 score, SCIM subscore two and total score (Table 2).

Bladder outcome prediction

Both models showed a good predictive power in the ischemic SCI cohort: the aROCs of the full and simplified model was 0.825 (95% confidence interval [CI]: 0.717-0.933) and 0.822 (95% CI: 0.721-0.923), respectively (Figure 1).

Discussion

Bladder function and management is a very relevant issue in rehabilitation of SCI patients. Despite the large amount of literature on bladder management and urinary complications, a limited number of articles focused on bladder function recovery prediction after SCI. The articles by Shenot[9] and by Weiss[19] focused on the prognostic value of great toe position sense, pinprick sensation and bulbo-cavernous reflex preservation for normal voiding recovery, although with slightly different definition of bladder function recovery (Shenot[9] : "voiding without surgical intervention or collecting devices, although pharmacologic agents may be used"; Weiss[19]: "volitional voiding, defined as no collecting devices, no medication, and no surgical intervention") and found that all these parameters are slightly sensitive in predicting volitional voiding recovery, but did not predict detrusor overactivity and detrusor sphincter dyssynergia. Therefore, they concluded that urodynamic examination is mandatory. Curt et al[20] assessed the importance of AIS and somatosensory evoked potentials and reported a good relationship between these data and the degree of recovery of somatic nervous control of bladder function. However, AIS and somato-sensory evoked potentials did not show a correlation with the urodynamic impairment. Schurch[21] focused on the predictive capacity of the toes voluntary plantar flexion of and reported a significant relationship between plantar flexion score and the presence or absence of voluntary contraction of the external urethral sphincter but not with the type of neurogenic lower urinary tract dysfunction. Scivoletto et al[22] reported in a mixed population of patients with traumatic and non-traumatic SCI a relationship between lesion severity at admission and micturition control recovery in a mixed population of patients with traumatic and non-traumatic SCI, with a good prognostic significance of AIS.

Based on data from 1250 patients with traumatic SCI derived from the EMSCI study, we very recently validated two simple and reliable models to predict good bladder control 1 year after traumatic SCI.[14] The full model integrates three simple clinical parameters derived from ISNCSCI and SCIM[14]:

LEMS, light-touch sensation of the S3 dermatome, and the SCIM subscale respiration and sphincter management. The simplified prediction rule exclusively relies on LEMS introducing a very simple, rapid, noninvasive, and inexpensive tool that can be used without the need of any specific equipment. However, none of the above-mentioned articles focused on spinal cord ischemia. Up to date, there is no data on bladder function after vascular lesions of the spinal cord with the exception of the study by Scivoletto et al[23], which assessed the extent of bladder function recovery in patients with ischemic compared to those with traumatic lesions but no potential predictors of bladder function recovery have been investigated. Moving from this point we decided to apply the same models to a cohort of patients with ischemic lesions derived from the EMSCI database. The two models showed a good predictive power with an aROC of 0.825 for the full model and 0.822 for the simplified model. The predictive value of the two models is slightly lower in the present ischemic cohort than in the patients with traumatic SCI considered for the derivation and validation of the model.[15] This may depend on differences in etiology of SCI and/or on other differences such as the smaller ischemic sample or differences of the baseline characteristics between the two samples. Indeed, the two cohorts showed minor demographic and clinical differences, example in term of mean age, level, and completeness of the lesion. Namely we found more patients with incomplete lesions and fewer patients with a cervical lesion level with ischemic as compared to traumatic etiology. Our study provides the first validated prediction models of bladder outcome after ischemic SCI. The introduction of these models in the clinical practice may ameliorate the counseling and the early orientation of a patient-tailored rehabilitation program for these patients. The study has some limitations that need to be addressed: the number of patients in this study was rather small, despite we used the data of the largest European database. This reflects the relative small number of patients with ischemic SCI admitted to specialized SCI centers.[24] The low number of subjects resulted in broad confidence intervals of the aROCs and in the impossibility of exploring the effects

of differences in the clinical composition of the traumatic and ischemic patient groups. However, based on the validity of the model in the population of traumatic SCIs and on the representativeness of our sample of the entire ischemic population, we believe that the results presented here may be seen as sufficiently relevant to justify application in clinical practice. Furthermore, as the EMSCI is a continuous project, we program to validate these findings in the future utilizing the data of all next ischemic patients. Moreover, due to the fact that not all patients had systematic urodynamic assessment at predefined time points, we could not compare 1-year bladder outcome with urodynamic findings. Therefore, we do not know how many of the patients with full bladder recovery also had a normal urodynamic function or needed medication to control the urinary tract.

Conclusions

Our study demonstrates the validity of the two prediction models for bladder outcomes also in patients with ischemic SCI, thus providing a reliable clinical and research tool. These models will be of help to answer patients' questions about bladder outcome and to tailor appropriate bladder management.

Table 1: Baseline characteristics of the sample

	All (n = 85)
Age, y: mean (SD)	55.2 (15)
Sex, n (%) of males	56 (66%)
Neurological level	
C1-C8: n (%)	26 (30.6%)
T1-T12: n (%)	T1-T12: n (%) 42 (49.4%)
L1-L5: n (%)	L1-L5: n (%) 11 (12.9%)
S1-S5: n (%)	S1-S5: n (%) 0 (0%)
No level assessable*	1 (1.2%)
Not testable: n (%)	5 (5.9%)
Severity of neurological deficit	
AIS A: n (%)	18 (21.2%)
AIS B: n (%)	12 (14.1%)
AIS C: n (%)	17 (20%)
AIS D: n (%)	33 (38.8%)
AIS E: n (%)	1 (1.2%)
Not testable: n (%)	4 (4.7%)
LEMS: mean (SD)	17.9 (17.3)
SCIM total score: mean (SD)	39.4 (24.2)

* This is the patient with AIS E lesion.

Table 2 Characteristics of the subjects who achieved or did not achieve complete bladder control

	Incomplete bladder function recovery (n = 62)	Complete bladder function recovery (n = 23)	P-value
Age in years: mean (SD)	56.7 (13.8)	51.0 (17.6)	0.121
Sex, n (%) of males	44 (71.0%)	12 (52.2%)	0.104
Total motor score: mean (SD)	55.2 (19.2)	79.0 (17.2)	<0.001
Upper extremity motor score: mean (SD)	42.6 (12.8)	45.5 (9.3)	0.334
Lower extremity motor score: mean (SD)	12.5 (14.5)	32.3 (16.0)	<0.001
Best light touch S3 both sides: Mean (SD)	0.9 (0.7)	1.3 (0.5)	0.014
SCIM subscore 2: mean (SD)	15.1 (7.4)	25.1 (12.7)	<0.001
SCIM total score: mean (SD)	32.3 (17.7)	58.4 (29.0)	<0.001

Figure 1

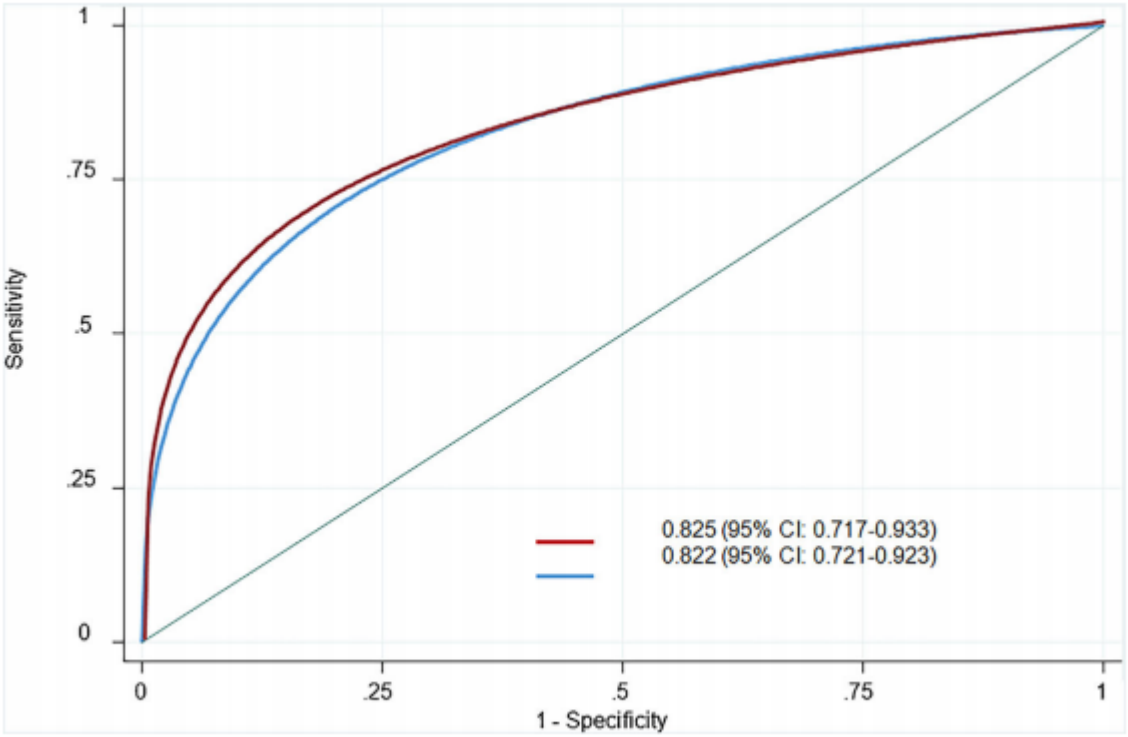

Figure 1: ROC plots for the two prediction models (full model in red and simplified model in blue)

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Prediction of bowel outcome after traumatic spinal cord injury

This chapter is derived from the study:

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Bowel Outcome Prediction After Traumatic Spinal Cord Injury: Longitudinal Cohort Study.

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Introduction

Neurogenic bowel dysfunction is an aggravating, life-long syndrome, which affects about 80% of patients with spinal cord injuries. The estimated prevalence is 250,000 in the United States and up to 250,000 in Europe.[1-5]

Impaired spinal neural control of bowel and sphincter functions may cause serious clinical conditions, depending mainly on the level and severity of the spinal cord lesion. [6] The clinical presentation is typically dominated by stool retention, and ultimately, severe constipation and fecal incontinence. [6]

Moreover, neurogenic bowel dysfunction often leads to severe, potentially life-threatening complications, such as intestinal obstruction (i.e., constipation up to the mechanical ileus), autonomic dysreflexia, urinary tract infections, sepsis, hemorrhoids, rectal bleeding, and prolapse. [7, 8] Additional factors related to spinal cord injury, such as loss of a rectal fullness sensation, difficulties in mobility, and impaired hand/arm function, may further complicate evacuation. [6] These aspects, together with the frequent dependence on a caregiver for bowel management, can severely limit working activities, social participation, and quality of life. [6, 8]

Programs that aim to achieve the highest degree of independence in bowel management, by achieving continence and reliable bowel movements (i.e., regular and time-efficient), represent a key aspect of rehabilitative treatments for patients with spinal cord injuries. [9, 10]

Currently, several management strategies are available, and typically, several methods are applied either consecutively or in combination, including diet, oral medications, rectal stimulants, abdominal massage, and irrigation techniques. Eventually, different maneuvers might be applied, like functional electrical stimulation of the skeletal muscles, and ultimately, surgical interventions, such as implanting a sacral anterior root stimulator, applying a Malone antegrade continence enema, and performing a permanent colostomy. [6, 11]

However, despite all efforts in the rehabilitation phase and the different existing approaches, most patients with chronic spinal cord injuries report problems in bowel management. [8, 11] This issue might be due to the largely empirical nature of current bowel management strategies, because only a small number of studies is available, and those have limited methodological quality. [11]

Patients with spinal cord injuries consider efficient bowel control, together with bladder function recovery, highly relevant medical needs. Thus, there is a need for high-quality research in this field.[12] Early predictions of bowel function outcomes would be instrumental for counseling patients and their families and for the prompt activation of structural interventions that might be necessary for the successful reintegration of patients into the community setting. [9] Moreover, it is important to identify patients that have a high probability of achieving efficient bowel control with standard care. [13] This identification would promote the optimization of future clinical trial designs for evaluating the efficacy of new bowel management interventions, because it could facilitate the stratification of intervention groups for the likelihood of spontaneous recovery. [13]

Although there are valid prediction models for locomotion, [14] upper limb function, [15] and bladder function, [16-18] no similar tool is available for bowel function. Thus, we aimed to derive and validate a model for predicting the achievement of independent bowel management, with reliable bowel movements and continence, at one year after traumatic spinal cord injury.

Methods

Study Design

The prediction model was derived and validated with data from patients included in the European Multicenter Study about Spinal Cord Injury (EMSCI) (www.emsci.org) (ClinicalTrials.gov Identifier: NCT01571531). The EMSCI is a prospective, longitudinal cohort study that started in July 2001. The study included patients with acute traumatic and ischemic spinal cord injuries, based on defined

inclusion criteria, and the patients were managed according to common standard examinations.[19-23] All patients were tested at fixed time intervals after the injury, as follows: between 0 and 15 days (*very acute*), between 16 and 40 days (*acute I*), between 70 and 98 days (*acute II*), between 150 and 186 days (*acute III*), and between 300 and 400 days (*chronic*). The examinations consisted of a standard set of clinical, neurological, neurophysiological, and functional assessments. The study conformed to the standards established by the Declaration of Helsinki and was approved by the local ethics committees of all participating centers. Before inclusion, patients were informed about the research protocol and signed written informed consent forms.

The present study conformed to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) statement (https://www.tripod-statement.org) and to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (https://www.strobe-statement.org).

Patient Populations

A previous study conducted by the EMSCI study group developed a prediction rule of ambulation after traumatic spinal cord injury. [14] According to that methodology, we performed a derivation and a temporal validation with two EMSCI cohorts.

To derive the prediction model, we extracted data from the EMSCI database for all patients with a traumatic spinal cord injury that occurred between July 2001 and December 2012. To validate the prediction model, we prospectively collected data for all patients included in the EMSCI that sustained a traumatic spinal cord injury between January 2013 and December 2014 (with one-year follow-up data, ending at the latest, in December 2015).

Predictive Variables

As potential predictors, we investigated the same variables analyzed previously to derive the prediction models of bladder function. [16] These variables included: patient age and gender, all variables derived from the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), [24, 25] and all variables from versions II and III of the Spinal Cord Independence Measure (SCIM). [26, 27] The ISNCSCI is a well-accepted neurological assessment strategy proposed by the American Spinal Injury Association (ASIA) to establish the level and severity of traumatic spinal cord injuries. [24, 25] This system rated injuries according to a six-level scale, where 0 indicated the absence of movement, and 5 indicated complete movement against gravity and full resistance. The assessment also evaluated the muscle strength of five key muscle groups in each limb. Light-touch and pinprick sensation impairments were rated for each dermatome in the body on a 3-point scale, where 0 indicated no sensation, 1 indicated altered sensation, and 2 indicated full sensation. In addition, voluntary anal contraction and the sensation of deep anal pressure were examined. The ISNCSCI also recorded some cumulative scores, including the upper extremity motor score (UEMS), lower extremity motor score (LEMS), and total light-touch and pinprick scores. Thus, the ISNCSCI provided assessments at the neurological level, motor level, and sensory level. The ASIA Impairment Scale (AIS) was used to grade five levels of severity, from A (complete lesion) to E (normal sensation and motor function) in all tested dermatomes and myotomes. ISNCSCI evaluations were performed by trained physicians, whose experience in the use of ISNCSCI was certified after a centralized EMSCI instruction course. [28] Motor and sensory scores and AIS grades were computed automatically by the validated ISNCSCI calculator developed by EMSCI (www.ais.emsci.org). [29]

Functioning was assessed with the SCIM, a validated tool specifically developed to evaluate the capacity and level of independence in daily life activities of patients after a spinal cord injury. [26, 27] The SCIM tested patients in tasks relevant to spinal cord-injuries in three activity domains: the self-

care subscale (scores 0 to 20); respiration and sphincter management (scores 0 to 40), which included an item related to bowel management; and transfer (scores 0 to 40). The total SCIM score ranged between 0 and 100, with higher scores indicating more independence. After its introduction, two revised versions of the SCIM were developed, versions II and III, respectively. [26, 27] The two subsequent versions showed small differences from the first version, but they used the same subscales and total scores. The EMSCI applied SCIM version II in the first phase and later adopted version III. The version used in the initial evaluation was used in follow-up assessments. SCIM assessments were performed by health professionals (nurses, occupational therapists, physiotherapists) with specific instructions and experience in the use of this tool. All predictive variables were recorded within the first 40 days after the spinal cord injury. When available, variables were included (n=1195) that were recorded at the *acute I* time-point (16 to 40 days after injury). When the *acute I* assessment was missing, the *very acute* time-point (within 15 days after injury) was considered (n=55).

Outcome Measure

The primary outcome was independent bowel management with regular bowel movements, and appropriate timing, with no or rare accidents (i.e., fecal incontinence less than twice a month). This outcome was assessed with a bowel diary, which patients maintained for one year after the spinal cord injury (time point *chronic* in the EMSCI time schedule), and the outcome was measured with item 7 (sphincter management - bowel) of the SCIM. [26, 27]

Patients were dichotomized, based on bowel function, at one year after spinal cord injury, as follows: (a) independent bowel management with regular bowel movements, appropriate timing, and no or rare accidents (less than twice a month; i.e., the item 7 score was 10 points in SCIM version II and 8 or 10 points in SCIM version III) or (b) irregular timing, a very low frequency of bowel

movements, or dependence on bowel management (i.e., item 7 score <10 points, in SCIM version II, and <8 points, in SCIM version III).

Statistical Analysis

To derive the prediction model from the EMSCI data, we applied multivariable logistic regression analyses with the same statistical approach used previously to generate the prediction models of ambulation and bladder function after a traumatic spinal cord injury. [14, 16] Missing outcome data were anticipated, and a weighting factor approach was used to correct for missing data. Complete cases were weighted by the inverse probability of being a complete case. [30] The factors mainly associated with missing outcome data were the center, the year of inclusion, and age. Based on these parameters, we estimated the probability of missing data and defined a weighting factor (w) = 1/(1 − probability of missing). We rarely observed missing data for the predictors (<5% for the SCIM and ISNCSCI data).

All ISNCSCI scores that rated each side of the body were analyzed. However, for this study, instead of considering the two sides ("right" and "left") separately, we grouped the two sides together, analyzing the best and the worst score of each side. In 80 patients, data were missing on the S4-S5 dermatome sensation, deep anal pressure, and voluntary anal contraction. Subsequently, the AIS grades for these patients were derived, based on the S1 score, by applying the method proposed by Zariffa et al. [31]

A total of 182 covariates were considered for the model elaboration. These covariates are reported in the supplementary data. Based on the Akaike information criterion (AIC), and after applying a stepwise forward procedure, we identified potential predictors. [32] The AIC reflects the relative quality of a statistical model, given the independent variables used. It allows an evaluation of the extent of change in the quality of the model, when parameters are added (or removed). Thus, the

AIC is used to select a specific model. We created 182 logistic models by fitting only one single explanatory variable. Subsequently, we selected the model with the best AIC. Then, we added variables to create a multivariable model; each variable was retained, as long as it significantly improved the area under the receiver operating characteristics curve (aROC).

The receiver operating characteristics curve (ROC) is a method for representing the characteristics of a test. For all test values, the ROC Y-axis indicates the sensitivity (or the true positive rate; i.e., the proportion of positive cases that are correctly identified by the test). The ROC X-axis indicates the false positive rate (i.e., the proportion of negative cases that are wrongly classified as positive by the test). Thus, the aROC represents a global measure of the accuracy of a test. The aROC value might range from 1 (perfect discrimination between positive and negative cases) to 0.5 (no discrimination beyond chance). The variable selection procedure was interrupted when the aROC did not show a significant increase ($p \leq 0.05$). The ISNCSCI sensory scores of thoracic dermatomes and interactions were not considered.

We described patient characteristics as the percentage or mean (standard deviation), and we performed comparisons with parametric and nonparametric tests, as appropriate. Statistical analyses were performed with the R statistics package (R version 2.14.0, www.R-project.org/) and the Stata 14.2 statistics software package (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). The statistics code is available upon request.

Results

Patients

For the model derivation, 2366 patients with traumatic spinal cord injuries were enrolled between July 2001 and December 2012 from 18 EMSCI centers. The initial (*very acute* and *acute I*) ISNCSCI assessments were missing for 178 patients, and the late outcome, measured one year after injury,

was missing for 938 patients. Consequently, the prediction analysis was performed on data for 1250 patients. Table 1 shows the clinical characteristics of patients included in the model derivation and those excluded from the analysis, due to the lack of a one-year outcome. The two groups showed significant differences in age, the percentage of patients with paraplegia, and the percentage of patients with complete lesions (AIS=A).

In the derivation group, at the initial assessment (measured within 40 days from the injury), 167 (13.4%) patients exhibited independent, efficient bowel management. Of these, 153 (91.6%) patients showed unchanged bowel management at the one-year follow-up.

At one year after the spinal cord injury, among all 1250 patients, 725 (58.0%: 143 of 254 females [56.3%] and 582 of 996 males [58.4%]) showed independent, efficient bowel management. Among these, 143 (19.7%) were females, and 263 (37.7%) had tetraplegia.

For model validation, a total of 586 patients with traumatic spinal cord injuries were enrolled between January 2013 and December 2014. The late outcome, measured at one year after injury, was available in 206 patients. However, complete initial ISNCSCI and SCIM assessments were missing for 17 and 6 patients, respectively (three patients had incomplete data for both the ISNCSCI and the SCIM). Therefore, 186 patients with complete datasets were included in the validation analysis. The clinical characteristics at inclusion are shown in Table 1, for patients included in the model derivation and for patients lost at the one-year follow-up. The derivation group included significantly more patients with complete lesions (AIS=A) and significantly fewer patients with lesions at the sacral neurological level, compared to the validation group (Table 1). In the validation group, independent, efficient bowel management was observed in 33 (17.7%) patients at the initial assessment, and all of these patients had maintained independent, efficient bowel management at the one-year follow-up.

At one year after the spinal cord injury, 122 (65.6%) patients showed independent, efficient bowel management. Among those, 19 (15.6%) were females, and 54 (44.2%) had tetraplegia.

Prediction models

The first predictor identified was the ISNCSCI total motor score, a cumulative score defined as the sum of the UEMS and the LEMS. The aROC of the simplified model, based on this single predictor, was 0.837 (95% CI: 0.815–0.859; Figure 1 and the calibration plot in supplementary Figure 2). The relationship between the ISNCSCI total motor score, measured at the time of inclusion, and the corresponding estimated probability of achieving independent, efficient bowel management at one year is shown in Figure 3 and Table 2.

We then applied a sensitivity analysis to this model, after excluding 55 patients with only *very acute* measurements and 33 patients that displayed independent, efficient bowel management at inclusion. In this analysis, the aROC was 0.820 (95% CI: 0.768 to 0.883).

The second predictor identified was item 3a in SCIMs II and III; i.e., independence in dressing the upper body. The addition of this second predictor to the first predictor conferred a small, but significant (p=0.0035) increase in the predictive performance of the derivation cohort (aROC = 0.848, 95% CI: 0.827–0.870; Figure 1 and the calibration plot in supplementary Figure 4).

The complete function of the full model, based on the two predictors, and an example of its application is shown in the appendix.

The validation cohort confirmed that both models had very high predictive power. The aROC of the model based only on the total motor score was 0.817 (95% CI: 0.754–0.881); the aROC of the model based on the two predictors, i.e. the ISNCSCI total motor score and item 3a of the SCIM, was 0.836 (95% CI: 0.775–0.896). The addition of item 3a of the SCIM in the validation cohort did not significantly improve the model (p=0.2315).

Discussion

Main findings

The present study provided the first models for predicting the achievement of independent, reliable bowel management at one year after traumatic spinal cord injury. The aROCs of our two models (0.837 and 0.848) indicated high predictive accuracy; i.e., the models displayed a high frequency of discriminating correctly between positive and negative cases in the prediction process. The first model relied on a single predictor, the total motor score of the ISNCSCI, which reflected the sum of the muscle strength of all key muscle groups evaluated. This predictor is commonly assessed as part of a standard neurological examination of patients with spinal cord injuries. Experienced examiners showed very good agreement on the total ISNCSCI motor score. [33] Collecting the values of this predictor was simple, rapid, noninvasive, and inexpensive, and its assessment required no specific instrument.

The second model included a second predictor; i.e., item 3a of the SCIM (level of independence in dressing the upper body). The second predictor conferred a small improvement in the aROC for the derivation cohort, but no significant improvement for the validation cohort. Therefore, we recommend using the first model, which was based on the single predictor, the total motor score of ISNCSCI.

Moreover, our study showed that, at 1 year after a traumatic spinal cord injury, 58% of patients achieved independent, reliable bowel management.

The results in context of the literature

Liu et al.[34] performed a cross-sectional study to identify potential predictors of severe neurogenic bowel dysfunction after a spinal cord injury. That study found that a higher spinal level, the completeness of nerve damage, and a longer duration with a spinal cord injury (more than 10 years)

were associated with greater dysfunction severity. [34] In the present study, the level of injury and the AIS grade were considered among the potential predictors, but they did not emerge as main predictors in our analysis. However, it could be argued that the main predictor found in our study, the total motor score, reflected the degree of neurological impairment associated with the spinal cord injury, [24] and consequently, it was related to the spinal level and the completeness of nerve injury. Moreover, the study by Liu et al. [34] showed major differences from the present study, in terms of the design, sample, and outcome measures. They performed a monocentric study, which included 142 patients with chronic spinal cord injuries (injury durations were 1 to over 10 years). Their patients completed two questionnaires (the Neurogenic Bowel Dysfunction Score and the Beck Depression Inventory) through mail correspondence.

In a recent study, the main predictor that emerged in the present study, the ISNCSCI total motor score, was also identified as a predictor of complete functional recovery at one year after spinal cord injury.[35]

Belliveau et al. applied artificial neural network models to predict the self-reported ambulation ability and self-care activities at one year after discharge. [36] However, their models for predicting non-ambulation outcomes were only moderately accurate, and thus, they required further optimization. [36]

Previous studies have shown that changes in sensory scores for the thoracic segments were modestly correlated with the changes in overall neurological and functional status, due to the high variability and the difficulty in localizing these dermatomes accurately and repeatedly. [37, 38] Therefore, we opted to exclude the ISNCSCI thoracic sensory scores from the potential predictors in the present analysis.

In the present study, we did not evaluate the effect of injury duration on the bowel outcome. Many authors have agreed that, at one year after spinal cord injury, bowel function stabilizes; thus, the

one-year bowel outcome might reflect the evolution of chronic bowel function; [6, 39-41] however, other authors have reported that function deteriorated with time post-injury. [42]

Strengths and limitations

The main strengths of this study were the high number of patients included and the amount of data analyzed to derive and validate the prediction models. To the best of our knowledge, our cohort was one of the largest ever analyzed regarding the evolution of bowel function after traumatic spinal cord injury.

Another strength of this study was the rigorous, methodological collection of prospective data from the EMSCI database. Of note, we recently applied the same methodology for deriving a prediction model of bladder function after traumatic spinal cord injury. [16] That model was subsequently validated in a large, independent cohort, based on data from the National Spinal Cord Injury Database, [18] on US patients with traumatic spinal cord injuries, and additionally, on patients with ischemic spinal cord injuries. [17]

Finally, the outcome measure employed in the present study (i.e., the SCIM) was reliable and valid; it might be the best primary outcome measure for functional capacity in future phase 3 clinical trials. [43] It should be noted that the SCIM is an objective outcome measure; it does not consider any subjective evaluation of outcome or the level of patient satisfaction.

One potential limitation of the present study was that the EMSCI initially applied SCIM version II, and then, promptly adopted version III, after its introduction. Consequently, in our derivation cohort, some patients were evaluated with SCIM version II and others with SCIM version III. In contrast, all patients that were included at a later time for the prospective validation were evaluated with SCIM version III. [26, 27] The two versions of SCIM were slightly different in the scoring of the second predictor identified, item 3a of SCIM. [26, 27] This small difference in item 3a scoring between

the two SCIM versions might partly explain why the addition of this second predictor conferred a small improvement of the aROC when applied to the derivation cohort and no improvement to the validation cohort . Another potential explanation might be the limited size of the validation cohort. In our analysis, SCIM scores were treated as continuous variables, as suggested by Pasta. [44] This choice might be considered controversial, and it should be considered a methodological limitation of our analysis.

All our patients received rehabilitative treatment, including state-of-the-art management of neurogenic bladder and bowel dysfunction. Nevertheless, it should be noted that the treatments were not standardized among the different EMSCI centers; thus, confounding-by-center effects could not be excluded. However, despite the presumed heterogeneity in bowel management regimes applied in the various centers, our analysis identified a main predictor of recovery, which was confirmed in the prospective validation.

Another drawback of our study was the lack of external validation. This should be performed in the future, by applying our models to a sample of patients that were not included in EMSCI, to assess the generalizability of our findings. Moreover, the EMSCI dataset did not provide a clear distinction between patients with upper versus lower motor neuron lesions. Future studies could evaluate the model performance in these two categories.

Finally, another limitation of our study was the substantial number of patients that missed the one-year follow-up. However, the cohorts of patients with and without a 1-year follow-up showed only a few differences, in terms of baseline characteristics. Moreover, our analysis took this limitation into account with the weighting approach, which limited the possible impact of missing data.

Implication for research

Currently, a large spectrum of conservative and surgical interventions is available for the management of bowel dysfunction after spinal cord injuries. [11] However, the lack of high-level evidence studies and the consequent empirical use of different strategies might be one of the principle causes of the frequent failure of bowel management programs. [11] Many authors have highlighted the urgent need for well-designed clinical trials to evaluate the efficacy of different interventions. [11, 19, 39, 40]

The prediction model provided in our study might be used to identify patients with a high probability of achieving independent, efficient bowel management at one year after a spinal cord injury. Moreover, this information is essential for patient allocation in prospective studies. [13]

Recently a closed-loop optogenetic neuromodulation system has succeeded at targeting specific neurons to control urinary tract function.[45] These promising findings warrant animal and translational research to assess whether optogenetics could also play a role in the management of neurogenic bowel dysfunction in the future.[45]

Implications for practice

Our findings that 58% of patients with traumatic spinal cord injuries achieved independent, reliable bowel management at one year after injury was both statistically and clinically relevant. From a statistical point of view, the outcome distribution in our cohort (close to 1:1) made our sample an ideal dataset for the derivation of a prediction model. From a clinical perspective, one out of two patients achieved a positive bowel outcome at one year. Our prediction model can make it possible to inform all subjects involved in the rehabilitative process (patients, caregivers, rehabilitative team) at the beginning of the rehabilitative phase on the potential bowel outcome. Indeed, this prediction could provide a basis for early counseling for patients and family members. Clear counseling is a key

point in psychological support for patients and caregivers, and it promotes compliance to the treatments recommended by the rehabilitative team. [9] Moreover, early definition of the rehabilitative goals is essential for optimizing resource allocation in the rehabilitative phase. For example, in case of a very low probability of recovery, the team may promptly identify and instruct a caregiver, who can take charge of bowel management after discharge. [9] Finally, a reliable prediction could promote the prompt prescription of appropriate durable medical equipment and environmental modifications to favor a successful discharge. [9] Moreover, several authors have highlighted that an early prediction of outcome would be necessary to identify patients with poor outcome with a conservative approach. These patients may require additional evaluations for surgical interventions. [39, 40] The optimization of bowel management could result in improving the level of care for patients with spinal cord injuries and reducing the heavy total costs to society for conservative bowel management. [1,7,40,46]

Conclusions

Our study provided the first model for predicting whether a patient with spinal cord injury is likely to achieve independent, reliable bowel management at one year after traumatic spinal cord injury. The use of our model could improve the design of future clinical trials and facilitate planning for the level of care that might be required in patients affected by neurogenic bowel dysfunction after traumatic spinal cord injury.

Table 1: Characteristics of patients at the time of inclusion (within 40 days from spinal cord injury).

	Derivation cohort				**Validation cohort**		
	Lost at follow-up (n=938)	**p-value** ⟷	**Derivation (n= 1250)**	**p-value** ⟷	**Validation (n=186)**	**p-value** ⟷	**Lost at follow-up (n=400)**
Age, y: mean (SD)	46.5 (19.2)	<0.001	42.5 (17.6)	0.196	44.3 (18.3)	<0.001	51.5 (19.8)
Sex, n (%) of males	733 (78.1%)	0.383	996 (79.7%)	0.200	156 (83.9%)	0.079	310 (77.5%)
Neurological level ¶							
C1-C8: n (%)	494 (53.0%)	0.092	617 (49.4%)	0.637	88 (47.3%)	0.326	171 (42.8%)
T1-T12: n (%)	300 (32.2%)	0.058	451 (36.1%)	0.326	60 (32.3%)	0.008	87 (21.8%)
L1-L5: n (%)	97 (10.4%)	0.321	147 (11.8%)	0.623	19 (10.2%)	0.342	31 (7.8%)
S1-S5: n (%)	4 (0.4%)	0.412*	2 (0.2%)	<0.001*	15 (8.1%)	<0.001	83 (20.8%)
Not testable: n (%)	37 (4.0)	0.081	33 (2.6%)	0.999*	4 (2.2%)	0.018*	28 (6.8%)
Plegia							
Tetraplegia: n (%)	407 (43.4%)	0.101	610 (48.8%)	0.814	89 (47.9%)	0.326	173 (43.3%)
Paraplegia: n (%)	491 (52.4%)	0.032	600 (48%)	0.637	93 (50.0%)	1.000*	199 (49.8%)
Not testable: n (%)	40 (4.3 %)	0.189	40 (3.2%)	0.647	4 (2.1%)	0.018	28 (6.9%)
Severity of neurological deficit ¶							
AIS A: n (%)	376 (40.1%)	0.040	556 (44.5%)	0.002	60 (34.7%)	0.035	95 (29.7%)
AIS B: n (%)	98 (10.5%)	0.576	140 (11.2%)	0.451	17 (9.8%)	0.877	35 (10.9%)
AIS C: n (%)	151 (16.1%)	0.638	192 (15.4%)	0.132	37 (21.4%)	0.034	51 (15.9%)
AIS D: n (%)	275 (29.3%)	0.294	341 (27.3%)	0.660	54 (31.2%)	0.368	102 (31.9%)
AIS E: n (%)	6 (0.6%)	0.184*	3 (0.2%)	-	-	-	-
Not testable: n (%)	32 (3.4%)	0.002	18 (1.4%)	0.207	5 (2.9%)	0.003	37 (11.6%)
Total motor score: mean (SD)	50.7 (26.2)	0.493	51.5 (27.6)	0.103	55.0 (25.0)	0.344	52.8 (26.7)
SCIM respiration and sphincter management: mean (SD)	16.3 (10.3)	0.664	16.1 (10.9)	0.724	15.8 (10.3)	0.026	13.7 (10.7)
SCIM total score: mean (SD)	30.4 (25.5)	0.830	30.1 (23.7)	0.830	30.5 (23.7)	0.040	26.1 (24.2)

*Fisher's exact test (two-sided).

¶ Based on International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI).

SD: standard deviation; EMSCI: European Multicenter Study about Spinal Cord Injury; AIS: ASIA (American Spinal Injury Association) Impairment Scale; SCIM: Spinal Cord Independence Measure.

Table 2

Total motor score	**Probability for an independent and reliable bowel management**
0	4.9%
1	5.2%
2	5.6%
3	6.0%
4	6.3%
5	6.7%
6	7.2%
7	7.6%
8	8.1%
9	8.6%
10	9.2%
11	9.7%
12	10.3%
13	11.0%
14	11.6%
15	12.3%
16	13.1%
17	13.8%
18	14.7%
19	15.5%

20	16.4%
21	17.3%
22	18.3%
23	19.3%
24	20.4%
25	21.5%
26	22.6%
27	23.8%
28	25.0%
29	26.3%
30	27.6%
31	29.0%
32	30.4%
33	31.8%
34	33.3%
35	34.7%
36	36.3%
37	37.8%
38	39.4%
39	41.0%
40	42.6%
41	44.3%
42	45.9%

43	47.6%
44	49.2%
45	50.9%
46	52.6%
47	54.2%
48	55.9%
49	57.5%
50	59.1%
51	60.7%
52	62.3%
53	63.8%
54	65.4%
55	66.8%
56	68.3%
57	69.7%
58	71.1%
59	72.5%
60	73.8%
61	75.0%
62	76.3%
63	77.5%
64	78.6%
65	79.7%

66	80.7%
67	81.8%
68	82.7%
69	83.7%
70	84.6%
71	85.4%
72	86.2%
73	87.0%
74	87.7%
75	88.4%
76	89.1%
77	89.7%
78	90.3%
79	90.9%
80	91.4%
81	91.9%
82	92.4%
83	92.9%
84	93.3%
85	93.7%
86	94.1%
87	94.4%
88	94.8%

89	95.1%
90	95.4%
91	95.7%
92	95.9%
93	96.2%
94	96.4%
95	96.7%
96	96.9%
97	97.1%
98	97.2%
99	97.4%
100	97.6%

Table 2: Relationship of the ISNCSCI total motor score at the time of inclusion and corresponding estimated probabilities for an independent and reliable bowel management one year after traumatic SCI (derivation cohort)

Figure 1

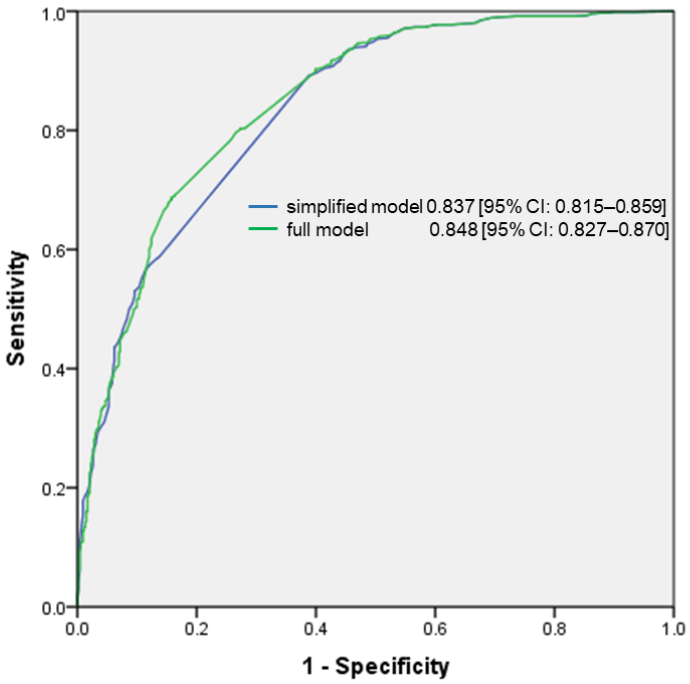

Figure 1: Receiver operating characteristics curve and corresponding area under the receiver operating characteristics curve (aROC) for two prediction models. The two models (simplified = based on the ISNCSCI total motor score; full = based on the total ISNCSCI motor score plus SCIM item 3a) predicted the achievement of independent, reliable bowel management at one year after traumatic spinal cord injury.

Figure 2

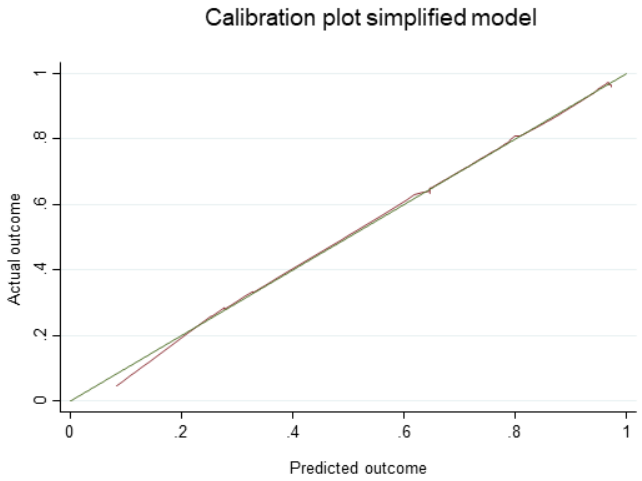

Figure 2: Calibration plot for the simplified model. This model predicts the achievement of independent, reliable bowel management at one year after traumatic spinal cord injury, based on the ISNCSCI total motor score.

Figure 3

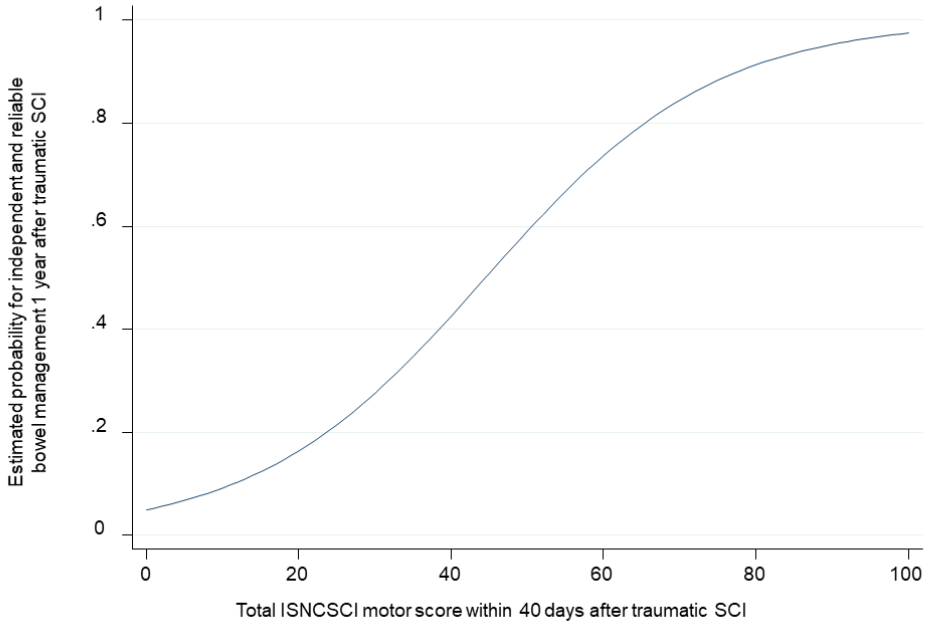

Figure 3: Relationship between the ISNCSCI total motor score, evaluated at the time of inclusion, and the corresponding estimated probability of achieving independent, reliable bowel management at one year after traumatic spinal cord injury.

Figure 4

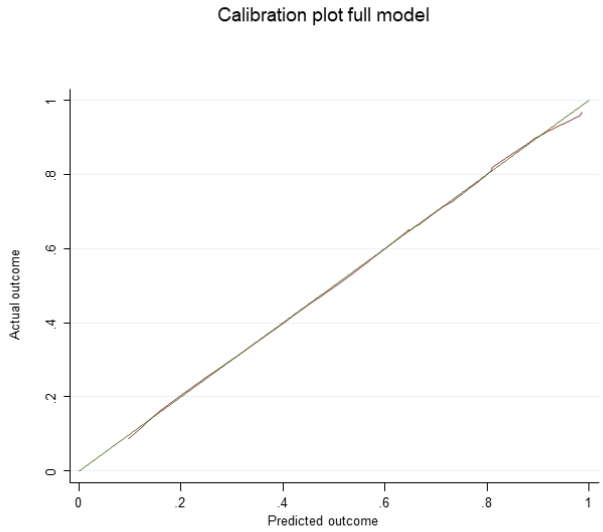

Figure 4: Calibration plot for the full prediction model. This model predicts the achievement of independent, reliable bowel management at one year after traumatic spinal cord injury, based on the ISNCSCI total motor score plus SCIM item 3a.

Appendix

Complete function of the full model and example of its application Probability of independent and reliable bowel management one year after traumatic SCI = e(-2.25046 + SCIM3a x 0.4178468 +total motor score x 0.0486938) / (1+ e(-2.25046 + SCIM3a x 0.4178468 +total motor score x 0.0486938))

Example of the model:

Assuming an item 3a of SCIM value of 4 and an ISNCSCI total motor score value of 52 the calculations are:

(1) -2.25046 + 4x0.4178468 + 52 x 0.0486938 = 1.9530048

(2) e1.9530048 =7.0498

(3) p= 7.0498 / (1+ 7.0498) = 87.6%

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External validation confirms the validity of a simple model to predict bowel outcome after traumatic spinal cord injury

This chapter is derived from the study:

Pavese C et al.

External validation confirms the validity of a simple model to predict bowel outcome after traumatic spinal cord injury

Manuscript in preparation

Introduction

The prediction of functional outcomes after spinal cord injury (SCI) plays a central role in the definition of proper rehabilitative objectives shared among team, patient and caregivers. This process favors a consistent development of the rehabilitation phase and an accurate planning of discharge.[1]

Over the last years, several models have been introduced for the prediction of the main functional outcomes after SCI, such as upper limb function, ambulation and bladder control.[2-5]

Our group has recently derived and validated in patients with traumatic SCI included in the European Multicenter Study about Spinal Cord Injury (EMSCI; www.emsci.org; ClinicalTrials.gov Identifier: NCT01571531) two models to predict bowel function one year after traumatic SCI.[6]

However, in order to use and implement the predictive models, their generalizability in new populations external to EMSCI should be evaluated.[7]

Aim of this study was to verify the prediction performance of our models in an independent cohort of patients with traumatic SCI.

Methods

Patients

We included in the study all patients with acute traumatic SCI admitted at the Spinal Cord Rehabilitation Unit of Santa Lucia Foundation, Rome, Italy, before this center entered the EMSCI network in February 2013. Data were retrospectively retrieved by a physician who was blinded to the prediction models characteristics. The cohort of patients considered for this validation study is the same evaluated in a previous study to verify the prediction power of our bladder outcome models.[4]

Prediction models

In our previous study, we derived two models to predict a positive bowel outcome one year after traumatic SCI.[6] A positive bowel outcome was defined as independent bowel management with regular bowel movements and appropriate timing with no or rare accidents (i.e. fecal incontinence less than twice a month). [6]

The simplified model was based on a single predictor, the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) total motor score, a cumulative score (range 0 – 100) derived from the sum of five key muscle strength value for each limb.

The equation to calculate probability (P) of independent and reliable bowel outcome 1 year after traumatic SCI was:

$$P = \frac{e^{f}}{1 + e^{f}} \text{ , where } f = \beta_1 + \beta_2 * \mathrm{M}_{tot}$$

The full model relied on two predictors, the ISNCSCI total motor score and the SCIM 3a score, an item assessing the independence in dressing the upper part of body (range 0-4).

The equation to calculate probability (P) of independent and reliable bowel outcome 1 year after traumatic SCI was:

$$P = \frac{e^{f}}{1 + e^{f}} \text{ , where } f = \beta_1 + \beta_2 * \mathrm{M}_{tot} + \beta_3 * \mathrm{SCIM3a}$$

Statistical analysis

Patients characteristics were expressed as mean (±standard deviation) or number (percentage), as appropriate.

Receiver operating characteristic (ROC) analysis was used to describe the discrimination performance of models. Visual inspection, Brier score and Spiegelhalter z-test were used to assess

the calibration of the model. To evaluate the potential clinical utility of the model, we compared the predicted probability with the real outcome of our study.

Furthermore, we chose the best cut-off point that maximized both sensitivity and specificity in order to correctly classify most of the patients.

A p-value <0.05 was considered statistically significant. STATA version 13.1 was used to perform the analysis.

Results

A total of 135 patients evaluated between 2004 and 2013 were considered for the study. Among these, 24 (18%) were lost at follow up. The final sample consisted of 111 patients, mean age 40 (±16) years, 102 (92%) males; the neurological level was cervical in 45 (41%) patients, thoracic in 57 (51%), lumbar in 8 (7%), sacral in 1 (1%). The ASIA Impairment Scale (AIS) grade was A in 63 (57%), B in 12 (11%), C in 12 (11%), D in 24 (22%).

The ROC analysis showed excellent values of area under the ROC curve for the simplified and the full models: 0.939 (95%CI=0.87-1.00) and 0.922 (95%CI=0.85-0.99), respectively (Figure 1a and b). Considering a cut-off point of 0.60, the simplified and the full model showed the following values: sensitivity both 91%, specificity 90% and 74%, positive predictive values 70% and 48%, negative predictive values 98% and 97%, accuracy 90% and 77%, respectively.

The calibration curve for the simplified and the full models are showed in Figure 1 c and d. The simplified model showed an intercept value of -1.754, a slope of 3.147 and a Brier score of 0.213 (Spiegelhalter's z-statistic= 0.434; p= 0.332). The full model showed had an intercept of -1.953, a slope of 2.437 and a Brier score of 0.235 (Spiegelhalter's z-statistic= 2.362; p= 0.0091).

Finally, based on sensitivity analysis of the simplified model (Figure 2a), we defined a cut-off value which enables to stratify patients into 2 groups with low (P <0.6) or high (P ≥0.6) probability to recover a positive bowel outcome at 1 year (Figure 2b).

Discussion

Our study demonstrates in an independent sample an excellent discrimination of our two models in the prediction of bowel outcome one year after traumatic SCI, in line with the findings of Khan and colleagues.[8] The simplified model showed higher specificity, positive predictive values and accuracy. Concerning calibration, for both models visual inspection revealed a partial overlap between predicted probabilities and observed proportion. The non-significant p values for Spiegelhalter statistics indicated a better and acceptable calibration for the simplified model.[9]

Therefore, based on statistical and clinical considerations, we suggest to prefer the simplified model in the prognostication of bowel outcome after traumatic SCI.

The sensitivity analysis of the simplified model allowed us to identify a cut-off value to stratify patients in two groups of probability of bowel outcome recovery.

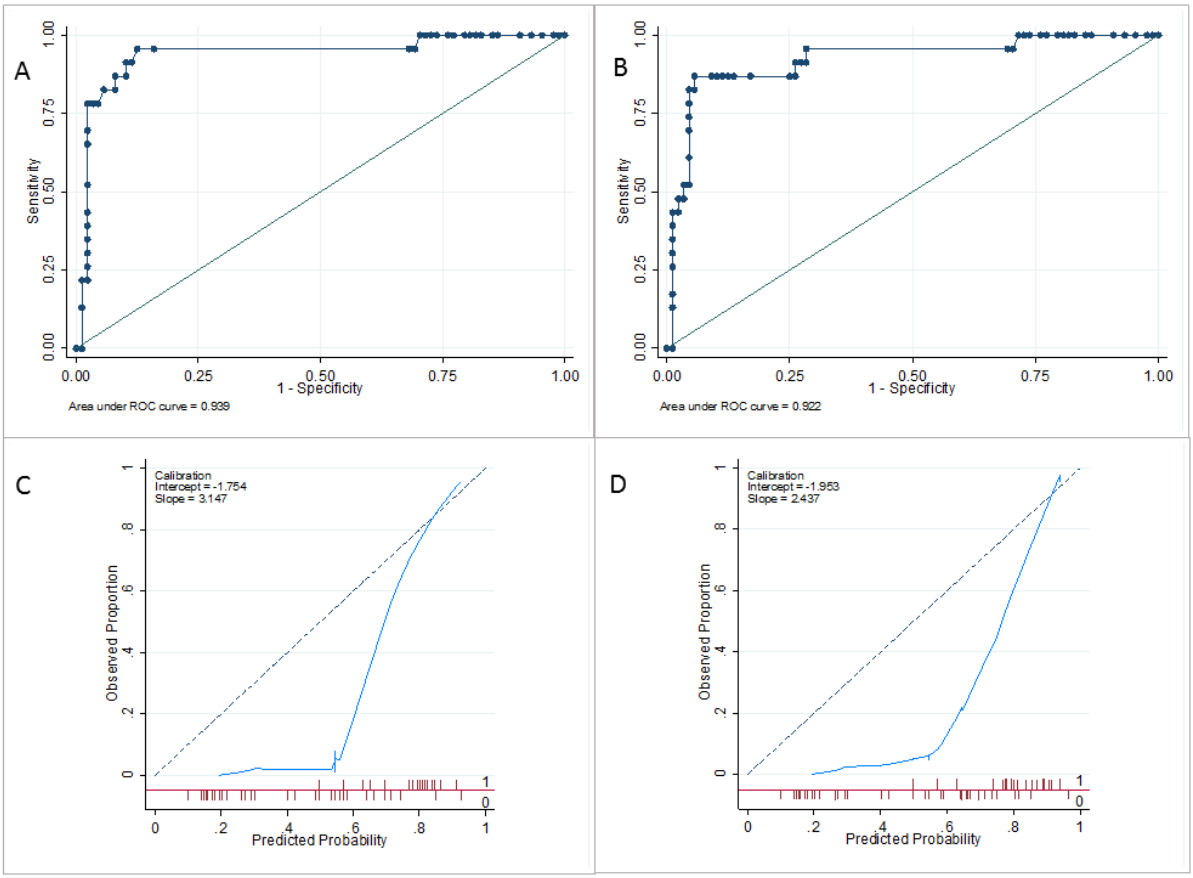
Our study is limited by the retrospective data collection and by the relatively small number of patients included for the analysis.

The validation in independent samples represents a mandatory step to assess the use and the implementation of a prediction model.[7] Our data, together with the results by Khan and collaborators,[8] further support the validity of our simplified model for the prediction of bowel outcome after traumatic SCI.

Conclusions

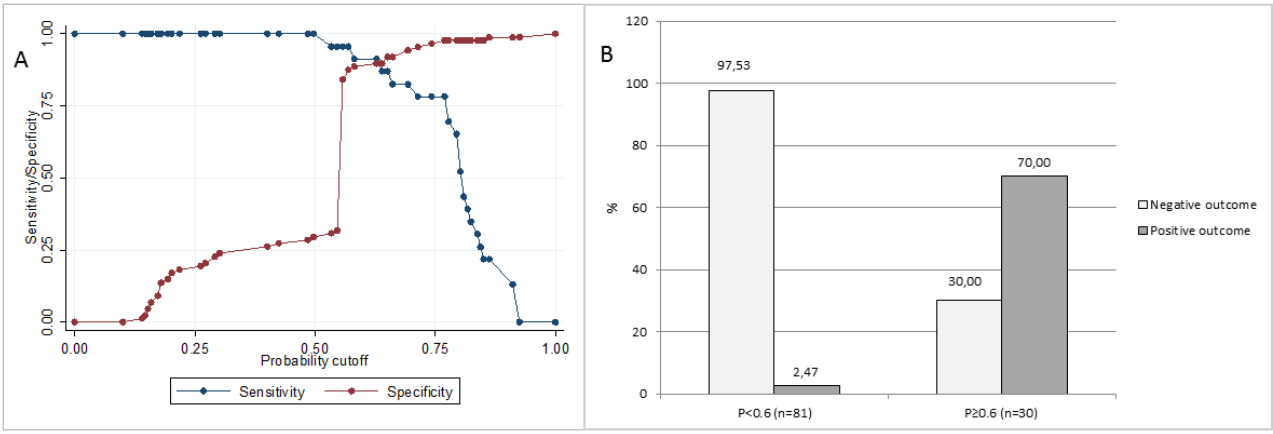
We validate our simplified model for the prediction of bowel outcome one year after traumatic spinal cord injury in an independent clinical sample. Our model may be employed in clinical setting for counselling and rehabilitation planning and in the research field for the design of future clinical trials.

Figure 1: Receiver operating characteristics curve and calibration plot



Area under the receiver operating characteristics curve of the simplified (A) and full (B) model; calibration plot of the simplified (C) and full (D) model.

Figure 2: Sensitivity analysis of the simplified model and stratification of patients



Based on the sensitivity analysis of the simplified model (A), we identified a cut-off value of probability of positive outcome (P), which enables us to stratify the sample in two groups (B): patients with P<0.6 are considered at low probability, while patients with P≥ 0.6 are considered at high probability to recover a positive bowel outcome 1 year after SCI.

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Prediction of bowel outcome after ischemic spinal cord injury

This chapter is derived from the study:

Pavese C et al.

Prediction of bowel outcome after ischemic spinal cord injury

Manuscript in preparation

Introduction

Data concerning epidemiology and spontaneous evolution of non-traumatic spinal cord injury are scarce, due to the rarity and the heterogeneity of these conditions in comparison with traumatic lesions.[1] However, the aging of global population will increase the incidence and epidemiological relevance of non-traumatic spinal cord injury in the future years.[1]

Like traumatic spinal cord injury, ischemic lesions are characterized by a single sudden event for the onset of spinal cord damage. However, recent studies showed controversial results in the comparison of functional recovery after spinal cord injury of ischemic and traumatic etiology. [2,3]

Indeed, it is difficult to compare the functional recovery between these two cohorts of patients, due to the different characteristics of the two populations: patients with an ischemic etiology show older age and experience fewer cervical and complete injuries than patient with traumatic spinal cord injury. [2,3] A recent study from data of the European Multicenter Study about Spinal Cord Injury (EMSCI) demonstrated in two matched populations that the two spinal cord etiologies display a similar course of functional evolution.[4]

Therefore, we postulated that a prediction model of functional outcome derived and validated in a cohort of patients with traumatic spinal cord injury may be successfully applied to a sample of patients with ischemic spinal cord injury.

Our group has already demonstrated that the bladder outcome model derived from traumatic patients included in EMSCI was valid also when applied to patients with ischemic spinal cord injury.[5]

We have recently developed and validated a model to predict independent and reliable bowel outcome one year after traumatic spinal cord injury.[6]

Aim of the present study is to verify in ischemic patients the predictive performance of a model to predict bowel outcome after traumatic spinal cord injury.

Methods

Patients

We considered for the study patients with ischemic SCI prospectively included in the European Multicenter Study about Spinal Cord Injury (EMSCI) (www.emsci.org) (ClinicalTrials.gov Identifier: NCT01571531). EMSCI is a multicenter network started in 2001 with the aim to collect with standardized protocols the neurological, neurophysiological and functional data of patients with traumatic or ischemic SCI over the first year after spinal lesion. Inclusion criteria are: single event traumatic or ischemic SCI evaluated within 40 days from injury. Exclusion criteria are: previous neurological impairment including peripheral nerve pathology above the level of lesion, polyneuropathy, severe craniocerebral injury or dementia. Patients included in EMSCI are evaluated per protocols in fixed time points: between 0 and 15 days (*very acute*), between 16 and 40 days (*acute I*), between 70 and 98 days (*acute II*), between 150 and 186 days (*acute III*), and between 300 and 400 days (*chronic*).

For the present study, we considered the predictors collected in the acute I phase when available; if not available, we considered the predictors collected in the very acute time point. The outcome was derived from data collected in the chronic time point.

For the present analysis, we extracted from the database the data of all patients with date of injury until April 2019, where the collection of one-year outcome was theoretically possible.

Prediction models

According to our previous study, a positive outcome was defined as independent bowel management with regular bowel movements and appropriate timing with no or rare accidents (i.e. fecal incontinence less than twice a month).[6] The bowel outcome was derived from the

dichotomization of item 7 (sphincter management- bowel) of Spinal Cord Independence Measure (SCIM): a positive outcome was defined by a score of 10 in SCIM version II and a score of 8 or 10 in SCIM version III; a negative outcome was defined by a score < 10 points in SCIM version II and < 8 points in SCIM version III).[7,8]

The first prediction model, the so called "simplified model", was based on a single predictor, the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) total motor score, a cumulative score derived from the sum of the strength value evaluated in five key muscle for each limb. This score may range from 0 to 100, with higher values indicating better strength.[9]

The formula to calculate probability (P) of independent and reliable bowel outcome 1 year after SCI applying the simplified model was:

$$P = \frac{e^{f}}{1 + e^{f}}\ , where\ f = \beta_1 + \beta_2 * \mathrm{M}_{tot}$$

The second model, the so called "full model", relied on two predictors, the ISNCSCI total motor score and the SCIM 3a score, an item assessing the independence in dressing the upper part of body. This item may assume a value between 0-3 in SCIM version II and 0-4 in SCIM version III, with higher values indicating a better level of independence.

The formula to calculate probability (P) of independent and reliable bowel outcome 1 year after SCI applying the full model was:

$$P = \frac{e^{f}}{1 + e^{f}}\ , where\ f = \beta_1 + \beta_2 * \mathrm{M}_{tot} + \beta_3 * \mathrm{SCIM3a}$$

In our previous study, we verified that the addition of the second predictor conferred a small but significant increase of the predictive performance in the derivation cohort but no improvement in the validation cohort.[6]

Statistical analysis

Descriptive statics were used to summarize the sample characteristics. Normality of data was assessed used Shapiro-Wilk test. To evaluate differences between patients lost at follow-up or not, we used Pearson Chi squared or Fisher exact test and Student t or Mann Whitney-U test as appropriate.

To assess the performance of prediction models we evaluated discrimination and calibration. Discriminative ability was assessed by area under the Receiver Operating Characteristic (ROC curve), while calibration was assessed by visual inspection of calibration plot, Brier scores (BS) and Spiegelhalter z-test. For both models, calibration slope and intercept were estimated. Furthermore, for an easy clinical use in clinical practice, we compared the predicted probability with the real outcome of our study and we chose the best cut-off point that maximized both sensitivity (Se) and specificity (Sp) in order to identify most of the patients correctly. Statistical significance was set at 0.05, all analyses were performed by STATA13.

Results

For the study we recruited 331 patients, but 189 (57.10%) were lost to follow-up. The final sample was composed by 142 patients. Table 1 shows the clinical characteristics of patients, comparing the patients included for the analysis with patients lost at follow-up. The two cohorts (patients included in the analysis and patients lost at follow-up) did not show significant difference in terms of personal and clinical characteristics.

In the final study sample 92 (64.79%) patients reached a positive bowel outcome at 1 year.

In the ROC analysis, the simplified model showed an AUC of 0.783 (95%CI=0.702-0.860; Figure 1) with an accuracy of 71%, sensitivity of 96%, specificity of 26%, positive predictive value of 70% and negative predictive value of 77%.

For the full model, the AUC was 0.806 (95%CI= 0.728-0.885; Figure 2) with an accuracy of 72%, sensitivity of 98%, specificity of 26%, positive predictive value of 71% and negative predictive value of 87%.

Figure 3 and 4 show calibration plot for both models. The calibration curve of the simplified model showed an intercept of -0.015 and a slope of 1.385. For this model Brier score was 0.177 (Spiegelhalter's z-statistic= -1.204; p= 0.886). The calibration curve of the full model had an intercept of -0.734 and a slope of 1.049. For this model Brier score was 0.178 (Spiegelhalter's z-statistic=2.255; p=0.012).

Finally, through a sensitivity analysis and medical considerations, we identified a cut-off value for probability of developing a positive outcome at 1 year based on the simplified model (Figure 5) of 0.60. Applying this cut-off to our sample, we were able to stratify patients into two groups: patients with low probability (P<0.60) and high probability (P≥0.60) of bowel outcome recovery at 1 year (Figure 6).

Discussion

Our study demonstrates that both models for the prediction of bowel outcome presented an acceptable discrimination with a good accuracy when applied to a sample of patients with ischemic spinal cord injury. However, the calibration procedure displayed acceptable results only for the

simplified model.[10] Overall, these data confirm the validity of the simplified model in the prediction of 1-year bowel outcome in subjects affected by ischemic spinal cord injury.

These data are in line with previous validation studies performed on patients with traumatic SCI, where the simplified model was identified as the better tool for the evaluation of bowel prognosis.[6,11]

The sensitivity analysis allowed us to stratify patients in two groups with different probability to reach of an independent and reliable bowel management at 1 year.

Patients with a probability P<0.60 are considered at risk to fail the recovery of bowel control. Therefore, for these patients appropriate and timely counselling and interventions in view of discharge may be planned.

The recovery of bowel function represents an urgent priority for patients with spinal cord injury, due to the high negative impact that neurogenic bowel dysfuncton has on health, quality of life and participation.[12]

However, to date there is scarce evidence concerning the protocol to adopt for the treatment of bowel problems and different treatment options are applied in sequence or combination based on empirical approach.[13,14] Therefore, there is an urgent need for clinical trials to evaluate the effect of different treatment options. [13,14] In this context, the application of our prediction model will be of help for the design of future trials to evaluate the efficacy of in use or new treatments: The application of our model will allow the correct allocation of patients in the groups of treatment based on the probability of recovery when treated with standard therapy.

Conclusions

We validate our simplified model for the prediction of bowel outcome one year after ischemic spinal cord injury. The application of our model may have positive implications in the management of patients with ischemic spinal cord injury and help the design of future clinical trials in this field.

Table 1. Baseline characteristics of patients included in the analysis and patients lost at follow-up

Characteristics	**Lost at follow-up (n=189)**	**Study sample (n=142)**	**P-value**
Age (years), mean±SD	58.42±17.99	54.73±15.39	0.0503§
Sex (male), n(%)	107(56.61)	92(64.79)	0.133*
MS, median(Iqr)	56(50-80)	56(50-79)	0.6021#
Exam stage, n(%)			0.521*
Acute I	175(92.59)	134(94.37)	
Very acute	14(7.41)	8(5.63)	
Severity of Neurological deficit – AIS grade, n(%)			0.656**
A	40(21.16)	32(22.54)	
B	27(14.29)	18(12.68)	
C	40(21.16)	40(28.17)	
D	78(41.27)	50(35.21)	
E	1(0.53)	-	
NT	3(1.59)	2(1.41)	
NLI, n(%)			0.717**
C	52(27.51)	37(26.06)	
INT	1(0.53)	-	
L	16(8.47)	18(12.68)	
NT	2(1.06)	1(0.70)	
T	118(62.43)	86(60.56)	

§ t-test for independent data; # Mann-Whitney U test; */** Pearson Chi-squared/Fisher exact test.

SD: standard deviation; MS: ISNCSCI total motor score; AIS grade: ASIA impairment scale; NLI: neurological level of injury; INT: intact; NT: not testable

Figure 1. Area under the receiver operating characteristics curve (AUC) – Simplified model.

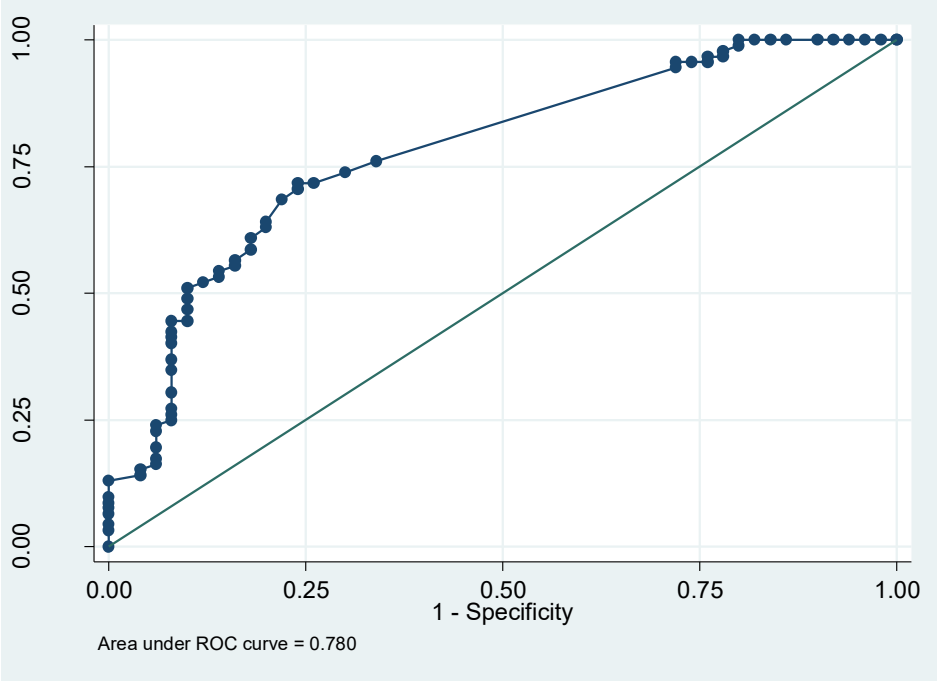


Figure 2. Area under the receiver operating characteristics curve (AUC) – Full model

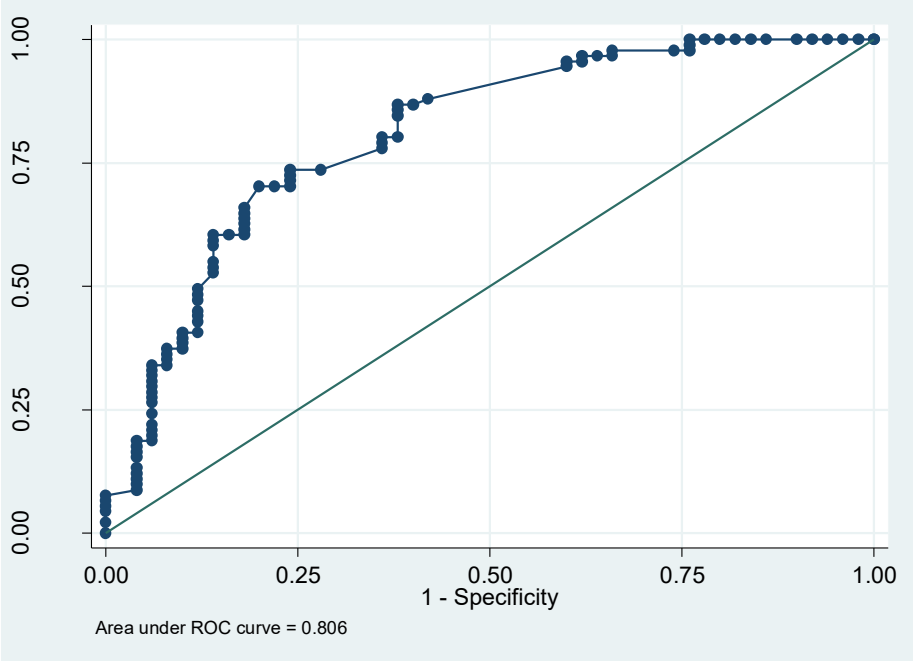


Figure 3. Calibration plot - Simplified model

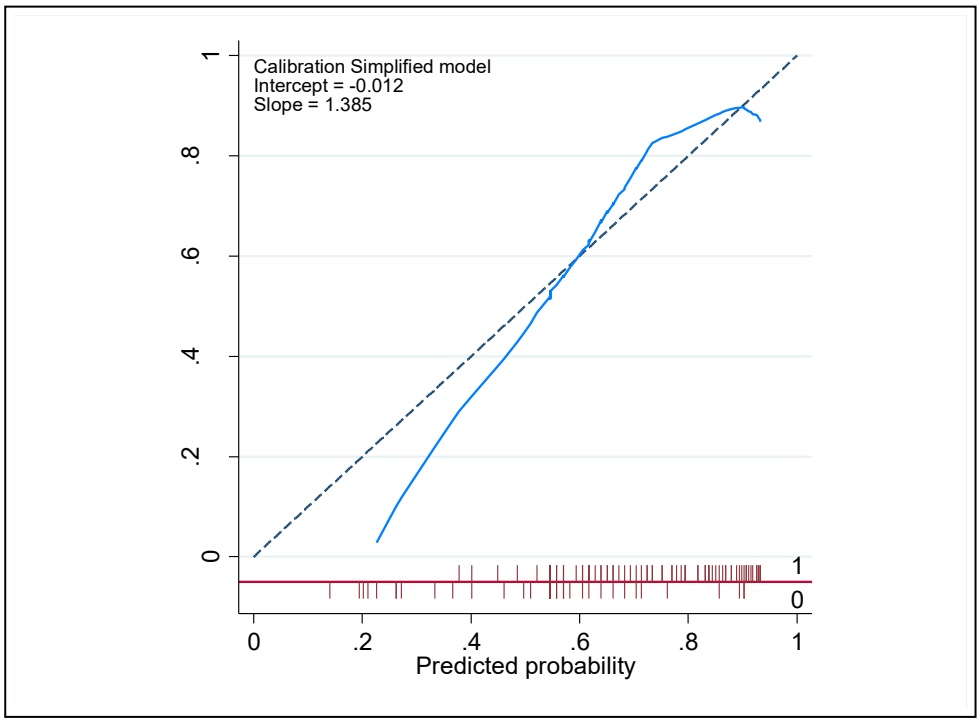


Figure 4. Calibration plot – Full model

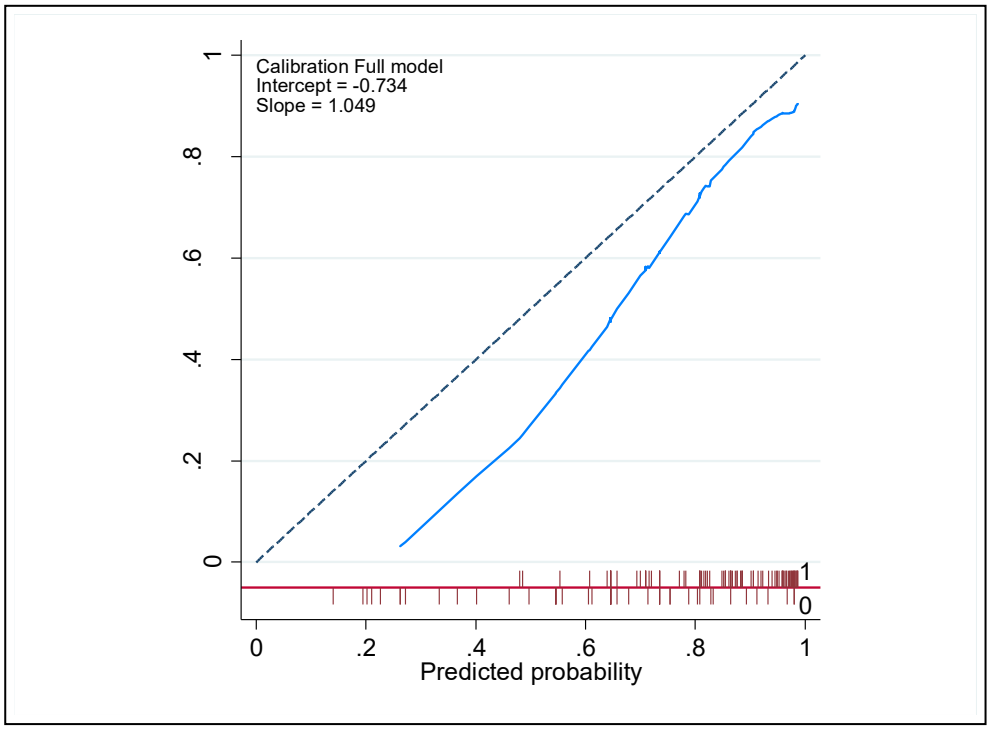


Figure 5. Sensitivity analysis for the simplified model

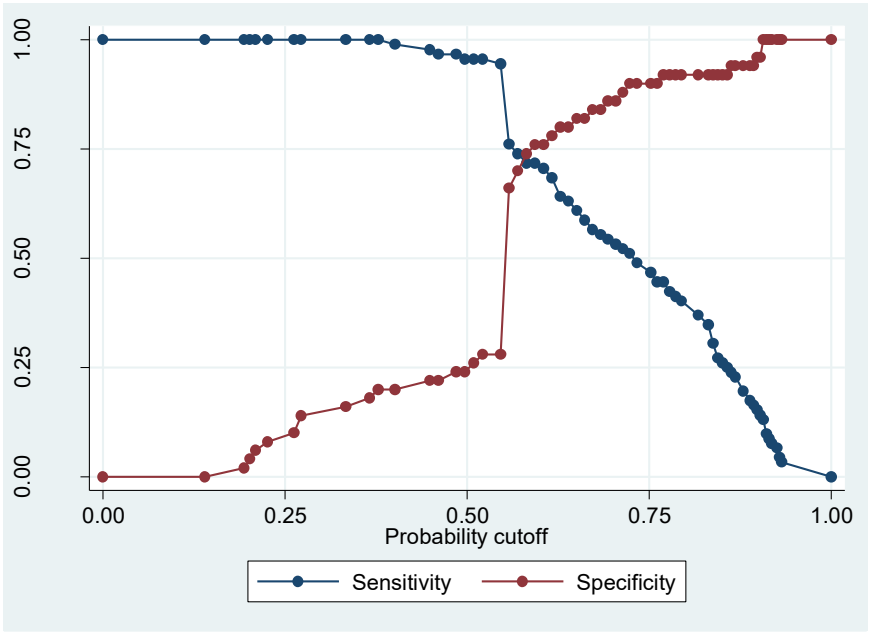
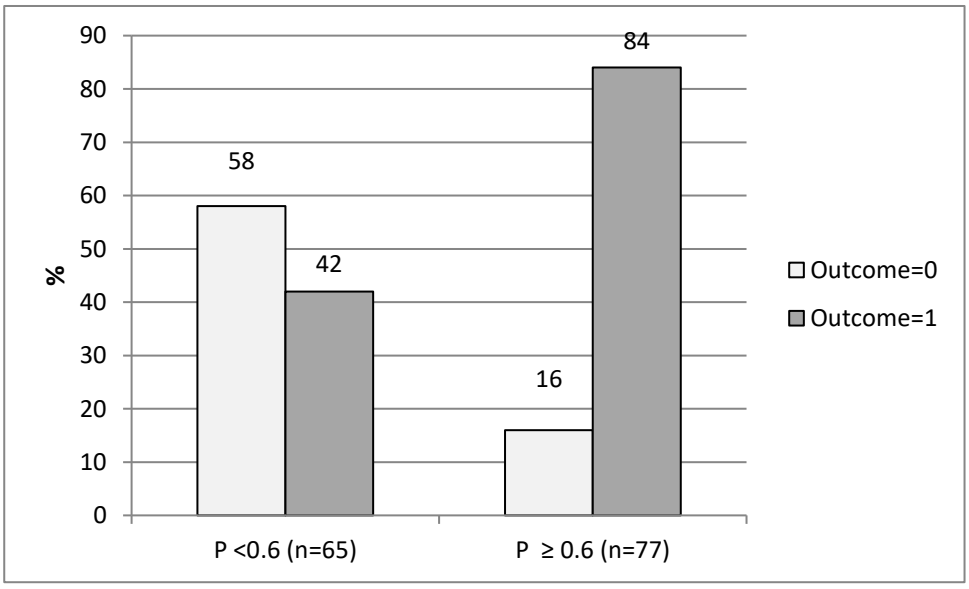


Figure 6. Distribution of Y by probability cut-off levels – Simplified model



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Functional outcomes after central cord syndrome

This chapter is derived from the study:

Blasetti G, Pavese C, Maier DD, Weidner N, Rupp R, Abel R, Yorck BK, Jiri K, Curt A, Molinari M, Schubert M, Scivoletto G.

Comparison of outcomes between people with and without central cord syndrome.

Spinal Cord. 2020;58:1263-1273.

Introduction

The epidemiology of traumatic spinal cord injury (SCI) in the western countries has been changing over the last decades. The United States Spinal Cord Injury Statistical Center[1] reported an increase in the average age of patients, from 29 years in the 1970s to 43 years in the last report. Comparable changes are reported in recent epidemiological studies from European countries.[2-5] For example, in Italy the average age of SCI patients increased from 38.5 years in 1997–1999 [6] to 54 years in 2013–2014 [4].

The causes of SCI have also changed: 20 years ago, the most frequent cause was traffic accidents, while at present, SCI occurs more often due to falls from a low height, in particular among people over the age of 55.[4,7]

The third epidemiological evidence is a change of the neurological level of injury (NLI) and severity of SCIs with a progressive increase in incomplete cervical spinal cord injuries (iCSCI).[1] With regard to cervical lesions, there has been an increase in C1–C4 lesions (from 21.7% in the years 1994–1998 to 31.2% in the years 2009–2013)[8] and an increase of incomplete lesions (from 20.9% in the years 1997–1999[6] to 43.3% in the years 2013–2014).[4]

Central cord syndrome (CCS) is considered the most common incomplete tetraplegia, accounting for about 9% of all traumatic SCIs [9,10] with an increasing incidence.[11]

CCS is characterized by a disproportion of impairment in the upper and lower limbs, with more pronounced muscle weakness and reduced function in the upper extremities, neurogenic bladder dysfunction and different degrees of sensation loss.[12]

CCS has a bimodal age distribution with a cut-off around the age of 50, with a peak at a younger age (where CCS is attributable to “high-energy impact”) and a peak at an older age (where CCS is most

likely due to a “low-energy impact” event).[11, 13] In elderly patients, CCS is usually produced by a hyperextension trauma of the neck with preexisting cervical spondylosis or stenosis of the cervical canal.[13]

CCS is considered a spinal syndrome with a better prognosis in terms of neurological and functional recovery compared with other iCSCI.[12-16] Patients with CCS tend to show good improvement in total motor score, bladder management, daily life independence and walking.[17,18]

However, these data rely mainly on a relatively small case series of CCS patients. Also, comparisons of patients with CCS to those with other types of iCSCI typically do not take into account possible confounding factors known to influence outcome, which may be different between these two types of iCSCI. Disappointingly, a formal comparison between patients with CCS and iCSCI is lacking.

Therefore, the aim of the present study is to compare the neurological and functional outcome of patients with CCS and other forms of iCSCI.

Methods

Data were derived from the European Multicenter Study about Spinal Cord Injury (EMSCI) database (https://www. emsci.org, ClinicalTrials.gov Identifier: NCT01571531). EMSCI is a prospective longitudinal cohort study, involving 25 European spinal cord injury centers in the systematic collection of patients’ data during the first year after traumatic and vascular SCI. The study, started in 2001, includes a large sample of spinal cord injured patients who have been treated with state-of-the-art therapies and rehabilitation. Before entering the study, all patients gave informed consent to participate. The study conforms to the standards expressed in the Declaration of Helsinki and was approved by the ethical committee of the participating centers. EMSCI time schedule and core set EMSCI establishes the data collection in fixed time points from injury, i.e. within 15 days and 1, 3, 6 and 12 months after injury. The assessments of the essential core set include clinical,

functional and independence evaluations. Clinical assessment was based on sensory and motor scores derived from ISNCSCI, allowing evaluation of NLI and severity as well as upper (UEMS) and lower extremity motor scores (LEMS).[19,20] Within the EMSCI database, a validated EMSCI-ISNCSCI calculator (http://ais.emsci. org)[21] electronically calculates AIS and all other classification variables. Functional assessments of ambulation include the following: (1) the 6-min walk test (6MWT)[22], which measures the distance covered by a subject walking at his/her own preferred in 6 min; (2) the 10-m walk test (10MWT)[23], which measures the time required by a subject to walk a 10-m distance; (3) the Walking Index for Spinal Cord Injury II (WISCI II)[24], which grades the ability of patients to walk a 10-m distance: the score ranges from 0 (inability to walk) to 20 (ability to walk without aids or assistance). Independence in daily life activities is evaluated through Spinal Cord Independence Measure (SCIM) versions II and III[25,26], comprising three domains: self-care (sub-score 0–20), respiration and sphincter management (sub-score 0–40) and mobility (sub-score 0–40), and provides a total score (range 0–100), with 100 indicating full independence.

Study design

From the EMSCI database, we extracted data of all patients who suffered iCSCI within 40 days from injury, with a date of injury between July 2001 and 2016. In order to assess incidence and range of severity of CCS, a “central myelopathy index” (CMI) was calculated in the same way as a previously published score developed to quantify BrownSéquard-like spinal hemi-syndrome.[27] For each patient, the percent ratio of average segmental motor scores below NLI was calculated from upper and lower extremities. A CMI of 50% (100%), for example, would indicate an average segmental motor score of 2.5 (0) for all cervical segments (including T1) below NLI and an average segmental motor score of 5 in all lumbar/sacral myotomes. This allowed us to describe CCS as a continuum of patients presenting with a range of severity of CCS, rather than applying an arbitrary cut-off

difference between UEMS and LEMS. To compare the neurological and functional outcome of patients with CCS and other forms of iCSCI, CCS was defined by a difference between LEMS and UEMS of at least ten points in favour of LEMS, in line with the diagnostic criteria suggested by Middendorp.[28] Outcomes of this group were then compared with iCSCI. A preliminary analysis showed that patients with CCS were significantly older than the average patient with iCSCI (56.3 ± 16.3 vs 49.3 ± 19.5, $p < 0.001$). Furthermore, they had a higher incidence of NLI C1–C4 (68% vs 50%, $p < 0.01$) and higher percentage of AIS D lesion (82% vs 63%, $p < 0.01$). As with age, NLI and AIS grade are all well-known prognostic factors for SCI, so a matching procedure based on these features was used to create two comparable cohorts of patients with CCS and iCSCI. The match was exact for AIS grade and NLI, while for age an interval within ±5 years was tolerated. The patients were not matched by gender because the effect of gender on SCI outcome is questionable. The matching was performed using R package MatchIt.[29]

Outcome measures

The primary outcome was the level of independence at enrolment (i.e. within 40 days), 6 and 12 months after SCI, evaluated through SCIM II/III total score and the analysis of its sub-scores: self-care, respiration and sphincter management and mobility. Furthermore, bladder and bowel independence were also assessed as the percentage of patients with a SCIM "Sphincter management-bladder" score of 15 (for bladder management) and "Sphincter management-bowel" of 10 (for bowel management) at the first and last evaluations. The secondary outcomes were as follows:

(1) The neurological status at enrolment, 6 and 12 months after SCI, evaluated through AIS grade, total motor score, UEMS and LEMS. Neurological improvement was assessed also in terms of AIS grade change in the matched cohorts.

(2) The walking capacity at enrolment, 6 and 12 months after SCI, evaluated through WISCI II, 6MWT and 10 MWT. Walking capacity was also assessed, based on WISCI scale, as the percentage of patients unable to walk (WISCI II levels 0–3), those needing physical assistance to walk (WISCI II levels 4, 6–8, 10, 11, 14 and 17) and those walking without assistance (all the remaining WISCI levels) both at the first and last evaluations. Statistical analysis Data are reported as mean (standard deviation) or median (range) if continuous, as percentage if categorical. Variables from the two samples (patients with CCS and iCSCI) were compared over the three time points with two-way ANOVA for repeated measures ("between" factor: group, two levels, (CCS or TI); "within" factor: time, three levels (T0–T2) and "dependent" variables: total motor score, UEMS, LEMS, SCIM 2/3 and WISCI II, 10MWT and 6MWT). We also calculated the improvement of each outcome measure between T0–T1, T1–T2 and T0–T2, and compared them with the same statistics. Chi square test was used to evaluate AIS grade improvement, independence in bladder and bowel management and walking with/without physical assistance. Statistical analyses were performed with SPSS for windows (version 21.0, Chicago, IL).

Results

From the EMSCI database we extracted data of 1033 patients with incomplete tetraplegia. Of these, 866 could be rated with a CMI and 546 presented with the complete dataset over the first year after incidence (Figure 1). From this sample, the matching procedure selected 110 dyads comparable for age distribution, NLI and severity (Table 1).

Baseline comparison

At T0 (i.e. within 40 days from injury), the two groups were comparable in terms of ISNCSCI total motor score. Based on the definition of CCS, these patients displayed lower UEMS, but higher LEMS, than iCSCI patients (Table 2). The distribution of matched dyads with respect to NLI was comparable and thus deemed representative for the entire sample (Figure 2a). Calculation of CMI indicated that asymmetry of motor scores with UEMS < LEMS is a continuum with decreasing likelihood for increasing CMI (Figure 2b). A majority of cervical SCI patients has no relevant CCS. Of 866 patients, 621 (73%) had a CMI of 20% or less, which was about equivalent to a motor score difference less than ten points between UEMS and LEMS. A CMI of more than 60% was very rare (eight cases, < LEMS irrespective of NLI, thereby including segments which were actually intact, or underestimating proportionate UEMS–LEMS differences in cases with low NLI. The mean CMI of the matched groups was 37% (CCS) and 8% (iCSCI), respectively. The majority of patients with a CMI > 0 were AIS D, whereas few AIS C patients had high CMI (Fig. 3b/lower plot). The CCS cohort showed a lower level of global independence (as evaluated by the total SCIM), and of independence in self-care and mobility (Table 2). With regard to bladder control, at T0, 15 (14%) CCS patients and 27 (25%) iCSCI ones had voluntary bladder control with a SCIM “Sphincter management-bladder” score of 15 ($p < 0.05$). With regard to bowel management, at T0, 13 (12%) CCS patients and 27 (25%) iCSCI ones had good bowel control with a SCIM “Sphincter management-bowel” score of 10 ($p < 0.05$). The evaluation of walking capacity with WISCI II, 6MWT and 10MWT showed no difference in the two groups. In particular, at first evaluation, 68 (61.8%) patients in the CCS group and 67 (61%) in the iCSCI were unable to walk; 22 (20%) patients in both groups walked unassisted ($p > 0.05$).

Recovery over time

Both populations showed a significant improvement of all the neurological, functional and walking measures between T0 and T1. Between T1 and T2, we observed a further tendency for improvement, but this was not significant (Figure 3–5). When comparing the two populations, CCS patients showed a higher, but not significantly, incidence of AIS grade improvement one year after SCI: an improvement between T0 and T2 was observed in 22/110 patients with CCS and 15/110 with iCSCI ($p > 0.05$). At all times CCS patients showed significant lower UEMS and higher LEMS compared with iCSCI. Total motor scores always were comparable in the two populations (Table 2, Figure 3) and total motor score recovery between T0 and T2 was independent of CMI in both AIS C and D patients (Figure 3a/upper graph). UEMS improvements were significantly higher in patients with CCS than iCSCI (Table 3, Figure 4). With regard to daily life activities, the comparison of matched cohorts showed that patients with CCS had lower SCIM "self-care" scores at all time-points. At T0, patients with CCS also presented with significantly lower SCIM "mobility" ($p < 0.05$), "external mobility" ($p < 0.05$) and "total" SCIM-scores ($p < 0.05$), but these differences disappeared at the following assessments. SCIM "respiration and sphincter management" and "internal mobility" scores and walking tests were always comparable in the two groups (Table 2) (Figure 5). SCIM sub-score improvements were comparable between the two populations (Table 3, Figure 5). At final evaluation 53 (49%) patients in both groups had voluntary bladder control. At T2, good bowel control was seen in 47 (43%) CCS patients and in 57 (52%) iCSCI patients ($p > 0.05$). With regard to walking capacity, WISCI, 6MWT and 10MWT scores were comparable at all time-points (Figure 6) as well as the respective improvements (Table 3). At the final evaluation, 7 (6%) patients in the CCS group and 13 (12%) in the iCSCI group did not walk; 100 (91%) patients with CCS and 95 (86%) with iCSCI walked without assistance ($p > 0.05$).

Discussion

Our study analyzed the neurological and functional evolution of patients with CCS, a spinal cord syndrome often described as less incapacitating compared with other forms of iCSCI. In recent years, the epidemiology of SCI has changed, associated with increasing age and incidence of iCSCI. Cervical lesions in the elderly population will represent a unique challenge for health care systems because of the various medical co-morbidities that are associated with age and because of the more difficult recovery of daily life independence after SCI at an older age. CCS is already the most common spinal cord syndrome, accounting for about 9% of all SCI[9] and 27% of iCSCI in the present study. It is anticipated that in the near future, CCS due to falls will represent one of the main causes of SCI.[7,30,31] We examined prospective neurological and functional data from a large sample of patients with CCS compared with patients with iCSCI. The parameterization by CMI demonstrates that CCS is a continuum rather than a distinct subgroup of patients with iSCI. The demographic and neurological features of our data in line with the literature indicate that patients with CCS are older, and have higher NLI and a higher frequency of AIS D (Figure 1a and 2b).[9,12] In order to obtain two groups of patients as homogeneous as possible, we matched a selection of patients based on age, AIS and NLI, for a representative comparison of outcomes in CCS and iCSCI. The comparison of these groups indicates that patients with CCS do have poorer outcomes than those with iCSCI. Despite better improvement of UEMS in CCS (compare Figures. 3a with 5a and see Table 3), they always remained lower compared with iCSCI. The low UEMS of patients with CCS was reflected in reduced self-care scores, due to the persistent deficit in manual ability. CCS was not characterized by a better recovery of gait, despite having higher LEMS than patients with iCSCI at all time-points. The ability to walk following iSCI or CCS may be assisted or enabled by upper extremity devices, i.e. crutches, walkers, etc. Lack of upper extremity arm strength hinders grasp and/or antigravity support at the shoulder and elbow, making it difficult for patients to walk. Therefore, patients with CCS will probably require

a high level of daily assistance after discharge. Currently available literature states nearly unanimously that CCS is a syndrome characterized by a good prognosis in terms of neurological and functional recovery. However, these previous studies presented a low number of patients, used variable or diffuse definitions of CCS, employed unsuited outcome parameters, lacked a comparison of properly matched groups, or were not prospective and subject to center effects, leading to bias in outcome and prognosis.[18,32-34] Mckinley et al.[9] compared the demographic characteristics of 175 patients who presented with one of the six main clinical spinal cord syndromes and used the Functional Independence Measure (FIM) and its sub-scores to compare their functional recovery. Although many demographics and in part functional data are in line with what we observed, McKinley et al.'s sample was collected retrospectively and from a single treatment center. Furthermore, few outcome measures were analyzed and FIM is less sensitive than SCIM.[32] However, CCS remained the syndrome with the lowest motor and self-care FIM scores at entry and among those with the lowest improvement at discharge. The article lacks a precise definition of CCS, but above all there is no matching between the groups: patients with NLI C2 to S2 were included, thus functional recovery trends are not reliable. Wirz et al.[33] compared 15 patients with CCS and 15 with BSS, assessed by neurological status, walking capacity and activities of daily life independence at 1 month and 6 months from the acute event. The authors did not find any significant difference in functional recovery between the two syndromes in the first 6 months after injury. CCS patients showed higher scores in ambulatory-related assessments than BSS patients, but this difference did not reach statistical significance; with regard to daily life independence and specifically to self-care, CCS patients presented with lower values at first evaluation, but then showed comparable outcomes to those of BSS patients. Compared with the present study, Wirz included fewer patients who were examined at only two reference time points. Furthermore, CCS was only compared with another very rare spinal syndrome, thus lacking a comparison with the majority of iCSCI. Another study[34]

examined the data of 248 patients with incomplete tetraplegia, extracted from the EMSCI database, and divided into three groups: non-CCS (UEMS ≥ LEMS), intermediate-CCS (UEMS = (1–9 points) < LEMS) and CCS (UEMS = (≥9 points) < LEMS). The authors reported that good neurological and functional recovery of these patients was not correlated with CCS but rather with AIS at admission. However, the patients from the three groups were not comparable with respect to NLI, and evaluation of walking was based only on one item of SCIM; while in the present study, a more detailed evaluation was applied to assess different aspects of walking. Compared with previous studies, our analysis has several strengths: it is a prospective study with the largest number of patients with CCS. Comparison with iCSCI patients is not confounded by varying age, severity or NLI between groups and full ISNCSCI and functional datasets were obtained by trained examiners and classified by a validated computer algorithm.[21] The study also has some limitations due to the nature of the database. Compared with previous studies, we were not able to analyze the frequency and impact of complications, the length of acute and rehabilitation stay, and the discharge dispositions, because these data were not collected. In addition, based on the data available, it is not possible to compare low-energy and high-energy impact lesions to discover possible differences in outcome. Finally, although multicentric, the EMSCI data mostly comes from European countries. It would be interesting to compare these data with data from USA or Asia with possible differences in demographics and clinical features of the patients. Conclusions Our results provide important findings for clinical and rehabilitation aspects of incomplete cervical SCI. As CCS is becoming increasingly frequent, present data are important to establish the prognosis of these patients and provide resources needed during and after rehabilitation. Due to the particular self-care deficit of CCS patients, it is important to conceive specific rehabilitation programs aimed at improving upper limb and hand recovery. According to the health policy of some European countries, patients with minor SCI trauma (AIS D, i.e. the majority of patients of this study) do not have access to specialized

SCI centers despite their evident deficits in self-care. Among them are a considerable group of CCS patients, who by this policy are denied specifically efficient rehabilitation. Finally, it will be important to account for the different clinical presentations and recovery profiles of CSS and iCSCI to model their prognosis and thus allow inclusion of these special spinal syndromes in clinical trials.

Table 1

		CCS (n=110)	iCSCI (n=110)
Mean age at injury (SD)		54.8 (15.8)	54.9 (16.2)
NLI	C1	3 (3%)	3 (3%)
	C2	6 (5%)	6 (5%)
	C3	12 (11%)	12 (11%)
	C4	56 (51%)	56 (51%)
	C5	26 (24%)	26 (24%)
	C6	7 (6%)	7 (6%)
AIS	C	26 (23.6%)	26 (23.6%)
	D	84 (76.4%)	84 (76.4%)

Table 1. Demographic and clinical features of the patients with CCS and TI.

Abbreviations: SD standard deviation, NLI neurological level of injury, AIS American Spinal Injury Association Impairment Scale

Table 2

		T0	T1	T2	P at To	P at T1	P at T2
		Mean (SD)	Mean (SD)	Mean (SD)			
Total motor scores	**CCS**	62.9 (19.6)	82.4 (15.3)	87 (12.6)	0.63	0.407	0.829
	TI	64.4 (25.7)	80.3 (20.1)	86.4 (16.1)			
Upper extremity motor scores	**CCS**	**22.7 (10.6)**	**36.9 (10)**	**40.5 (7.8)**	**0.000**	**0.009**	**0.046**
	TI	**32.7 (12.2)**	**40.4 (9.8)**	**43.1 (8)**			
Lower extremity motor scores	**CCS**	**40.2 (9.7)**	**45.5 (6.3)**	**46.5 (5.6)**	**0.000**	**0.000**	**0.012**
	TI	**31.7 (15.5)**	**40 (12.4)**	**43.2 (9.4)**			
SCIM self care	**CCS**	**3.6 (5.2)**	**11.1 (7.2)**	**13.7 (6.2)**	**0.000**	**0.000**	**0.010**
	TI	**7.3 (7.0)**	**15 (6.3)**	**16.5 (5.7)**			
SCIM respiration and sphincter management	**CCS**	17.1 (9.4)	30.6 (10.7)	33.6 (8.8)	0.89	0.814	0.781
	TI	19.6 (11.9)	31.1 (11.2)	33.0 (10.6)			
SCIM mobility	**CCS**	**7.8 (10.9)**	27.0 (13.8)	32.2 (11.3)	**0.044**	0.661	0.392
	TI	**11.3 (13.4)**	26.1 (13.9)	30.3 (13.2)			
SCIM mobility indoors	**CCS**	3.1 (3.7)	7.7 (3.3)	8.7 (2.5)	0.126	0.809	0.585
	TI	3.9 (4.0)	7.8 (3.5)	8.4 (3.2)			
SCIM mobility outdoors	**CCS**	**4.7 (7.5)**	19.2 (10.9)	23.4 (9.1)	**0.036**	0.527	0.363
	TI	**7.3 (10.0)**	18.2 (11.0)	21.8 (10.3)			
SCIM total	**CCS**	**28.6 (23.3)**	68.8 (29.8)	79.6 (24.2)	**0.011**	0.410	0.936
	TI	**38.2 (30.7)**	72.2 (30.2)	79.9 (28.4)			
WISCI	**CCS**	4.7 (7.7)	14.4 (7.7)	16.3 (6.5)	0.337	0.446	0.210
	TI	5.8 (8.0)	13.5 (7.9)	14.7 (7.7)			
10MWT	**CCS**	25.9 (23.9)	14.5 (12.7)	13.8 (12.3)	0.395	0.623	0.578
	TI	21.4 (20.6)	15.9 (19.7)	12.6 (11.1)			
6MWT	**CCS**	190.9 (179.0)	349.8 (175.7)	387.4 (159.3)	0.989	0.501	0.307
	TI	191.5 (209.4)	327.7 (208.4)	350.7 (201.4)			

Table 2. Comparison of the two populations at the three time points

p refers to the comparison between CCS and iCSCI at T0, T1 and T2.

Abbreviations: SD standard deviation, SCIM Spinal Cord Independence Measure, WISCI Walking Index for Spinal Cord Injury, 10MWT 10-m walk test, 6MWT 6-min walking test. Statistically significant values are in bold.

Table 3

		Improvement T1-T0	Improvement T2-T1	Improvement T2-T0	P at T1-T0	P at T2-T1	P at T2-T0
		Mean (SD)	Mean (SD)	Mean (SD)			
Total motor scores	**CCS**	20.6 (13.3)	4.9 (12.3)	23.6 (14.5)	0.11	0.52	0.48
	iCSCI	17.6 (13.7)	3.9 (4.3)	21.7 (16.9)			
Upper extremity motor scores	**CCS**	**14.5 (7.9)**	3.7 (6.2)	**16.8 (8.9)**	**0.001**	0.09	**0.001**
	iCSCI	**8.3 (6.6)**	2.2 (2.6)	**10.5 (8.3)**			
Lower extremity motor scores	**CCS**	**6.2 (6.6)**	**0.9 (2.1)**	**6.8 (7.2)**	**0.005**	**0.02**	**0.01**
	iCSCI	**9.4 (9.4)**	**2 (2.9)**	**10.7 (10.4)**			
SCIM self care	**CCS**	7.7 (6.1)	2.6 (2.5)	10.2 (6.5)	0.7	0.6	0.15
	iCSCI	7.9 (6.1)	1.6 (2.9)	9.2 (6.9)			
SCIM respiration and sphincter management	**CCS**	13.3 (10.2)	2.3 (3.2)	15.9 (10.9)	0.5	0.3	0.9
	iCSCI	12.4 (10.6)	2.1 (6.1)	14.6 (11.9)			
SCIM mobility	**CCS**	**18.8 (12.4)**	5.1 (5.4)	24.4 (14.4)	**0.044**	0.661	0.392
	iCSCI	**14.9 (11.8)**	4.2 (6.3)	19.1 (14.3)			
SCIM mobility indoors	**CCS**	4.7 (3.7)	1 (1.1)	5.6 (3.9)	0.7	0.2	0.9
	iCSCI	3.9 (3.8)	0.6 (1.3)	4.5 (4)			
SCIM mobility outdoors	**CCS**	**14,4 (9.9)**	4.2 (4.7)	18.4 (11.2)	**0.02**	0.5	0.7
	iCSCI	**10.8 (9.5)**	3.6 (5.4)	14.7 (11.3)			
SCIM total	**CCS**	40.1 (25.4)	9.4 (9.1)	49.4 (26.5)	0.2	0.4	0.7
	iCSCI	34.1 (26.1)	7.7 (14.9)	41.7 (30.3)			
WISCI	**CCS**	**9.8 (7.9)**	1.8 (4.5)	11.6 (8.3)	**0.01**	0.4	0.25
	iCSCI	**7.7 (7.6)**	1.2 (2.1)	8.9 (8)			
10MWT	**CCS**	**11.4 (12.9)**	0.7 (42.7)	12.1 (12.3)	**0.03**	0.623	0.578
	iCSCI	**5.5 (9.6)**	2.3 (6.7)	10.2 (11.1)			
6MWT	**CCS**	159 (187.6)	37.7 (72.4)	196.8 (197.4)	0.04	0.2	0.09
	iCSCI	136.2 (172.5)	23.1 (77.3)	159.7 (177.2)			

Table 3. Comparison of the two populations improvements between the different time points.

p refers to the comparison between CCS and ICSCI at T1 vs T0, T2 vs T1 and T2 vs T0.

Abbreviations: SD. Standard Deviation; SCIM. Spinal Cord Independence Measure; WISCI. Walking Index for Spinal Cord Injury; 10MWT. Ten Meters Walk Test; 6MWT. Six Minutes Walking Test.

Figure 1: Flow chart of the selection of cases

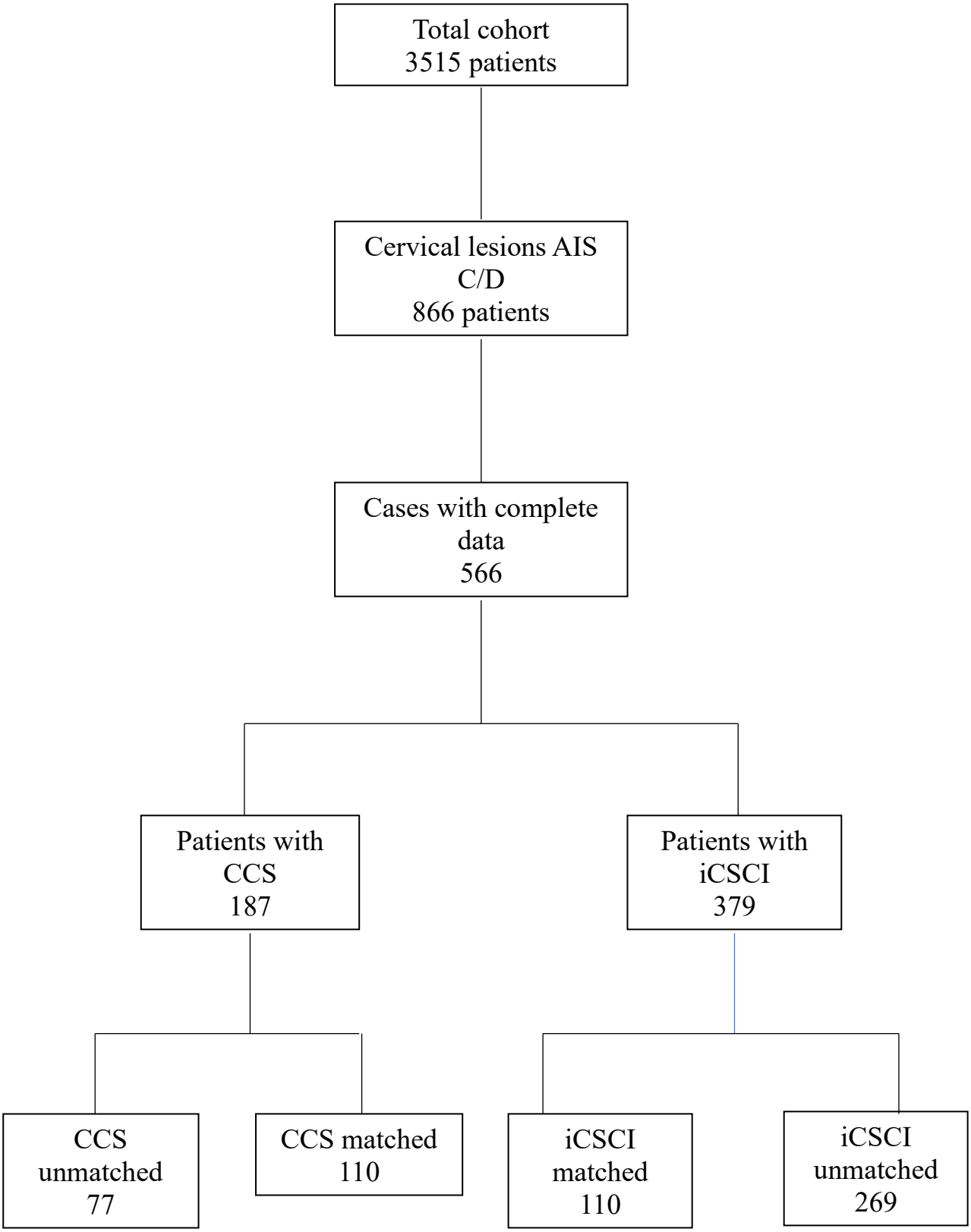
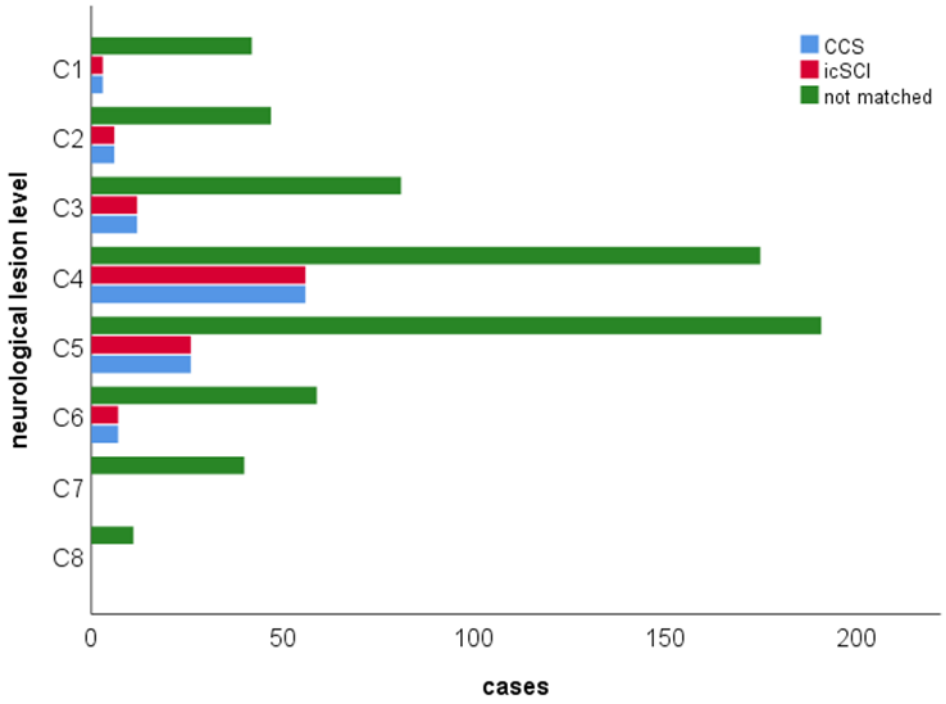


Figure 2

A



B

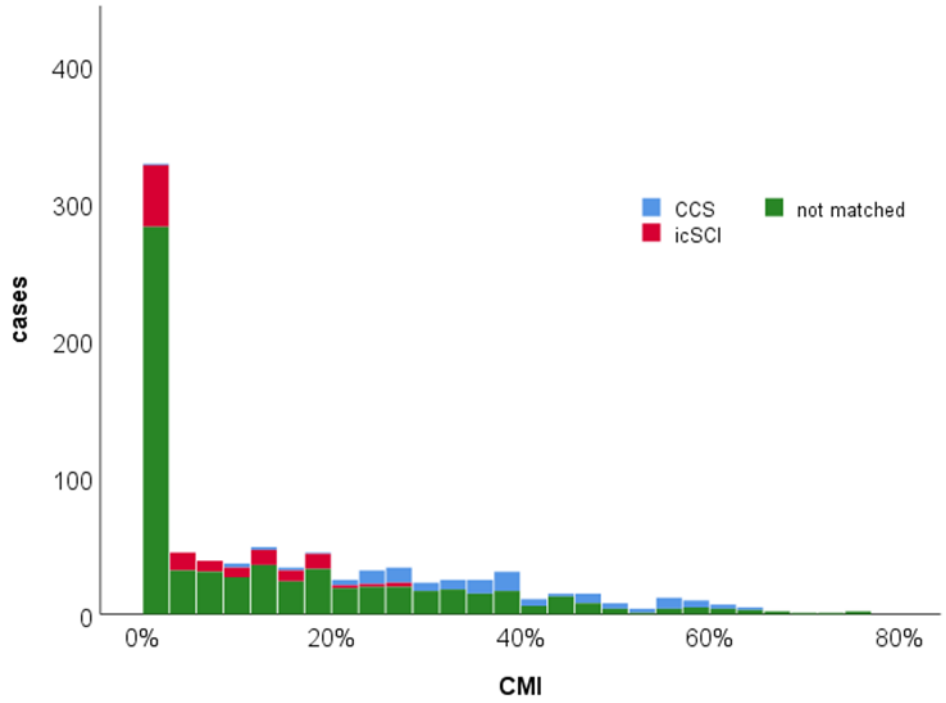


Figure 2A, B: Distribution of matched (CSS, iCSCI) cases with respect to NLI (A) and CMI (B)

Figure 3

Figure 3 A

Figure 3 B

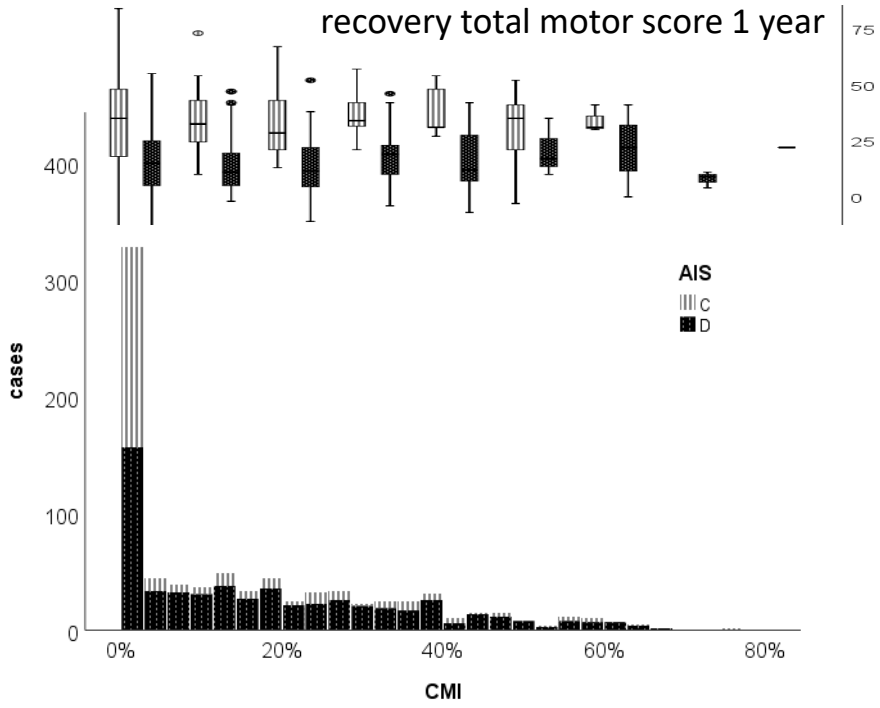


Figure 3A, B: Distribution of total motor score recovery at 1year (AIS C and D, respectively) over CMI (A) and distribution of AIS over CMI (B).

Figure 4

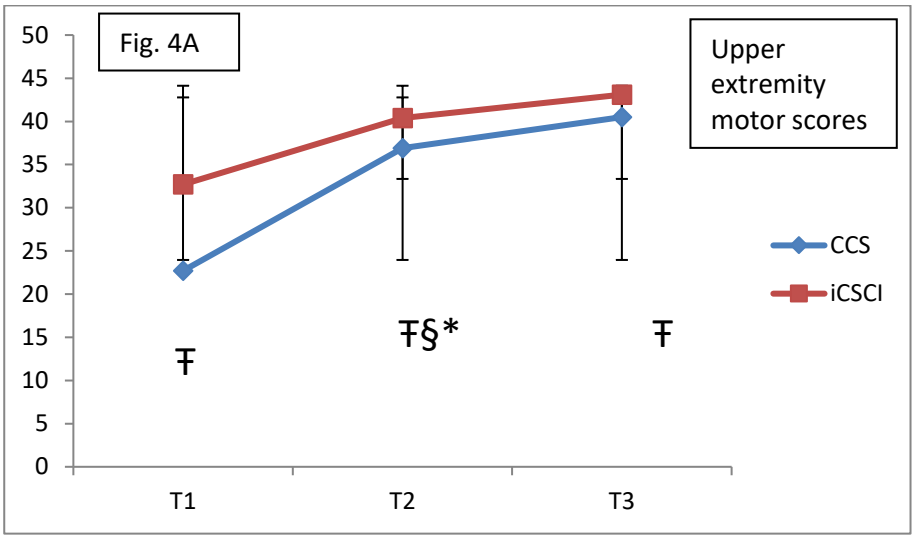


Fig. 4A
Upper extremity motor scores
50
45
40
35
30
25
20
15
10
5
0
T1
T2
T3
Ŧ
Ŧ§*
Ŧ
CCS
iCSCI

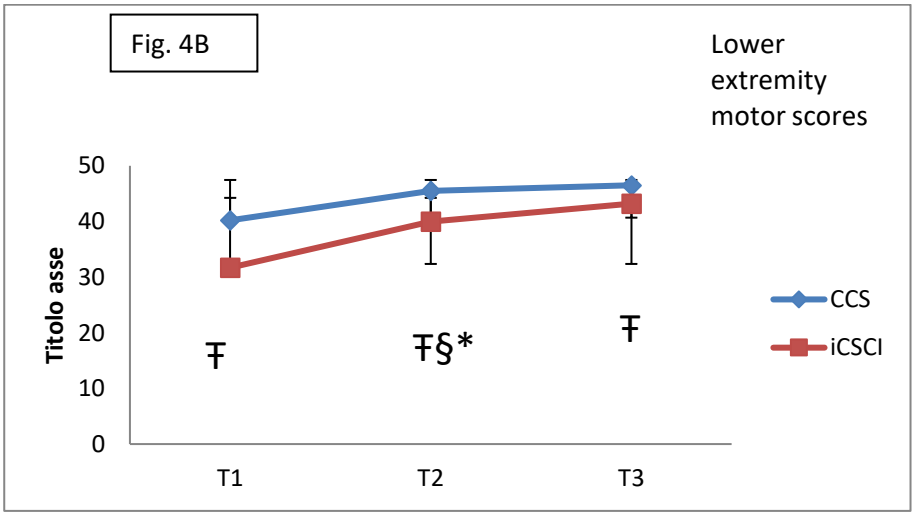


Fig. 4B
Lower extremity motor scores
Titolo asse
50
40
30
20
10
0
T1
T2
T3
Ŧ
Ŧ§*
Ŧ
CCS
iCSCI

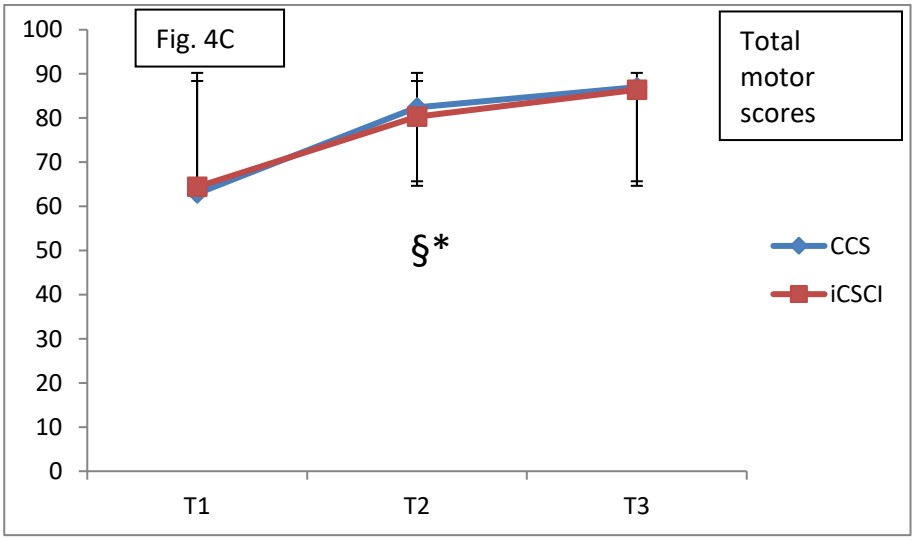


Fig. 4C
Total motor scores
100
90
80
70
60
50
40
30
20
10
0
T1
T2
T3
§*
CCS
iCSCI

Figure 4 A-C: Motor scores (A: UEMS, B: LEMS, C: Total); course of recovery for T1 (1 month), T2 (6 months), and T3 (12 months) after SCI

§: significant difference between times for CCS

*: significant difference between times for iCSCI

Ŧ: significant difference between CCS and iCSCI

Figure 5

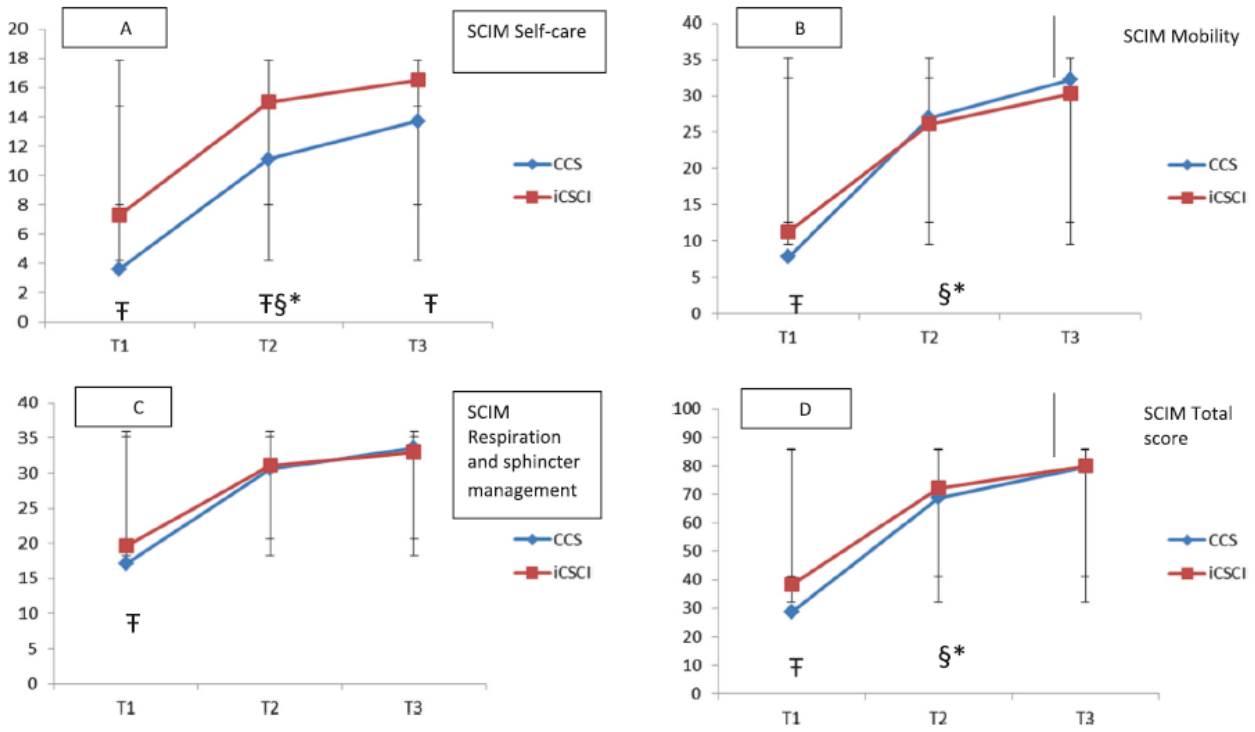


Figure 5: A-D: SCIM sub-score for self care (A), mobility (B), respiration and sphincter management (C) and total SCIM (D); course of recovery

Significance levels are given below the figures as:

§: significant difference between times for CCS

*: significant difference between times for iCSCI ("within" factor)

Ŧ: significant difference between CCS and iCSCI ("between" factor)

Figure 6

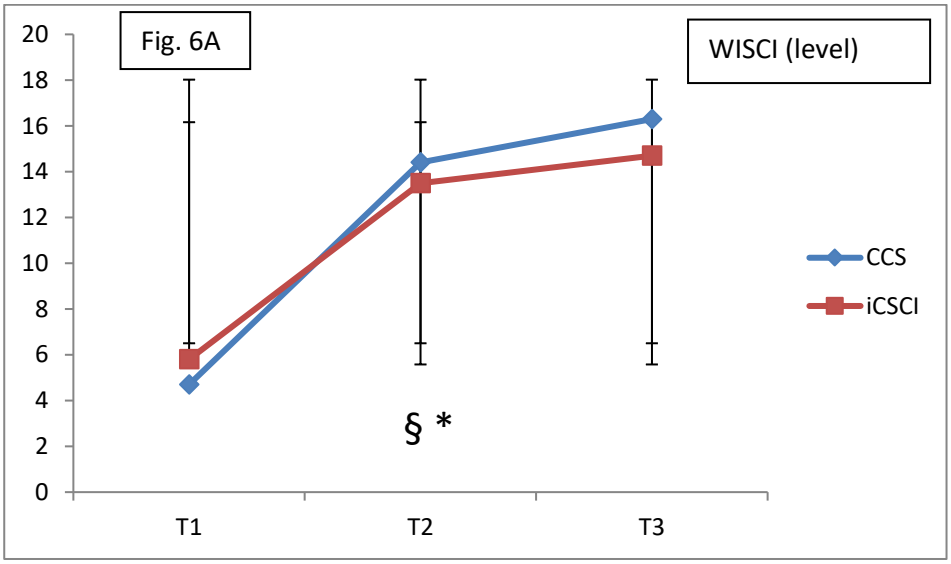


Fig. 6A
WISCI (level)
20
18
16
14
12
10
8
6
4
2
0
§ *
T1
T2
T3
CCS
iCSCI

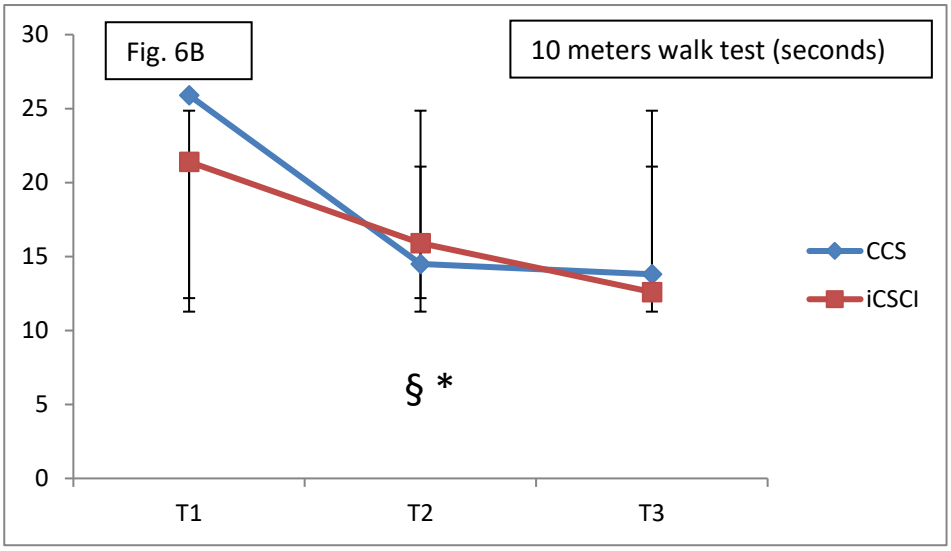


Fig. 6B
10 meters walk test (seconds)
30
25
20
15
10
5
0
§ *
T1
T2
T3
CCS
iCSCI

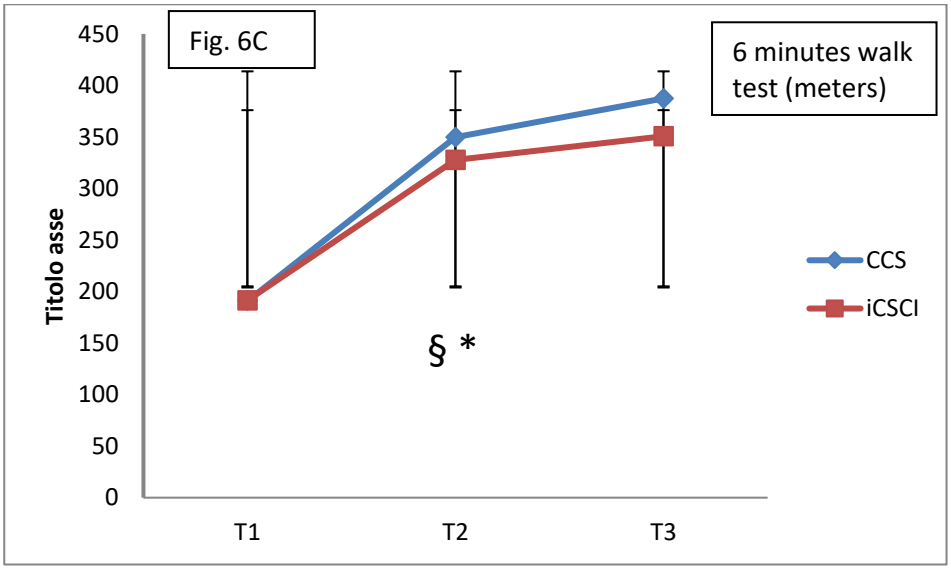


Fig. 6C
6 minutes walk test (meters)
Titolo asse
450
400
350
300
250
200
150
100
50
0
§ *
T1
T2
T3
CCS
iCSCI

Figure 6 A-C: Walking indices (A: WISCI, B: 10mWT, C: 6mWT); course of recovery. §: significant difference between times for CCS; *: significant difference between times for iCSCI

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Validation of the International Standards for Neurological Classification of Spinal Cord Injury in patients with non-traumatic SCI

This chapter is derived from the study:

Validity and reliability of the International Standards for Neurological Classification of Spinal Cord Injury in patients with non-traumatic spinal cord lesions.

Manuscript in preparation

Introduction

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) are at present the gold standard for the neurological evaluation of subjects with spinal cord injury (SCI).[1] This grading system allows the definition of the lesion level and severity and the classification of spinal syndromes (anterior spinal cord syndrome, Brown- Sequard syndrome, etc.).[1]

The ISNCSCI represent a common language among all SCI professionals and constitute the main prognostic factor after a SCI. An early evaluation by the ISNCSCI (i.e. within 72 hours after a SCI) allows to predict the neurological and functional status at one year after a traumatic lesion and, consequently, it allows to counsel patients' about their prognosis and to optimize the resources allocation during the acute phase of SCI treatment.[2,3] Furthermore, the ISNCSCI are widely used in the research setting both as evaluation tool and outcome measure for clinical trials aiming at evaluating the efficacy of new therapeutic interventions for SCI patients.[2,3]

Since 1982 there have been several versions of the ISNCSCI and all these versions have been validated with regard to validity, reliability and repeatability.[1,4-11] Consequently, the use of the ISNCSCI has been endorsed by the International Spinal Cord Society and the American Spinal Injury Association.[12]

The ISNCSCI are widely used also for the evaluation and prognosis prediction of subjects with non-traumatic spinal cord lesions[13, 14], although there are not studies aiming at specifically evaluating the psychometric qualities of this measure for this specific population of subjects.[15] Non-traumatic spinal cord lesions represent a various group of pathologies with different presentation and evolution and are progressively becoming more and more frequent and relevant in the Western Word. Although the incidence and prevalence of non-traumatic SCI are not perfectly known because of the paucity of dedicated studies, the incidence is calculated to be between 6 and 76 new cases

per million per year.[16] In some studies,[13,17] non-traumatic SCIs represent up to 60% of all new admission for rehabilitation.

Aim of the study is to evaluate the psychometric characteristics of the ISNCSCI in a population of subjects with non-traumatic SCI.

Materials and methods

All patients with non-traumatic SCI consecutively admitted to three Italian SCI centers have been enrolled in the study.

Inclusion criteria

- Non-traumatic SCI in the acute / subacute / chronic phase
- Any level and severity (ASIA Impairment) of injury
- Age over 18 years
- Cognitive conditions that allow collaboration in the exam

Exclusion criteria

- Dementia
- Outcomes of severe head injury with residual cognitive impairment
- Injury to the peripheral nervous system that may affect the evaluation of ISNCSCI
- Injury of limbs (for example fractures) or of other organs that could affect the evaluation of ISNCSCI

The patients underwent to:

- Recording of demographic and anamnestic data. As regards the beginning of the lesion, reference will be made to the appearance of the first symptoms, especially with regard to the degenerative pathologies of the spine with spinal cord involvement (spondylotic myelopathy) and neoplastic pathologies.

- Evaluation of neurological conditions according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Revision 2011)[1] with registration of right and left motor and sensory level and of the Neurological Level of Injury (NLI), of the total motor score (MS), of upper limbs (UEMS) and lower limbs (LEMS) motor scores, light touch and pin prick sensory scores. This assessment was carried out by two different experienced examiners in each center, 48-72 hours apart. One of the two examiners also assessed the functional status of the patients through the Spinal Cord Independence Measure (SCIM) version 2 or 3.[18]
- The patients were evaluated at the time of admission and at discharge, with the possibility of repeating the evaluation also during rehabilitation stay.

Statistics

Descriptive statistics: mean and standard deviation for continuous data; numbers and percentages for non-continuous data.

With regard to the NLI and the ASIA impairment, as these parameters are not of a numerical nature, they have been transformed into numbers. For the NLI the level C1 corresponds to 1, and the level S4-5 to the number 29. For the AISA impairment grade A correspond to 1 and grade E to 5.

Inter-rater reliability, i.e. the correlation between the assessments of the two examiners was assessed for the total Motor Scores, UEMS, LEMS, Light Touch and Pin Prick scores through the Spearman and Intraclass-Correlation-Coefficient (ICC) tests. Cronbach's Alfa was used to evaluate the internal consistency of the various components of the ISNCSCI. For motor and sensory scores, we also compared the data of the two examiners by means of Student' T test for paired samples to evaluate if there was any significant difference.

To establish the level of agreement between the two examiners regarding the levels of injury (Neurological Level of Injury, left and right sensory and motor level of injury) we used the Kappa

agreement analysis. Furthermore, for the assessment of the levels, we compared the levels established by the two examiners, counting, in cases where the assessments differed, how many levels the difference was (1 level, 2 or more levels).

As currently there is no gold standard for the neurological evaluation of subjects with SCI other than the ISNCSCI, we have evaluated the convergent construct validity of the standards through a correlation with the functional status of the patients (assessed with the SCIM). This correlation was performed by means of Spearman test between the total motor scores, the upper and lower limbs and the total SCIM score as well as the subscores "self-care" and "mobility".

All analyses were performed with SPSS 22.

Results

One hundred and forty patients (92 males, 48 females) were evaluated. Mean age was 59.6 ± 15.6 years (range 15-86). The level of the lesion was cervical in 30 patients, thoracic in 78 patients and lumbar in 32 patients. As for the ASIA Impairment Scale, 34 patients had an AIS A, 11 patients an AIS B, 33 patients and AIS C and 62 patients an AIS D. Fifty-two patients had an ischemic lesion, 34 a spondylosis of the spine with involvement of the nervous structures, 29 a neoplastic pathology and 25 an inflammatory / infectious pathology.

One hundred and three patients underwent only 1 examination upon admission, while the remaining 37 underwent 2 or more assessments for a total of 182 evaluations. Of these 182 evaluations, 169 had the ISNCSCI performed by 2 examiners and 168 had the SCIM. In 13 evaluations the ISNCSCI were performed by 1 examiner and all 13 had the SCIM. Therefore, the statistics between the different components of the ISNCSCI were performed in 169 evaluations and the correlations between the motor scores and the SCIM scores were run in 182 evaluations.

Inter-rater reliability gave very high results for motor scores (r between 0.931 - 0.982; p <0.001); the correlation for sensory scores was lower, but still good and significant (r = 0.905 for light-touch and 0.902 for pin-prick; p <0.001) (Table 1). Cronbach's alpha highlighted an excellent internal correlation of the ISNCSCI (Table 1). The comparison of the data of the two examiners did not show any significant difference (Table 2)

The agreement between the examiners regarding lesion levels was good and significant for all assessments (k = 0.609; p <0.001); also in this case the agreement was better for the motor part than the sensitive part of the ISNCSCI (Table 3). The Neurological Level of Injury was the same in 104/169 assessments (61%) and differed by 1 level in 35 subjects (21%) and by 2 or more levels in 30 subjects (18%); the right sensory level was the same in 102 evaluations out of 169 (60%) and differed by 2 or more levels in 37 evaluations (22%); the left sensory level was the same in 103/169 cases (61%) and differed by 2 or more levels in 30 evaluations (18%); the right motor level (assessed only in segments with key muscles) was the same in 30 out of 50 assessments (60%) and differed by 2 or more levels in 10 (20%); the left motor level was the same in 37/50 evaluations (74%) and differed by 2 or more levels in 8 (16%) (Table 4). As for the severity of the injury (AIS grade), the agreement between the two examiners was excellent (k = 0.968; p <0.001) (Table 3). The AIS grade was the same in 161/169 evaluations (95%) and differed by 1 grade in the remaining 8. All these patients were assessed as AIS C by 1 examiner and as D by the other.

In the entire set of assessments, the correlation between the SCIM self-care subscale and the upper limb motor score (UEMS) was moderate, although significant (r = 0.407; p <0.001). The correlations between the lower limb motor score (LEMS) and the SCIM mobility subscale and between the total motor score and the total SCIM score were good and significant (r = 0.666 and r = 0.683 respectively; p <0.001) (Table 5). The correlations improved by considering tetraplegic and paraplegic patients

separately, dividing the assessment at the time of admission from the follow-up one and dividing incomplete and complete lesions (Table 5).

Discussion

The purpose of this study was to evaluate the inter-rater reliability of the ISNCSCI in patients with non-traumatic spinal cord lesions, through the data collected by two trained examiners, and its implications in clinical practice and in clinical studies with serial evaluations and with more than one examiner. Overall, our study showed strong agreement for both the motor and sensory component of the ISNCSCI.

For total ISNCSCI scores, the agreement was slightly better for the motor component than the sensory component; however, all agreements were substantially good (all ICC > 0.90). As regards the NLI and the degree of AIS grade, the Kappa coefficient between the two examiners showed a good correlation with regard to the NLI and the sensory and motor levels (k> 0.60), and excellent for the AIS grade (k = 0.968). In our study the NLI between the two examiners was comparable in 104/169 assessments and differed by 1 level in 35 assessments and by 2 or more levels in the remaining 30.

At present, there is no study evaluating the psychometric properties of ISNCSCI in subjects with non-traumatic spinal cord injuries.[15] Therefore, we can compare our results only with previous studies evaluating these characteristics in patients with traumatic SCI. However, overall, the results of our study are in line with those reported for traumatic SCI.

Cohen and Bartko [19] examined the reliability of the standards with 29 examiners from 19 centers and demonstrated very strong agreement for the ASIA scores with ICC values between 0.96 for light-touch and pin-prick scores and 0.98 for the motor score. Marino [20] performed a study with 16 evaluators and 16 subjects with and reported inter-rater ICC values of 0.97 for motor scores, 0.96

for light-touch and 0.88 for pin-prick. Jonsson [21] assessed the inter-rater reliability of the standards in 23 patients with incomplete SCI and found Kappa values between 0 and 0.83 for the pin-prick, between 0 and 1 for the light-touch and from 0 to 0.89 for motor scores. Furthermore, they found fair to poor agreement for the neurological levels. Savic [22] examined the inter-rater reliability of ISNCSCI, evaluating 45 patients through 2 expert examiners. The results of this study showed that the total ASIA scores had a very strong correlation between the two examiners with ICC values greater than 0.99 for motor and light-touch scores and 0.97 for pin- prick. Regarding the level of the lesion, our cohort showed lower levels of agreement between the two examiners compared to Savic's study. As in Savic's study, lesion levels differ in most cases for one segment and only in a few cases does the sensory level differ by 2 or more segments. The percentage of concordance is comparable to what reported by Schuld[23] at least with regard to motor levels and is better for the AIS grade. Difference with previous studies could be explained by different methodologies (for example the number of examiners and patients), the experience of the examiners and the different composition of the cohorts of patients as some studies [20, 22] included approximately 50% of complete lesions (compared to 18% of the present series) which are easier to evaluate.[24]

Furthermore, we evaluated the validity of the convergent construct of the ISNCSCI by comparing them with a functional evaluation based on the SCIM. Within the entire cohort analyzed and considering all the assessments pooled together, the correlations were moderate to good, although significant. The correlation was weaker for the SCIM self-care score and upper limb motor score (UEMS) (r = 0.407) compared to the other scores. We therefore carried out more detailed analyzes by dividing the patients according to the level of injury (paraplegia and tetraplegia) and the evaluation times (first evaluation and follow-up ones) obtaining slightly better correlation scores (Table 5).

Also in this case, the only possible comparison is that with previous studies performed in patients with traumatic SCI. There are numerous articles that evaluate the relationship between ISNCSCI and functional status, using different methodologies and outcome measures. Overall, the results of these studies are comparable with ours, showing a moderate to good correlation between the ISNCSCI and functional status as assessed by the Quadriplegia Index of Function [25, 26], the Modified Barthel Index [27, 28], the Functional Independence Measure [27, 29] and the SCIM [30]. As demonstrated by Wirth [30], functional improvement partly occurs independently of neurological recovery. Subjects with complete motor SCI recover skills in SCIM unrelated to changes in motor scores. This improvement is believed to be due to a compensation mechanism (learning new movement strategies, including the use of new aids).

Limitations

Our study has some limitations. First of all, we have not evaluated the agreement between the two examiners regarding each individual myotome and dermatome.[19,20] The second limitation is that we have not evaluated the prognostic value of ISNCSCI. This is related to the fact that for most of our patients, in particular those with spondylotic myelopathies and with spinal cord dysfunction due to tumors, it is impossible to determine the beginning of the lesion and therefore and to perform the first evaluation in the right time. The only subjects in which it is possible to know exactly the beginning of the pathology are those with ischemic SCIs; unfortunately, the number of patients with ischemic SCI in our sample is too low to evaluate the prognostic value. The third limitation is that we have not assessed intra-rater reliability (i.e. the relationship between the two assessments made by the same examiner). The latter test requires, in fact, a time of at least 7-15 days between the two assessments to avoid the learning effect for both the examiner and the patients. Since all patients in our study had an acute / subacute lesion and underwent intensive rehabilitation, an improvement

in their status is expected in 7-15 days, making the relationship between the two assessments poorly reliable.

Conclusions

Our work fills a gap in the assessment of spinal cord injuries, demonstrating that the ISNCSCI are a valid and reliable assessment tool for patients with non-traumatic SCI.

ISNCSCI used in a population of subjects with non-traumatic SCI have shown to have roughly the same psychometric characteristics that they have in patients with traumatic injury.

With regard to the use in clinical trials cautions should be used if changes in the motor and sensory level are used as outcome measures with more than one examiner, because the change in level could be due to the variability between the two evaluators rather than to the efficacy of the treatment.

Table 1: Inter-rater correlations and internal consistency

	Spearmann r	p	ICC	p	Alfa Cronbach
MS Tot	0,965	0,001	0,954	0,001	0,954 (0.937-0.966)
UEMS	0,931	0,001	0,995	0,001	0,995 (0.993-0.996)
LEMS	0,982	0,001	0,995	0,001	0,995 (0.993-0.996)
LL	0,905	0,001	0,964	0,001	0,964 (0.951-0.957
PP	0,902	0,001	0,941	0,001	0,941 (0.921-0.957)

Table 2: Comparison of the means of the motor and sensory scores

	Examiner 1	Examiner 2	Differences between the two groups	P value
	Mean (SD)	**Mean (SD)**	**Mean (ranges)**	
MS	69.1 (22.1)	68.9 (23.9)	0.2 (-1.3 – 1.6)	0.8
UEMS	46.4 (9.4)	46.4 (9.4)	0.6 (-0.3 – 0.14)	0.6
LEMS	22.7 (18.5)	22.6 (18.6)	0.15 (-0.25 – 0.5)	0.5
LT	87.1 (21.3)	87.8 (21.2)	0.76 (-1.9 – 0.44)	0.2
PP	84.9 (22.3)	86,1 (23.7)	1.11 (-2.7 – 0.53)	0.2

Table 3: Kappa agreement for the neurological levels and AIS grade

	Kappa	**p**
NLI	0,609	< 0,001
sNLIdx	0,633	< 0,001
sNLIsin	0,601	< 0,001
mNLIdx	0,727	< 0,001
mNLIsin	0,801	< 0,001
AIS	0,968	< 0,001

Table 4: Agreement between levels of injury and AIS grade

AIS grade n. 169			NLI n.169			RS NLI n.169			LS NLI n. 169			Motor NLI											
												Total evaluations n. 169						Evaluations with key muscles available (C5-T1 and L2-S1) n. 50					
												RM NLI			LM NLI			RM NLI			LM NLI		
diff	n.	%	diff	n.	%	diff	n.	%	diff	n.	%	diff	n.	%	diff	n.	%	diff	n.	%	diff	n.	%
0	161	95	0	104	61	0	102	60	0	103	61	0	95	56	0	103	61	0	30	60	0	37	74
1	8	5	1	35	21	1	30	18	1	36	21	1	39	23	1	31	16	1	10	20	1	5	10
≥2	0	0	≥2	30	18	≥2	37	22	≥2	30	18	≥2	45	31	≥2	35	23	≥2	10	20	≥2	8	16

NLI: Neurological Level of Injury

RS NLI: Right sensory NLI

LS NLI: Left sensory NLI

RM NLI: Right motor NLI

LM NLI: Left motor NLI

AIS: ASIA Impairment Scale

Table 5: Correlations between ISNCSCI motor scores and SCIM scores

	Total cohort		First evaluations		Further evaluations		Tetraplegics		Paraplegics	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
UEMS/SCIM Self Care	0,407	0,001	0,377	0,001	0,677	0,001	0,659	0,001		
LEMS/SCI M Mobility	0,666	0,001	0,625	0,001	0,718	0,001	0,591	0,05	0,691	0,001
MS/SCIM Total Score	0,683	0,001	0,644	0,001	0,798	0,001	0,648	0,05	0,717	0,001

MS: total motor score

UEMS: upper extremities motor score

LEMS: lower extremities motor scores

SCIM: Spinal Cord Independence Measure

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Conclusions

The knowledge of spontaneous clinical evolution and the availability of models to predict the recovery of functional outcomes play a key role in the design of a successful rehabilitative plan after SCI. Reliable information about prognosis constitutes the basis to counsel patients and caregivers, to establish shared rehabilitative aims between patient and rehabilitation team and to timely and successfully plan discharge and social reintegration.[1]

The complexity and heterogeneity of this clinical condition is responsible for the so called “clinical–radiological paradox”, phenomenon referring to the substantial differences in functional recovery observed in patients with comparable spinal cord lesions.[2]

Therefore, there is an urgent need for valid instruments to evaluate patients with SCI, as well as for rigorous studies to define the clinical evolution and to identify predictive models in the different clinical categories.[3]

In this context, this project has deepened a few important aspects related to clinical evolution and prognosis of patients with traumatic and non-traumatic SCI.

In conclusion, the project indicates that:

- The addiction of neurophysiological measurements to clinical parameters improves the prediction of global functional outcome after traumatic cervical SCI;
- Our prediction models for bladder outcome display high performance also in patients affected by ischemic SCI;
- Bowel outcome after traumatic SCI is predictable and we have provided a valid model;
- The prediction model for bowel outcome after traumatic SCI is valid in an independent sample of patients with traumatic SCI;

- The prediction model for bowel outcome displays high performance also in patients affected by ischemic SCI;
- Patients with central cord syndrome have poorer outcomes of self-care ability in comparison with patients with other incomplete cervical SCI;
- The International Standards for Neurological Classification of Spinal Cord Injury is a valid and reliable tool for the assessment of patients with non-traumatic SCI.

The results of this project may have positive consequence in the care of patients with SCI and in the design of future clinical trials in this research field.

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