

Prediction of bowel management independence after ischemic spinal cord injury

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**Abstract:** **BACKGROUND:** Ischemic spinal cord injury (SCI) belongs to the heterogeneous group of non-traumatic SCI, while the course of sensorimotor and functional recovery is comparable to traumatic SCI. Recently, we derived from data of patients with traumatic SCI a valid model to predict an independent and reliable bowel management one year after SCI. **AIM:** To evaluate the performance of this model to predict an independent and reliable bowel management one year following ischemic SCI. **DESIGN:** Prognostic study - observational study. **SETTING:** European Multicenter Study about Spinal Cord Injury (EMSCI) ClinicalTrials.gov: NCT01571531. **POPULATION:** One hundred and forty-two patients with ischemic SCI of various level and severity of injury. **METHODS:** The prediction model relied on a single predictor collected within 40 days from injury, the International Standards for Neurological Classification of Spinal Cord Injury total motor score. Bowel outcome one year after SCI derived from the dichotomization of the Spinal Cord Independence Measure (SCIM) item 7 scores. We defined a positive outcome as independent bowel management with regular movements and appropriate timing with no or rare accidents (score of 10 in SCIM version II and score of 8 or 10 in version III). **RESULTS:** The model showed a fair discrimination with an area under the receiver operating characteristic (ROC) curve of 0.780 (95% confidence interval=0.702-0.860). In addition, the model displayed an acceptable accuracy and calibration. **CONCLUSIONS:** The study extends the validity of our rule to patients with ischemic SCI, thus providing the first model to predict an independent and reliable bowel management in this population. **CLINICAL REHABILITATION IMPACT:** The model may be employed in clinical practice to counsel patients, to define the rehabilitation aims and to estimate the need of assistance after discharge, as well as in the research field for the optimization of patients' allocation in the design of future clinical trials.

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# Prediction of bowel management independence after ischemic spinal cord injury

Running title: Bowel outcome prediction after ischemic SCI

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## **Abstract**

**Background:** Ischemic spinal cord injury (SCI) belongs to the heterogeneous group of non-traumatic SCI, while the course of sensorimotor and functional recovery is comparable to traumatic SCI. Recently, we derived from data of patients with traumatic SCI a valid model to predict an independent and reliable bowel management one year after SCI.

**Aim:** To evaluate the performance of this model to predict an independent and reliable bowel management one year following ischemic SCI.

**Design:** Prognostic study – observational study

**Setting:** European Multicenter Study about Spinal Cord Injury (EMSCI) ClinicalTrials.gov: NCT01571531.

**Population:** One hundred and forty-two patients with ischemic SCI of various level and severity of injury.

**Methods:** The prediction model relied on a single predictor collected within 40 days from injury, the International Standards for Neurological Classification of Spinal Cord Injury total motor score. Bowel outcome one year after SCI derived from the dichotomization of the Spinal Cord Independence Measure (SCIM) item 7 scores. We defined a positive outcome as independent bowel management with regular movements and appropriate timing with no or rare accidents (score of 10 in SCIM version II and score of 8 or 10 in version III).

**Results:** The model showed a fair discrimination with an area under the receiver operating characteristic (ROC) curve of 0.780 (95% confidence interval=0.702-0.860). In addition, the model displayed an acceptable accuracy and calibration.

**Conclusions:** The study extends the validity of our rule to patients with ischemic SCI, thus providing the first model to predict an independent and reliable bowel management in this population.

Clinical Rehabilitation Impact: The model may be employed in clinical practice to counsel patients, to define the rehabilitation aims and to estimate the need of assistance after discharge, as well as in the research field for the optimization of patients' allocation in the design of future clinical trials.

## **Introduction**

Data concerning epidemiology and spontaneous recovery of patients with non-traumatic spinal cord injury (SCI) are scarce, due to the lower incidence and the heterogeneity of these conditions in comparison with traumatic lesions [1]. However, the aging of global population increased the incidence and epidemiological relevance of non-traumatic SCI over the last decades, and we expect a progression of this trend in the future [1]. This epidemiological change entails a modification of patient population referring to SCI units and imposes an adaptation of the clinical approach, rehabilitative goals and support after discharge [2].

The prediction of functional outcomes after SCI plays a key role in the organization of the rehabilitative phase and in the achievement of a successful discharge [3]. In this context, it is mandatory to verify also in patients with non-traumatic SCI the performance of the prediction models usually applied in clinical practice, which are mainly derived from and validated in samples of patients with traumatic SCI [2].

Ischemia is a relevant etiology of SCI, accounting for 8 to 20% of non-traumatic SCI in Western Countries [1]. Like traumatic SCI, ischemic lesions derive from a single sudden event causing an acute spinal cord damage and the two populations display a similar course of neurological and functional recovery [4].

Our group has already demonstrated that the bladder outcome models derived from traumatic patients [5] are valid also when applied to patients with ischemic SCI [6]. Therefore, we hypothesized that other prediction models of functional outcomes derived and validated in cohorts of patients with traumatic SCI can be applied to ischemic SCI.

We have recently developed and validated a model to predict an independent and reliable bowel management one year after traumatic SCI [7, 8]. Aim of the present study was to

evaluate the performance of this model to predict bowel management independence one year after ischemic SCI.

## **Materials and methods**

### Patients

We considered for the present study data of all patients with ischemic SCI prospectively included in the European Multicenter Study about Spinal Cord Injury (EMSCI) ([www.emsci.org](http://www.emsci.org)) (ClinicalTrials.gov Identifier: NCT01571531). EMSCI is a multicenter database started in 2001, which collects neurological, neurophysiological and functional measures of patients with acute traumatic or ischemic SCI over the first year after SCI.

Inclusion criteria are: single event traumatic or ischemic para- or tetraplegia, possibility of execution of the first assessment within the first 6 weeks after SCI and capability to cooperate and express an informed consent.

The study conforms to the standards established by the Declaration of Helsinki and was approved by the local ethics committees of all participating centres. Before entering the study, patients were informed about the study procedures and provided written informed consent.

All EMSCI patients received a multidisciplinary rehabilitative treatment, including state-of-the-art management of neurogenic lower urinary tract and bowel dysfunction. However, the rehabilitative interventions are not standardized among the different EMSCI centers.

The EMSCI assessments include the evaluation of the neurological status according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) [9, 10] and the evaluation of independence in daily life activities through the Spinal Cord Independence Measure (SCIM) [11, 12].

Patients are evaluated per protocol in fixed time points after injury: 0–15 days (*very acute*), 16–40 days (*acute I*), 70–98 days (*acute II*), 150–186 days (*acute III*), and 300–400 days (*chronic*).

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

For the present analysis, we extracted the data of all patients with ischemic SCI with date of onset before April 2019, where the collection of one-year outcome was theoretically possible.

#### Prediction model

According to our previous study, a positive outcome was defined as independent bowel management with regular movements and appropriate timing with no or rare accidents (i.e. fecal incontinence less than twice a month) one year after SCI [7]. Bowel outcome was derived from the dichotomization of SCIM item 7 (sphincter management–bowel), an item focused on the evaluation of independence and reliability in bowel management. 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 [11, 12].

The prediction model was based on a single predictor, the ISNCSCI total motor score (*Mtot*) collected within 40 days from injury. This value derives from the sum of the strength scores of five key muscle for each limb and ranges from 0 to 100, with higher values indicating better strength [9, 10].

The equation to calculate probability (P) of independent and reliable bowel management one year after traumatic SCI is:

$$P = \frac{e^f}{1 + e^f}, \text{ where } f = \beta_0 + \beta_1 * M_{tot}$$

where  $\beta_0 = -2.25046$  is the intercept and  $\beta_1 = 0.0486938$  is the regression coefficient.

### Statistical analysis

Descriptive statistics were used to summarize the sample characteristics. Normality of data was assessed with Shapiro-Wilk test. To evaluate differences between patients with and without follow-up, we used Pearson Chi squared or Fisher exact test and Student t or Mann Whitney-U test.

To evaluate the model performance, we analyzed discrimination and calibration.

Discrimination refers to the model's ability to distinguish between subjects with and without the outcome (independent bowel management one year after SCI).

Discrimination was assessed with the area under the Receiver Operating Characteristic (ROC) curve, which plots the sensitivity (true positive rate) against 1 - (false positive rate) for consecutive cutoffs for the probability of the outcome. Strong performing models have larger area under the curve values: a perfect model making correct predictions for every subject has a value of 1 (perfect discrimination), whereas a useless model giving random predictions results in an area under the curve of 0.5 [13]. The area under the curve values are interpreted as follows: 0.9-1.0 excellent discrimination, 0.8-0.9 good discrimination, 0.7-0.8 fair discrimination, 0.6-0.7 poor discriminative ability. Discrimination is assumed to be useful if the area under the curve is  $\geq 0.75$  [14].

Calibration evaluates the agreement between the predicted and observed number of events. Calibration was assessed by visual inspection of calibration plot, Brier scores, Spiegelhalter z-test, calibration slope, and intercept and Hosmer-Lemeshow (HL) goodness of fit test [15]. Statistical significance was set at  $p < 0.05$ . The analyses were performed with STATA 13.1.

## Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

## Results

From EMSCI database we extracted data of 331 patients with ischemic SCI, but 189 (57%) were lost to follow-up. Therefore, the analysis was performed on data of 142 patients. Table I shows the clinical characteristics of patients, comparing the groups of patients with and without follow-up. No significant differences in demographic and clinical characteristics were found between the two groups.

The predictor was collected in the very acute phase in 8 (6%) patients, and in the acute I phase in 134 (94%). In the final study sample, 92 out of 142 (65%) patients reached an independent bowel management 1 year.

In the ROC analysis, the model showed an area under the curve of 0.780 (95% confidence interval=0.702-0.860) (Figure 1A) with an accuracy of 71%, a sensitivity of 96%, a specificity of 26%, a positive predictive value of 70% and a negative predictive value of 77%.

The calibration curve showed an intercept of -0.012 and a slope of 1.385; the Brier score was 0.177 (Spiegelhalter's z-statistic= -1.204; p=0.886) (Figure 1B), the Hosmer-Lemeshow test p-value was 0.14.

## **Discussion**

Our study confirms the validity of our prediction model of bowel management independence in patients with ischemic SCI, showing a fair performance in terms of accuracy, discrimination and calibration [16]. Although our model showed an acceptable discrimination, the discrimination capacity in the ischemic cohort was lower than reported in the traumatic samples of derivation and internal and external validation [7,8,17], but in line with previous validations of other prediction models in non-traumatic samples [2,6].

Ischemic SCI belongs to the heterogeneous group of non-traumatic SCI and different characteristics assimilate this pathology to the traumatic form: both etiologies derive from a single sudden event causing an acute spinal cord damage at a single level [18]. From a clinical point of view, recent studies showed controversial results in the comparison of sensorimotor and functional recovery after SCI of ischemic and traumatic etiology [19-21]. 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 patients with traumatic SCI [19-21]. A recent study using data derived from EMSCI demonstrated in two matched populations that the two spinal cord etiologies display a similar course of functional evolution [4]. Focusing on independence in bowel management, we observed in the present study that the percentage of patients with ischemic SCI who reach a positive outcome at one year is slightly higher in comparison with patients with traumatic SCI: 65% vs. 58%, respectively [7]. However, these data derive from non-matched populations: further studies are necessary to deepen the comparison of bowel function recovery in the two samples.

Points of strength of our study are the high number of patients included, the prospective and standardized collection of EMSCI data and the multicenter design, which reinforces the generalizability of our findings. To the best of our knowledge, our study considers one of the largest cohorts of patients with ischemic SCI ever analyzed regarding the evolution of bowel function. Moreover, our model is simple and rapid to apply in the clinical setting, relying on a single predictor, the ISNCSCI *Mtot*. This parameter was already identified as a predictor of independence in daily life activities at 1 year after SCI [22]. In line with previous studies [5-8], we evaluated the predictor in a relative wide temporal range, i.e. within 40 days of injury, including both very acute and acute I EMSCI timepoints. However, we cannot exclude an evolution of ISNCSCI *Mtot* in the course of the 40 days of this temporal range, especially for patients with incomplete injury. In the derivation study, the sensitivity analysis performed after exclusion of patients with predictor collected in the very acute time point, showed only a slight variation of the area under the curve, thus indicating a scarce influence of timing of predictor evaluation on model performance [7].

The ISNCSCI are a rigorous grading system for the assessment of patients with SCI, and their measurement properties in non-traumatic SCI patients have recently been validated [10]. The SCIM is a valid tool for the assessment of independence after SCI, and its usage has been suggested for future phase 3 clinical trials [20]. However, it is important to highlight that our measure of bowel outcome at one year, SCIM item 7, reflects the degree independence in bowel management and the achievement of a regular and reliable function, but does not give information regarding duration and modality of defecation. Thus, further studies are needed to add to the prediction specific parameters related to bowel function after SCI (e.g. need of pharmacological intervention, duration and modality of defecation) in order to better understand the evolution of bowel activity.

Moreover, further studies are necessary to evaluate patient's satisfaction with bowel outcome and quality of life, domains that are not captured from the evaluation with SCIM. As limitation of the study, we highlight that all EMSCI patients received a rehabilitative treatment, including state-of-the-art management of neurogenic lower urinary tract and bowel dysfunction. Nevertheless, the treatments were not standardized among the different EMSCI centers. We can therefore not exclude confounding by center effects. Finally, another limitation of our study is the high number of patients lost at 1-year follow-up. This, however, seems to be of limited relevance considering that the cohorts of patients with and without a 1-year follow-up did not differ in baseline characteristics.

In the ischemic sample, the model showed a low value of specificity, which implies that a low quote of patients who will not reach independence in bowel management is correctly classified. This aspect should be considered in the application of the model in clinical practice. The recovery of bowel function represents an urgent priority for patients with SCI, due to the high negative influence that neurogenic bowel dysfunction has on health, participation and quality of life [24,25].

However, to date there is scarce evidence concerning the protocols to adopt for the treatment of bowel problems and different treatment options are applied in sequence or combination, based on empirical approach [26,27]. 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 approaches, optimizing the allocation of patients in the groups of treatment based on the probability of recovery when treated with standard therapy. Moreover, the introduction of our model in clinical practice will allow the identification of patients with high probability to reach an independent and reliable bowel management one year after ischemic SCI, with positive impact on the counselling, on the definition of realistic

rehabilitative aims shared between patients and the multidisciplinary team and on the organization of an adequate support after discharge.

### **Conclusion**

Our study validates the first model to predict an independent and reliable bowel management one year after ischemic SCI. This simple model may be employed in clinical practice to counsel patients, to establish realistic rehabilitative aims and to plan an adequate support for a successful discharge. Our model may also be used for the design of future clinical trials to identify patients with high probability to reach an independent bowel management one year after ischemic SCI.

Table I. Baseline characteristics of patients included in the analysis and lost to follow-up

|  | <b>Study sample<br/>(n=142)</b> | <b>Lost at follow-up<br/>(n=189)</b> | <b>P-value</b> |
|--|---------------------------------|--------------------------------------|----------------|
| Age (years), mean±SD                                       | 54.73±15.39                     | 58.42±17.99                          | 0.0503§        |
| Sex (male), n (%)  | 92 (64.8)                       | 107 (56.6)                           | 0.133*         |
| M <sub>tot</sub> , median (IQR)                            | 56 (50-79)                      | 56 (50-80)                           | 0.6021#        |
| <b>Severity of neurological deficit - AIS grade, n (%)</b> |                                 |                                      | <b>0.656**</b> |
| A  | 32 (22.5)                       | 40 (21.2)                            |                |
| B  | 18 (12.7)                       | 27 (14.3)                            |                |
| C  | 40 (28.2)                       | 40 (21.2)                            |                |
| D  | 50 (35.2)                       | 78 (41.3)                            |                |
| E  | -                               | 1 (0.5)                              |                |
| ND   | 2 (1.4)                         | 3 (1.6)                              |                |
| <b>NLI, n (%)</b>  |                                 |                                      | <b>0.717**</b> |
| Cervical   | 37 (26.1)                       | 52 (27.5)                            |                |
| Thoracic   | 86 (60.6)                       | 118 (62.4)                           |                |
| Lumbar   | 18 (12.7)                       | 16 (8.5)                             |                |
| ND   | 1 (0.7)                         | 2 (1.06)                             |                |
| Intact   | -                               | 1 (0.5)                              |                |

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

SD: standard deviation; IQR: Interquartile range; M<sub>tot</sub>: ISNCSCI total motor score; AIS grade: ASIA impairment scale; NLI: neurological level of injury; ND: not determinable

Figure 1. (A) Receiver operating characteristic curve (ROC) for prediction of independent bowel management 1 year after ischemic SCI based on  $M_{tot}$  within 40 days. The ROC Y-axis indicates the sensitivity (or the true-positive rate; ie, the proportion of positive cases that are correctly identified by the test) and X-axis indicates the false-positive rate (i.e., the proportion of negative cases that are wrongly classified as positive by the test). (B) Calibration plot of the model: comparison between observed and predicted probability to reach an independent bowel management 1 year after ischemic SCI. The red spike plot at the bottom gives the distribution of subjects with (1) and without (0) the outcome (independent bowel management one year after SCI).

SCI: spinal cord injury,  $M_{tot}$ : ISNCSCI total motor score.

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## **Conflicts of interest**

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

## **Authors' contribution**

Chiara Pavese, Giorgio Scivoletto, Martin Schubert, Armin Curt and Thomas M. Kessler have given substantial contributions to the conception and the design of the manuscript.

Data collection: Chiara Pavese, Giorgio Scivoletto, Mariangela V. Puci, Rainer Abel, Armin Curt, Doris Maier, Rüdiger Rupp, Martin Schubert, Norbert Weidner, Cristina Montomoli, Thomas M. Kessler have given substantial contributions to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript and revised it critically. All authors read and approved the final version of the manuscript.

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