

Inclusive Trial Designs in Acute Spinal Cord Injuries: Prediction–Based Stratification of Clinical Walking Outcome and Projected Enrolment Frequencies

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Abstract

Background: New therapeutic approaches in neurological disorders are progressing into clinical development. Past failures in translational research have underlined the critical importance of selecting appropriate inclusion criteria and primary outcomes. Narrow inclusion criteria provide sensitivity, but increase trial duration and cost to the point of infeasibility, while broader requirements amplify confounding, increasing the risk of trial failure. This dilemma is perhaps most pronounced in spinal cord injury (SCI), but applies to all neurological disorders with low frequency and/or heterogeneous clinical manifestations.

Objective: Stratification of homogeneous patient cohorts to enable the design of clinical trials with broad inclusion criteria.

Methods: Prospectively–gathered data from patients with acute cervical SCI were analysed using an unbiased recursive partitioning conditional inference tree (URP–CTREE) approach. Performance in the 6-minute walk test at 6 months after injury was classified based on standardized neurological assessments within the first 15 days of injury. Functional and neurological outcomes were tracked throughout rehabilitation up to 6 months after injury.

Results: URP–CTREE identified homogeneous outcome cohorts in a study group of 309 SCI patients. These cohorts were validated by an internal, yet independent, validation group of 172 patients. The study group cohorts identified demonstrated distinct recovery profiles throughout rehabilitation. The baseline characteristics of the analysed groups were compared to a reference group of 477 patients.

Conclusion: URP–CTREE enables inclusive trial design by revealing the distribution of outcome cohorts, discerning distinct recovery profiles and projecting potential patient enrolment by providing estimates of the relative frequencies of cohorts to improve the design of clinical trials in SCI and beyond.

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Keywords

Spinal cord injury, clinical trials methodology/study design, unbiased recursive partitioning, stratification, rehabilitation, gait disorders

Introduction

Novel therapeutics for spinal cord injury (SCI) targeting locomotor recovery are currently in early clinical development.^{1,2} As animal experiments are encouraging, the exploration of human application is mandated. This process, however, involves several challenges beyond the establishment of the efficacy and safety of the therapeutic, with trial design, in particular the appropriate selection and enrolment of suitable trial participants, crucial for the success of this translational effort.^{3,4} Considering the incidence of SCI is relatively low and its clinical manifestations heterogeneous,⁵ the number of suitable individuals eligible for acute clinical trials is limited. Both aspects hamper the selection and stratification of study participants and require a well-designed algorithm for the identification of suitable participants.

Sequential cohort study designs are fairly common and attempt to maintain participant homogeneity by using, for example, restricted levels of injury severity as a stratification variable. The disadvantage of this practice is a staggered and therefore sometimes agonisingly slow recruitment process, prolonging the duration of a clinical trial and increasing costs. A prediction-based stratification approach would enable the enrolment of individuals with diverse sensorimotor impairments into a more inclusive, parallel cohort study design. However, this can only be achieved with suitable stratification algorithms that can identify homogeneous groups with respect to prediction of recovery without being limited to simple injury severity.^{3,6}

Such algorithms must reliably predict spontaneous neurological and functional recovery in order to allow the distinction of acute SCI patients with differing recovery trajectories towards predefined outcomes.^{6,7} In addition, the knowledge of the recovery profile of secondary outcome measures of each stratified subgroup would allow a better characterization of suitable study participants.

We implemented a prediction-based stratification algorithm in acute (0–15 days after injury) cervical SCI focused on walking function at 6 months after injury and based on an unbiased recursive partitioning technique using conditional inference trees (URP-CTREE).⁸ This approach (Figure 1) has the potential to improve the process of successful translation of promising interventions into clinical applications to meaningfully enhance locomotor function after neurological injury.

Methods

Data Source

The data for this analysis were obtained from the European Multicenter study about Spinal Cord Injury (EMSCI; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01571531) Identifier: NCT01571531), a network of European SCI centres prospectively collecting data from

people with acute SCI over the first year after injury. The neurological and functional status ≤ 15 days and 1, 3, 6 and 12 months after injury is monitored using a standardised assessment protocol. The network is ISO-9001 certified, and assessors are trained to ensure reliability of the collected data.⁹

Data of adults (≥ 18 and ≤ 70 years) with acute cervical (injury levels C1–T1) SCI, admitted between July 2001 and April 2018, were extracted from the database. Both traumatic and ischaemic patients were considered for the analysis, as recent findings demonstrate a comparable course of recovery.¹⁰

The study protocol was approved by the local ethics committees of participating centres and conducted in accordance with the Declaration of Helsinki.

Predictors and Outcome Variables

Clinical baseline predictors (first assessment ≤ 15 days after injury) and functional outcomes (assessment at 6 months after injury) were selected according to previously published literature¹¹ and based on common clinical research interests in the recovery of walking function. In addition to age at date of injury, the following items of the International Standards for Neurological Classification of Spinal Cord Injury¹² (ISNCSCI) were included as predictors: the single neurological level of injury (NLI), total lower extremity (LEMS) and upper extremity (UEMS) motor scores and total sensory scores (light touch [LT] and pin prick [PP] sensation).

The targeted functional outcome for this study was the 6-minute walk test (6MWT)¹³ at 6 months after SCI. To understand the underlying conditions of the stratified cohorts the following additional outcomes, generally proposed to be meaningful measures for clinical trials with a focus on walking function,⁷ were analysed at every assessment timepoint of the EMSCI protocol (up to 6 months): 6MWT, Spinal Cord Independence Measure III (SCIM III, mobility items 12–14 [assessing walking ability on different distances]), LEMS and UEMS.

Patient Populations

A total of 958 patients with acute cervical SCI were analysed. We extracted three different patient groups from the database: i) a *study group*, ii) a *validation group* and iii) a *reference group* (Figure 2).

The study group (N = 309) was used to develop the prediction model and recovery profiles. Only subjects with complete predictor and outcome data at all predefined assessment timepoints (≤ 15 days, 1, 3 and 6 months after injury) were selected.

The validation group (N = 172) was used to validate the prediction model. Requirements for inclusion were complete documentation of predictors ≤ 15 days and outcomes at 6 months

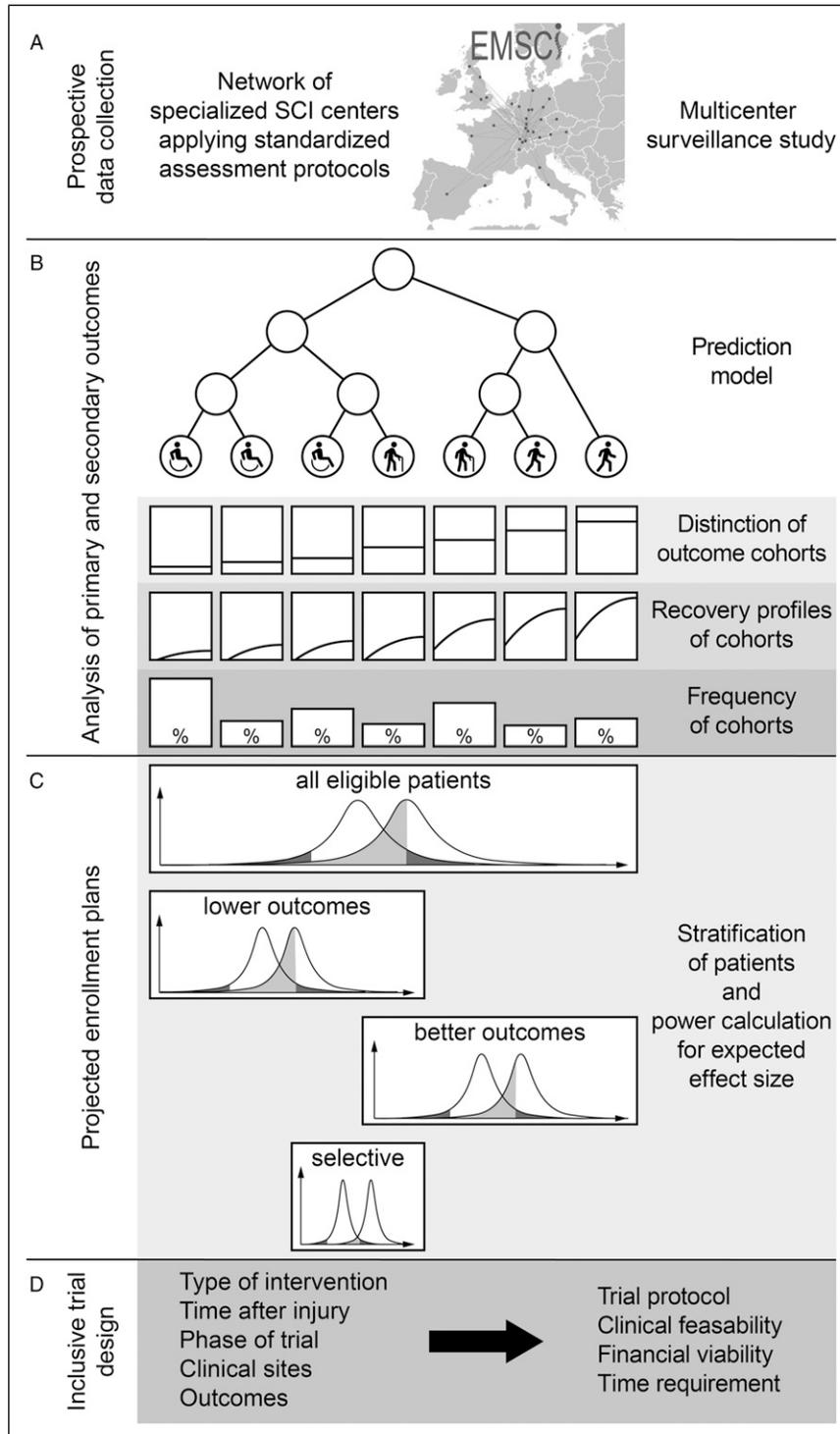


Figure 1. Concept overview. Illustrated are the different conceptual steps for the design of an inclusive clinical trial, with parts A and B being reported in this study, while parts C and D specifically depend on the study intervention. (A) The EMSCI network (<https://www.emsci.org>) includes specialized SCI centres performing standardized assessments in acute SCI, (B) that are applied to develop prediction models for the stratification of patients depending on the targeted primary outcome. The identified cohorts are further analysed in terms of secondary outcomes and recovery profiles, and the frequency of patients suitable for enrolment. (C) The power of a clinical trial relies on the appropriate selectiveness of the included cohorts and the expected effect size of a specific intervention. (D) Manifold aspects (e.g. type of intervention and time after injury) must be considered when designing a clinical trial, including the protocol, feasibility, finances and duration of a study. EMSCI, European Multicenter Study about Spinal Cord Injury; SCI, spinal cord injury.

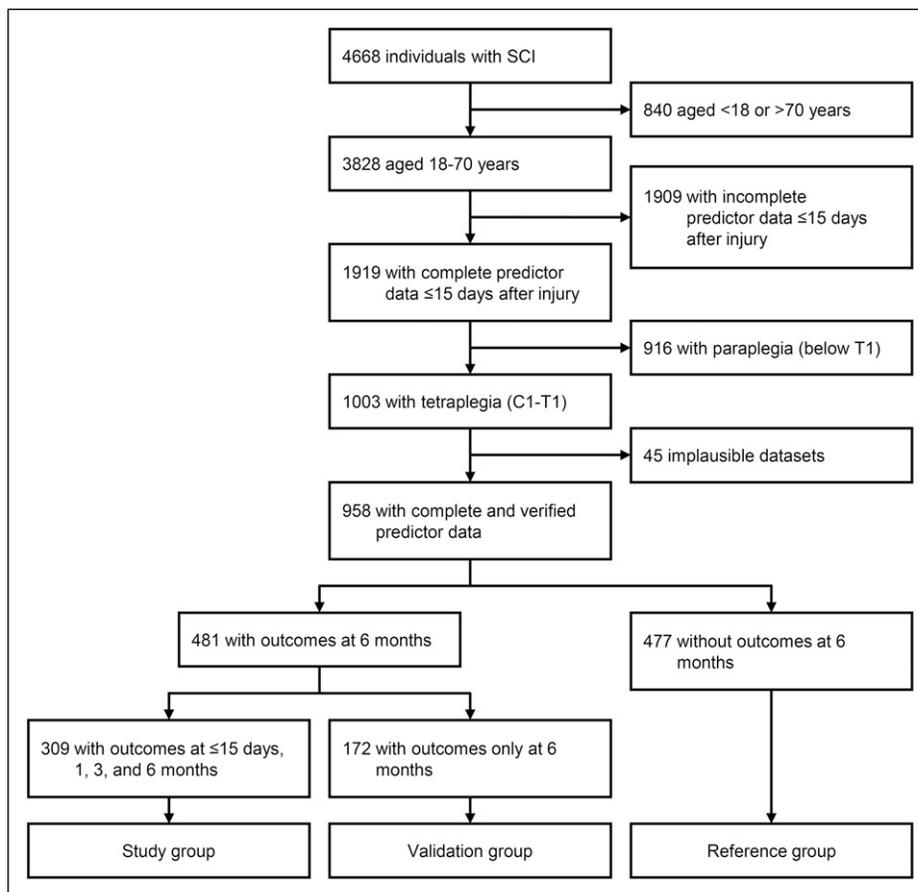


Figure 2. Flow chart of patient numbers. Selection criteria used for data presented here, extracted from the EMSCI database on 15th October 2018. The study group was used to develop the stratification model which was thereafter validated by an internal yet independent patient cohort (validation group). With the reference group the representativity of the study and validation groups were analysed. EMSCI, European Multicenter Study about Spinal Cord Injury; SCI, spinal cord injury.

after injury. Individuals already part of the study group were excluded from the validation group to ensure group independence.

The reference group ($N = 477$) was used to investigate whether the study and the validation groups were representative of the acute SCI population and if results could be generalized. Individuals with complete predictor data ≤ 15 days after injury were selected, excluding those already included in the study or validation groups.

A detailed explanation of the data plausibility check is provided in the [supplemental material](#).

As data completeness is known to vary with severity of injury in SCI and other datasets,^{14,15} we expected the distribution of American Spinal Injury Association impairment scale (AIS) grades in the three groups to be different. Therefore, we analysed the LEMS ≤ 15 days after injury and the 6MWT 6 months after injury in the three groups by AIS grade (see [supplemental material](#)).

Prediction Modelling

The URP-CTREE is a tree-based regression model. It successively investigates the dependence between defined

predictors and an outcome, with the aim of splitting a heterogeneous cohort into more homogenous ones.⁸ The result of such an analysis is a set of *nodes* and a simple cutpoint-based rule to assign prospective patients to one of these nodes. Examples of other applications of this method are provided elsewhere^{16,17} and the methodology is fully detailed in Hothorn et al.⁸ In brief, the URP-CTREE comprises two steps, which are repeated iteratively until an *a priori*-specified stopping criteria is met. Step 1 tests which predictor (at baseline) shows the strongest statistically significant association with the selected outcome (at end-point). If no such association can be found, the algorithm stops without implementing any split in the cohort. Alternatively, the predictor with the strongest statistical association is selected (P values are corrected for multiple-testing) and the algorithm continues with step 2. In this step, the actual splitting of the cohort is implemented, targeting a maximal discrepancy in the resulting nodes (i.e. the two resulting subcohorts are as distinct as possible). Steps 1 and 2 are recursively applied until no more statistically significant associations between any predictor and the outcome are found, resulting in a tree-structured model.

The performance of this method in terms of identifying homogeneous cohorts and prediction has been proven robust and reliable by a recent study by Buri et al.¹⁸

Stratification and Distribution of Outcome

With URP-CTREE, the distribution of the outcome is displayed in the nodes of the regression tree, which vary in levels of functional performance. Therefore, by analysing the outcome distribution, spanning from *floor* to *ceiling*, stratification of potential study participants can be considered.

The nodes with the poorest outcome level (median = 0; i.e. no recovery of any walking function over the first 6 months after injury) are referred to as floor nodes.

The threshold for the ceiling nodes must be set for each clinical outcome individually with respect to statistical properties. The endpoint threshold for this study was computed by subtracting twice the established minimal detectable change (MDC) from the maximally achievable score/value of the selected outcome, to provide a sensitive measurement tool. This procedure should ensure that even in individuals with a good recovery, further improvements remain detectable and thus may be attributed to the intervention under investigation. MDCs of the selected outcome measures are based on published values (6MWT [45.8 m],¹⁹ LEMS [1.87 points],²⁰ SCIM III₁₂₋₁₄ [1.96 points]²¹). For the continuous scaled 6MWT we used previously published data from healthy control participants (6MWT_{mean} = 652 m)²² as a maximum achievable value.

Recovery Profiles

The detailed information on outcome measures from patients pooled into each of the URP-CTREE's nodes allow for comprehensive clinical characterization. This may permit the further distinction of subgroups when comparing nodes with similar levels of magnitude of the targeted outcome. All selected outcomes (6MWT, LEMS, SCIM III₁₂₋₁₄ and UEMS) at all assessment timepoints (≤ 15 days, 1, 3 and 6 months) were extracted and used to generate recovery profiles for the individuals categorized into each node of the URP-CTREE.

Frequency Analysis

To evaluate how often patients eligible for our prediction model are admitted to the SCI centres of the EMSCI network, we performed a frequency analysis. A time window of five years (2013–2017) was defined, in which we pooled the data from the study, validation and reference groups (N = 359). Individuals were then entered into the stratification algorithm and allocated to cohorts, and the hypothetical recruitment frequency for each cohort was analysed.

Statistics

URP-CTREE analysis was performed using the computing environment R (version 4.0.4, Windows),²³ using the statistical package *party*.²⁴

Data Availability

The data used for this study, including anonymised individual participant data and a data dictionary defining each field or variable within the dataset, can be made available on reasonable request to the corresponding author (MB). Written proposals will be evaluated by the authors, who will render a decision regarding suitability and appropriateness of the use of data. Approval of all authors and the EMSCI consortium will be required and a data sharing agreement must be signed before any data are shared. The code to run the analysis can be found on our github repository (https://github.com/adriancathomen/R_code_for_URP-CTREE_manuscript.git). The study protocol as well as a detailed description of the project is accessible on the official website of the EMSCI network (<https://www.emsci.org>).

Results

Table 1 outlines characteristics and compares the study, validation, and reference groups. The majority of patients were male (~80%), mean age was ~45 years and midcervical single NLI were the most frequent presentation. The validation and reference groups were found to be comparable in terms of LEMS ≤ 15 days after injury, although there were significant differences for baseline LEMS in AIS C and D patients between the study group and the other groups (eFigure 1). However, as the 6MWT at 6 months after injury for the study and validation groups did not differ by AIS grades (eFigure 2), we concluded comparison of the three groups to be valid. The AIS conversion rate of the study group is provided in eTable 1.

Stratification and Distribution of Outcome

Figure 3 presents the URP-CTREE for the stratification of the 6MWT at 6 months based on data ≤ 15 days after injury. The URP-CTREE selected LEMS, PP, and age as predictor variables. The model indicated inner nodes (# 1, 2, 3, 6, 9 and 10), hence generating seven terminal nodes (# 4, 5, 7, 8, 11, 12 and 13) with a walking function distribution from very poor to good performance. Nodes 4, 5 and 7 showed almost none to no ambulatory function, characterized by the median inability to complete any distance during the 6MWT, representing a floor effect in this group of *non-walkers*. Nodes 5 and 7, however, showed partially restored walking function in approximately 50% of individuals. To further reveal cohorts with forms of lower extremity recovery other than ambulation in node 4, a two-stage

Table 1. Baseline Group Characteristics.

	Study Group N = 309	Validation Group N = 172	Reference Group N = 477
Cause of injury			
traumatic	301 (97.41%)	169 (98.26%)	457 (95.81%)
ischaemic	8 (2.59%)	3 (1.74%)	20 (4.19%)
Sex			
male	251 (81.23%)	138 (80.23%)	379 (79.45%)
female	58 (18.77%)	34 (19.77%)	98 (20.55%)
Age			
mean years \pm SD	43.25 \pm 16.22	45.66 \pm 14.61	46.91 \pm 15.66
NLI			
C1	16 (5.18%)	6 (3.49%)	22 (4.61%)
C2	15 (4.85%)	13 (7.56%)	34 (7.13%)
C3	28 (9.06%)	17 (9.88%)	54 (11.32%)
C4	127 (41.10%)	52 (30.23%)	150 (31.45%)
C5	71 (22.98%)	42 (24.42%)	150 (31.45%)
C6	28 (9.06%)	27 (15.70%)	42 (8.81%)
C7	10 (3.24%)	10 (5.81%)	13 (2.73%)
C8	7 (2.27%)	3 (1.74%)	7 (1.47%)
T1	7 (2.27%)	2 (1.16%)	5 (1.05%)
AIS			
A	150 (48.54%)	59 (34.30%)	111 (23.27%)
B	41 (13.27%)	28 (16.28%)	43 (9.01%)
C	62 (20.06%)	26 (15.12%)	114 (23.90%)
D	56 (18.12%)	59 (34.30%)	209 (43.82%)

Characteristics of study, validation, and reference groups. NLI and AIS recorded ≤ 15 days after injury. Further comparison of the three groups (focussing on AIS grade distribution) is provided in the supplemental material. AIS, American Spinal Injury Association impairment scale; N, number of patients; NLI, neurological level of injury; SD, standard deviation.

URP-CTREE approach with LEMS as targeted outcome was performed (eFigure 3). The AIS distribution ≤ 15 days after injury revealed individuals with a sensorimotor-complete injury (AIS A) were predominantly (97%) assigned into node 4. Approximately a third of patients with motor complete, sensory incomplete injuries (AIS B) were allocated to node 5 and generally showed no improvement in walking function, despite a partial recovery in LEMS. In contrast, based on the threshold for a ceiling effect, we did not find any node in which the maximum achievable value for the 6MWT was exceeded.

To check for the validity of the prediction model, an internal validation of the URP-CTREE was performed and is provided in the supplemental material (eFigure 4 and eTable 2). Validation of the study group was done by applying the decision rules (determined in the URP-CTREE) to the validation group and comparing the corresponding nodes of the two groups. Similar distributions for 6MWT within the nodes for study and validation subjects were observed.

Recovery Profiles

Figure 4 outlines the recovery profiles for the outcome measures mapping walking function, LEMS, and UEMS for

each node. The seven cohorts could be divided into three categories: i) non-walkers (nodes 4, 5, and 7), ii) *therapeutic walkers* (able to walk in a therapy setting, but not in daily living; nodes 8 and 11), and iii) *functional walkers* (able to walk in daily living; nodes 12 and 13) according to their 6MWT outcome.

The category of non-walkers (Figure 4(A)) was characterized by almost none or no recovery of walking function (in terms of 6MWT performance), although patients in nodes 5 and 7 regained some lower limb motor strength 6 months after injury as measured by the LEMS. Further differences could be found in median age and AIS (ranging from AIS A to C; Figure 3).

In the category of therapeutic walkers (Figure 4(B)), the difference in LEMS between nodes 8 and 11, with lower initial values in node 8, disappeared over the first 6 months of recovery. Higher LEMS at ≤ 15 days did appear to lead to better ambulatory function at 6 months (as measured by the 6MWT and SCIM III₁₂₋₁₄) in these patients.

Functional walkers (Figure 4(C)), pooled into nodes 12 and 13, differed at the first two timepoints of assessment (≤ 15 days and 1 month) across all outcome measures (except

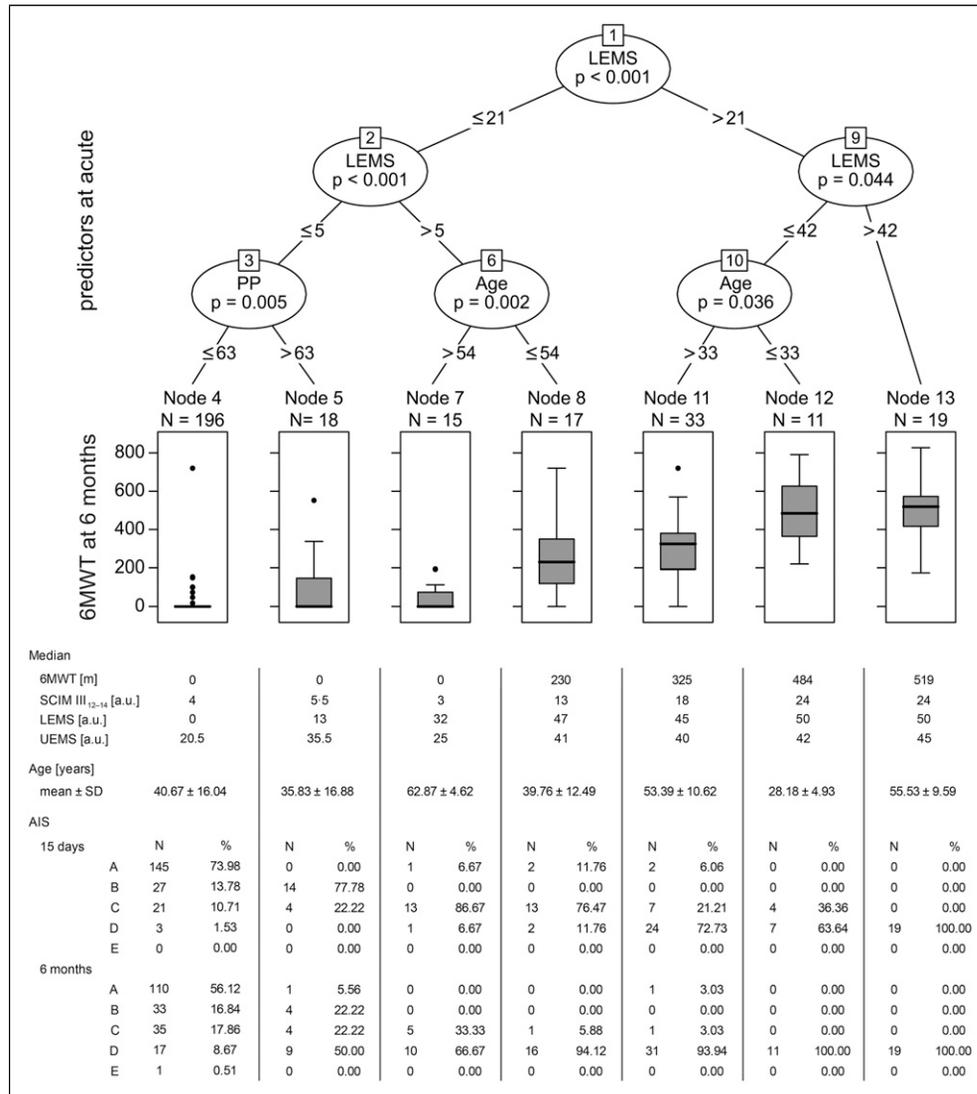


Figure 3. Stratification model for the outcome 6MWT for individuals (N = 309) with a cervical SCI. URP-CTREE for 6MWT at 6 months after injury (in boxplot with median), using the predefined predictors (age, LEMS, LT, NLI, PP and UEMS) characterizing the neurological and functional status of patients ≤15 days (acute) after injury and distribution of 6MWT, SCIM III₁₂₋₁₄, LEMS and UEMS outcomes at 6 months after injury, age and AIS grades for each node of the URP-CTREE. Significance level at $p < 0.05$. 6MWT, 6-minute walk test; AIS, American Spinal Injury Association impairment scale; a.u., arbitrary unit; LEMS, lower extremity motor score; LT, light touch; N, number of patients; NLI, neurological level of injury; PP, pin prick; SCI, spinal cord injury; SCIM III₁₂₋₁₄, spinal cord independence measure III: items 12–14; UEMS, upper extremity motor score; URP-CTREE, unbiased recursive partitioning conditional inference tree.

UEMS), however recovered similarly to full SCIM III₁₂₋₁₄ but limited 6MWT at 6 months post-injury.

Frequency Analysis

Figure 5 presents the frequency with which the 359 included patients, admitted to 26 SCI centres of the EMSCI network between 2013 and 2017, were allocated to the corresponding cohorts. Also shown are the relative distributions of various clinical parameters, including AIS, which is regularly used for patient selection in clinical trials. An example comparing the hypothetical selection of patients based on AIS (grade C;

83 patients) to URP-CTREE (Nodes 5–11; 124 patients; +49%) is highlighted in the figure.

Discussion

Clinical trials aim to recruit an appropriate number of participants within a reasonable time frame. This is a major challenge in acute SCI, but is applicable to all disorders with low frequency and/or heterogeneous clinical deficits. Here we report a method that permits inclusive clinical trial designs while maintaining homogeneous patient cohorts, along with projected patient enrolments, in acute cervical SCI (Figure 1).

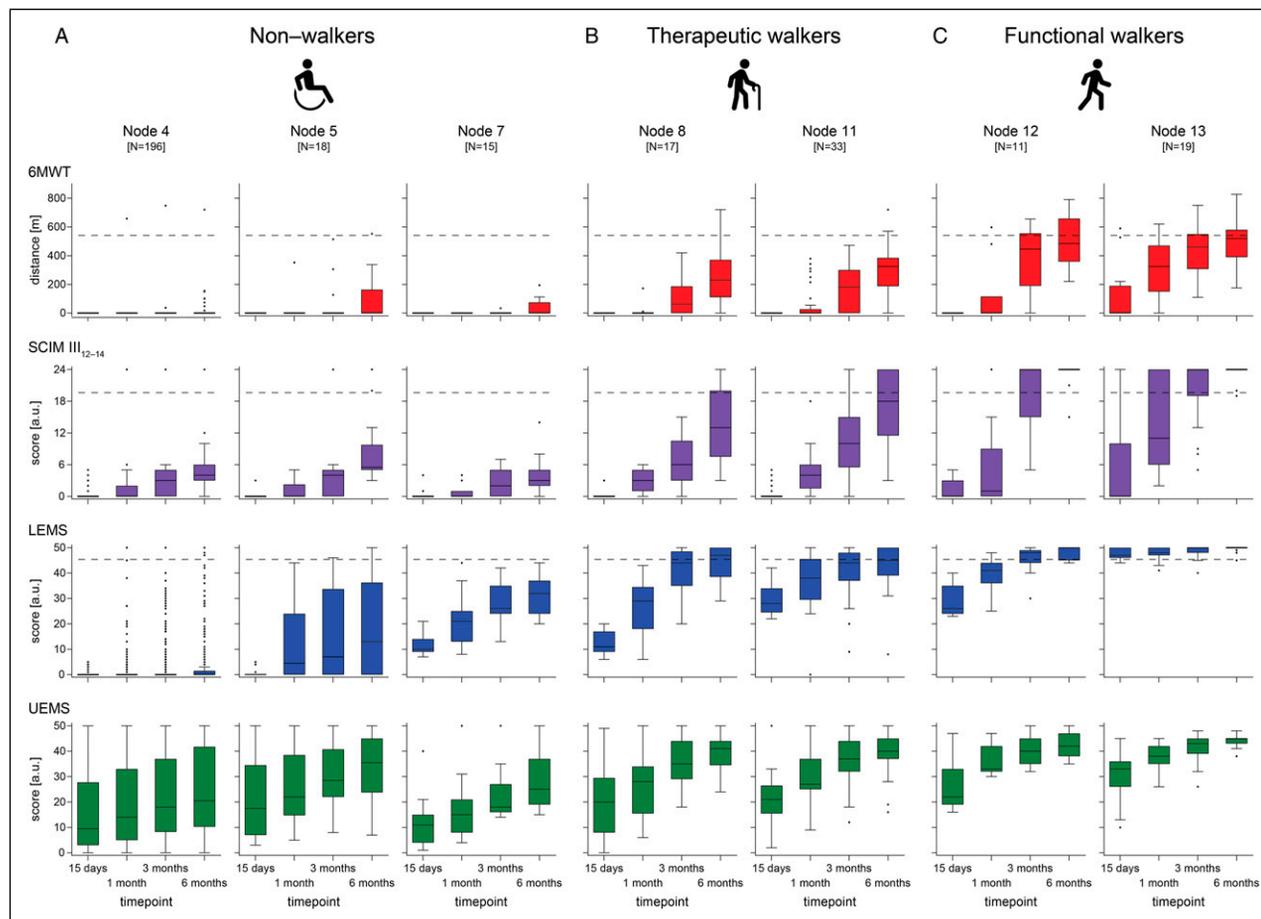


Figure 4. Neurological and functional recovery within different nodes using the 6MWT URP-CTREE. Recovery profiles (in boxplots with median) are shown over the first 6 months of rehabilitation for the categories of: (A) non-walkers (nodes 4, 5 and 7), (B) therapeutic walkers (nodes 8 and 11), and (C) functional walkers (nodes 12 and 13). The dotted lines in the recovery profiles indicate the corresponding ceiling threshold. A more detailed description on the computation of the thresholds is provided in the methods section. Ceiling threshold for: (i) 6MWT = 560.4 m, (ii) SCIM III₁₂₋₁₄ = 20.08 points, and (iii) LEMS = 46.26 points. 6MWT, 6-minute walk test; a.u., arbitrary unit; LEMS, lower extremity motor score; N, number of patients; SCIM III₁₂₋₁₄, spinal cord independence measure III: items 12–14; UEMS, upper extremity motor score; URP-CTREE, unbiased recursive partitioning conditional inference tree.

Identifying homogeneous subgroups in the heterogeneous population of cervical SCI offers the opportunity to lower the inter-subject variability of selected participant cohorts, potentially leading to smaller number of participants needed for an adequate power in a clinical trial.

The selection of participants in SCI trials is often based on rather gross injury categories (e.g. sensorimotor complete vs incomplete), which neglect the heterogeneity of clinical deficits and fail to distinguish conditions that may be amenable to specific interventions. Ideally, accurate prediction models could be employed to stratify the heterogeneous SCI patient population with respect to the potential for neurological and functional recovery.^{3,4,7} To this end, different clinical prediction algorithms, targeting endpoints related to lower extremity function, have been developed.²⁵⁻²⁸ To date, however, these algorithms principally define only dichotomous or ordinal scaled walking outcomes, which are insufficient in themselves for the development of

identification rules for homogeneous cohorts and do not consider the full spectrum of endpoint distribution.¹⁶ To address these deficits, and as a proof of concept for future trials, we developed a robust and reliable statistical prediction model,^{8,18} and applied it to prospectively gathered patient data from the EMSCI database. URP-CTREE has recently been investigated in terms of prediction performance and compared to traditional statistical techniques, such as logistic or linear regression, as well as to a novel machine learning approach, with favourable or equal results for URP-CTREE.¹⁸ Combined with the straightforward interpretability and the simple clinical application, we argue that URP-CTREE is a suitable approach for clinical trials in SCI.

Study Population

Despite different distributions in acute AIS grades, we were able to demonstrate that the three analysed patient cohorts

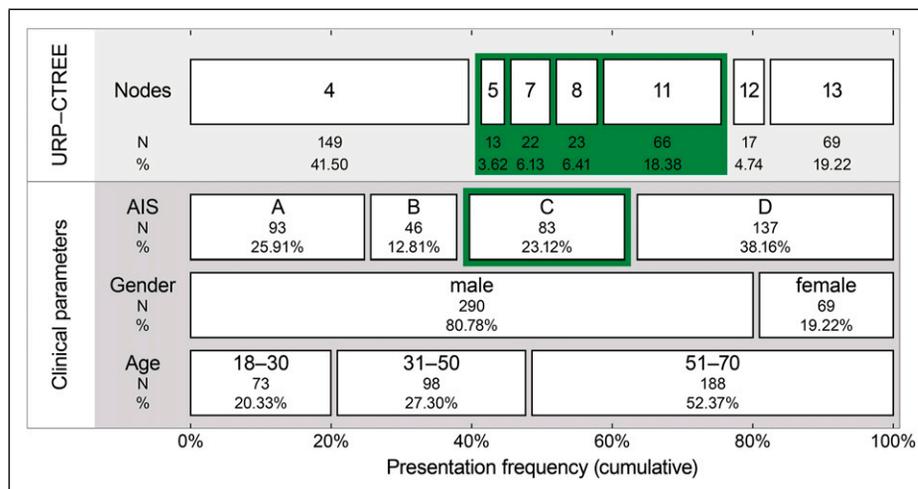


Figure 5. Frequency analysis and relative distributions of patients (N = 359) based on presentation incidence in 26 EMSCI centres between 2013–2017. The pooled data from the study, validation and reference groups over five years (2013–2017) were considered for this frequency analysis. Above: frequency of patients allocated to the cohorts according to the stratification algorithm. Below: distributions of general clinical parameters (AIS, gender and age). Green: an example with two different approaches of patient selection for a hypothetical clinical trial based on initial clinical predictors is highlighted. URP-CTREE nodes 5-11 (N = 124) versus AIS C (motor incomplete but limited muscle strength; N = 83), with 49% more patients available for inclusion with the URP-CTREE approach. The rationale for selecting nodes 5-11 is based on the promising potential of improvement in walking function due to a specific intervention. On the other hand, only AIS C patients were selected for inclusion in this hypothetical clinical trial, because (i) considering AIS D patients bears a substantial risk of including patients with an already good outcome and (ii) considering AIS A and B patients probably results in including patients with a too poor outcome to meet the requirements of proving a potential treatment effect. AIS, American Spinal Injury Association impairment scale; EMSCI, European Multicenter Study about Spinal Cord Injury; N, number of patients; URP-CTREE, unbiased recursive partitioning conditional inference tree.

(study, validation, and reference groups) were comparable in terms of LEMS ≤ 15 days and/or 6MWT at 6 months after injury. The potential of a bias introduced in the analysis by defining the different groups based on data availability could therefore be mitigated since we could demonstrate that this bias only concerns the frequency in which particular patient types (based on injury severity) occur in the different groups but not the baseline predictors and/or the corresponding endpoint outcome.

Stratification and Distribution of Outcome

URP-CTREE resulted in seven nodes covering the 309 individuals with acute cervical SCI entered into the model. Overall, the most relevant predictor of outcome of walking function was the initially preserved LEMS, in line with previous data.^{25,29} The LEMS was instrumental for the stratification of walkers and non-walkers, and also for the differentiation of the best outcome cohort. Additionally, age and PP were significant predictors for the 6-month 6MWT distance. Generally, younger people do better in functional outcome assessments such as the 6MWT or SCIM III₁₂₋₁₄ but show comparable values to older patients in terms of muscle strength (LEMS and UEMS). Age seems to be a determining factor for the distinct potential of functional recovery, similar to previous reports,³⁰ potentially prolonging the time frame

an individual needs to regain its walking function.³¹ The cohorts with almost none to no ambulation after 6 months were discriminated by the preservation of PP sensation. PP sensation probably represents a surrogate marker not only for spinothalamic integrity but also preservation of central spinal pathways more generally, hence the relation to motor recovery.³²

The distribution of the 6MWT at 6 months revealed floor effects in nodes 4, 5 and 7. The 6MWT provides excellent discrimination in good walkers, but does so poorly in individuals with low walking capacity.³³ In contrast, none of the nodes showed a ceiling effect in the outcome 6MWT compared to values from healthy controls,²² indicating that all identified cohorts share the potential of further improvement in the primary outcome. The question remains, however, as to whether the regained walking capacity in the cohort(s) with the best outcome will mask the detection of any additional treatment benefit. Despite some of the nodes presenting a similar 6MWT distribution at 6 months after injury, it is essential to notice that these nodes origin from different baseline characteristics, indicating a considerably different pattern of recovery. This fact is further displayed in the varying recovery profiles of secondary outcomes among the respective nodes.

Validity of the prediction model was confirmed with an internal validation of the URP-CTREE, since no external

source with the required data was available. Similar distributions for 6MWT within the nodes for study and validation groups could be observed. For this reason, and the fact that the EMSCI database has been compared to another large SCI database (Sygen),³⁴ and considered comparable,^{17,35} we conclude that our results may be confidently extrapolated to a broader population of patients with acute cervical SCI.

Recovery Profiles

Analysing recovery profiles goes beyond single endpoint stratification. It enables a more detailed understanding of different aspects of recovery patterns, in particular for cohorts with similar primary endpoint distributions. This information is valuable for the interpretation of results from a prediction model, as the model itself (targeting only one outcome) may be insufficient for the final evaluation of a therapeutic effect. Each outcome has its individual strengths and limitations in identifying improvements in differing cohorts.³³

In the group of non-walkers, nodes 5 and 7 experienced an increase in LEMS during rehabilitation. Despite the lack of walking function in these cohorts, the partial recovery in muscle strength emphasises the potential for further improvement, which may be augmented by an appropriate therapeutic intervention. Although LEMS increased to a median of 13 and 32 in these nodes, respectively, median walking function remained at 0 (Figure 4(A)). This points, intuitively, to a certain threshold of muscle strength which must be surpassed in order to regain any walking function. In this context, the analysis revealed a possible interfering factor. Individuals allocated to node 7 had a mean age of 63 years, possibly explaining the lack of walking function despite the comparably high values in LEMS. With increasing age, proportionally greater lower extremity muscle strength may be required to compensate for the age-related loss in motor and sensory function.³⁶ Other factors related to ageing, for instance declining cardiovascular fitness, may also potentially influence walking function.³⁷

Therapeutic walkers showed comparable recovery profiles with higher baseline values of LEMS in node 11. This was associated with slightly better functional outcomes at 6 months after injury. Initially less-impaired motor function appears to favour later recovery of walking function despite an otherwise comparable course of neurological recovery.

Functional walkers greatly improved in terms of their neurological and functional outcomes 6 months after injury. Despite this, differences in baseline characteristics and recovery progression could still be identified. The earlier recovery of functional outcomes in node 13 (compared to node 12) was based on differences in the initial LEMS, that is, time to recovery was the main distinction between these groups. This may mean that therapeutic benefit in functional walkers is manifested by accelerated recovery and a correspondingly

shorter hospitalisation rather than improvement in ultimate functional outcomes.

Central cord syndrome (CCS) is a clinical subtype of SCI diagnosed based on a disproportionate UEMS impairment compared to LEMS (a minimum of ten points motor score difference in favour of LEMS has been suggested to support the diagnosis).³⁸ While no stratified subgroup median met this criterion, patients meeting this definition of CCS occur more frequently in Nodes 11–13 (Figure 4).

Frequency Analysis

We presented the frequency at which patients eligible for our prediction model are admitted to the SCI centres of the EMSCI network over five consecutive years (a reasonable time span for a clinical trial). This analysis permits an estimation of the time needed to recruit a given number of patients into specific cohorts and thus estimate the likely speed of recruitment for a hypothetical clinical trial. Increasing subject homogeneity by narrowing inclusion criteria eventually results in recruitment of a lower number of study participants and prolongs the trial duration to the extent that a clinical trial may no longer be feasible. Applying broader inclusion criteria mitigates this but brings with it the risk of inhomogeneous cohorts. Our frequency analysis compared hypothetical recruitment using cohorts defined using the AIS and URP-CTREE and suggests that, with the latter, homogeneous cohorts can be maintained while broadening the pool of eligible patients.

Limitations

The classification into study, validation and reference groups, based on data availability, may have introduced bias as data completeness varies with injury severity of patients. Although the total number of patients analysed in the different cohorts is high, the stratification led in some nodes to rather small numbers, lowering statistical power and validity. Further, the assessments in EMSCI do not cover all variables (e.g. weight or secondary complications) which may influence outcome. The inclusion of more complex assessments (e.g. neurophysiological examinations or MRI measurements) could potentially provide additional useful information for the URP-CTREE model. However, such assessments are only performed in highly specialized SCI centres as they are time consuming and complex, factors which must be considered when weighing the feasibility of mandating such investigations in clinical trials. This study focused on a time interval of ≤ 15 days after injury and therefore applicability of these findings to patients with very acute SCI, for example, ≤ 72 hrs after injury cannot be assumed.³⁹

Conclusion

Using URP-CTREE, homogeneous cohorts of patients with cervical SCI can be identified with respect to ambulation at

6 months after injury. Subsequent analysis of secondary outcomes allows for comprehensive clinical characterization of the cohorts identified. Based on modelled stratifications, prediction rules can be defined, thus potentially optimising the inclusiveness of clinical trials and shortening study duration. Such inclusive clinical trial designs can facilitate future translational research in the field of SCI and beyond.

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Author Contributions

The study design was conceived by ACa, ACu, and MB. Data collection was done by RA, DM, NW, RR, ACu, and MB. Data analysis was performed by ACa and LS. Statistical analysis was done by ACa. ACa wrote the draft of the manuscript. All authors interpreted the data and critically reviewed the manuscript for intellectual content and approved the final version.

Declaration of Conflicting Interests

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