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Trajectory-Based Classification of Recovery in Sensorimotor Complete Traumatic Cervical Spinal Cord Injury

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Abstract

Objective

To test the hypothesis that sensorimotor complete traumatic cervical spinal cord injury (SCI) is a heterogenous clinical entity comprising several subpopulations that follow fundamentally different trajectories of neurologic recovery.

Methods

We analyzed demographic and injury data from 655 patients who were pooled from 4 prospective longitudinal multicenter studies. Group-based trajectory modeling was applied to model neurologic recovery trajectories over the initial 12 months postinjury and to identify predictors of recovery trajectories. Neurologic outcomes included upper extremity motor score, total motor scores, and American Spinal Injury Association Impairment Scale (AIS) grade improvement.

Results

The analysis identified 3 distinct trajectories of neurologic recovery. These clinical courses included (1) marginal recovery trajectory, characterized by minimal or no improvement in motor strength or change in AIS grade status (remained grade A); (2) moderate recovery trajectory, characterized by low baseline motor scores that improved approximately 13 points or AIS conversion of 1 grade point; (3) good recovery trajectory, characterized by baseline motor scores in the upper quartile that improved to near maximum values within 3 months of injury. Patients following the moderate or good recovery trajectories were younger, had more caudally located injuries, had a higher degree of preserved motor and sensory function at baseline examination, and exhibited a greater extent of motor and sensory function in the zone of partial preservation.

Conclusion

Cervical complete SCI can be classified into one of 3 distinct subpopulations with fundamentally different trajectories of neurologic recovery. This study defines unique clinical phenotypes based on potential for recovery, rather than baseline severity of injury alone. This approach may prove beneficial in clinical prognostication and in the design and interpretation of clinical trials in SCI.

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Glossary

AIS = American Spinal Injury Association Impairment Scale; **ASIA** = American Spinal Injury Association; **BIC** = Bayesian information criterion; **CI** = confidence interval; **FIM** = Functional Independence Measure; **GBTM** = group-based trajectory modeling; **ISNCSCI** = International Standards for Neurologic Classification of Spinal Cord Injury; **MAR** = missing at random; **MVC** = motor vehicular collision; **NACTN** = North American Clinical Trials Network; **NASCIS III** = Third National Acute Spinal Cord Injury Study; **RRR** = relative risk ratio; **SCI** = spinal cord injury; **STASCIS** = Surgical Timing in Acute Spinal Cord Injury Study; **TMS** = total motor score; **UEMS** = upper extremity motor score; **ZPP** = zone of partial preservation.

About two-thirds of traumatic spinal cord injuries (SCIs) in North America involve the cervical spinal cord.[1,2] According to the International Standards for Neurologic Classification of SCI, up to half of patients with cervical SCI are initially classified as American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A, defined as the absence of motor or sensory function in the distal most sacral segments on neurologic examination.[3,4] The prospects for significant neurologic recovery remain generally poor among cervical AIS grade A patients, despite timely modern treatment.[5] That said, the literature suggests a small but significant proportion experience higher rates of neurologic improvement than expected given the baseline degree of injury severity.[6] Therefore, from a natural history perspective, patients with cervical AIS grade A injuries likely represent a heterogenous cohort.

In addition to quantifying rates of recovery at standardized time points after injury (i.e., 6 months), another critical aspect to understanding natural history relates to defining the temporal profiles of neurologic recovery. In general, by focusing on rates of neurologic change at a specific time point, we erroneously assume that all patients follow a one-size-fits-all recovery trajectory.[7-9] However, this approach largely ignores the fact that natural recovery post SCI is an inherently complex and dynamic process. Furthermore, the evidence from several studies suggests the process of recovery is temporally nonlinear, irrespective of the severity of injury.[7-9]

In this study, our overall goal is to more accurately delineate the natural history and temporal profile of neurologic recovery for patients with cervical AIS grade A SCI.[10] We hypothesize that AIS grade A SCI is a heterogenous clinical syndrome comprising several subpopulations that follow fundamentally different trajectories of neurologic recovery. To investigate this hypothesis, we address 3 specific aims: (1) to identify unique trajectories of neurologic recovery for the cervical AIS A patient subgroup spanning from the immediate postinjury period until 1-year follow-up; (2) to identify which patient and injury characteristics are most closely associated with specific trajectories of neurologic recovery; and (3) to determine whether identified trajectories of neurologic recovery predict long-term functional status.

Methods

Study Population

The study population was identified from a pooled SCI cohort derived from 4 prospective multicenter datasets including the Third National Acute Spinal Cord Injury Study (NASCIS III) database, the Sygen Multicenter Acute Spinal Cord Injury Study database, the North American Clinical Trials Network for the treatment of SCI (NACTN) database, and the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) database. Datasets were harmonized based on their common data elements to produce a single pooled dataset. This was done by examining and resolving inconsistencies in variables definitions and coding using the data dictionary provided by data contributors. Key variables for the analysis were identified and standardized across datasets by recoding before pooling into a common dataset. For data validation, we compared results of frequency distributions and cross-tabulations among the source data, the primary publications on source data, and the pooled dataset. All data management and merging were done and independently validated by analysts with experience in the harmonization and development of pooled repositories of clinical data.

The present analysis included patients who met the following criteria: (1) sensorimotor complete traumatic SCI (grade A injury on the AIS of the International Standards for Neurologic Classification of Spinal Cord Injury [ISNCSCI] [revised 2011][4]) with neurologic examination completed within the first week after injury; (2) cervical neurologic level injuries (C1–C8); and (3) age 18 years or older. For patients with more than 1 neurologic examination performed within the first week post SCI, the first examination was used to determine study eligibility.

Neurologic and Functional Outcome Assessments

Neurologic assessments in the NACTN, STASCIS, and Sygen studies were performed in accord with the ISNCSCI.[4] In NASCIS III, motor and sensory assessments were based on the older Frankel SCI classification system. Because point data were available on relevant individual myotomes and dermatomes, we regraded the NASCIS III cohort using the ISNCSCI classification system. Recovery was evaluated as improvement in 3 metrics of neurologic function: (1) upper extremity motor score (UEMS), (2) total motor score (TMS), and (3) AIS grade. The UEMS is an aggregate score of the strength of 5 key muscle groups in each upper extremity resulting in a total score with range between 0 and 50 points (maximum 25 points per upper extremity). The TMS sums the motor scores for the upper and lower extremities, and hence has a range between 0 and 100 points. Longitudinal

data were obtained at baseline (within 7 days of the injury) and at 3, 6, and 12 months follow-up. Follow-up data at 3 months was not collected in the STASCIS. We inputted 2-month data for 3 months in the NASCIS III. Functional outcome was assessed according to the motor subscale of the Functional Independence Measure (FIM) at 12 months follow-up. The score ranges from 13 (total dependence) to 91 points (total independence).

Baseline Covariates

In the primary studies, demographic, clinical, and treatment information were collected by trained research assistants. For the present study, the following covariates were selected for analysis informed by clinical opinion and prior literature on neurologic recovery in SCI: age (kept as continuous predictor); sex; premorbid conditions, including history of hypertension, diabetes, malignancy, tobacco smoking, drug abuse, pulmonary or cardiac pathologies (dichotomized: present/absent); causative factor (motor vehicular collision [MVC], fall, or others, excluding penetrating injuries); systolic blood pressure (kept as continuous predictor); injury level (C1–C4, C5–C6, or C7–C8); Glasgow Coma Scale score (analyzed as continuous predictor); complications, defined as any acute adverse event involving the respiratory, neuropsychiatric, hematologic, cardiac, gastrointestinal, or renal systems (yes/no); light touch, pinprick, and sensory scores (analyzed as continuous variables); zone of partial preservation (ZPP), which refers to those dermatomes or myotomes caudal to the sensory or motor levels that remain partially innervated (analyzed as an ordinal variable after computing the total number of levels for each patient); time from injury to surgery (dichotomized as early [≤24 hours] or late [>24 hours]); and steroid administration (yes/no).

Statistical Analysis

Group-based trajectory modeling (GBTM) was applied to model longitudinal recovery trajectories over the initial 12 months postinjury for each neurologic endpoint. GBTM uses mixed models to predict unique trajectories in longitudinal data. Unlike standard growth curve modeling that assumes a one-size-fits-all model in characterizing longitudinal trajectory, group-based modeling provides statistical measures for distinguishing among clusters of trajectories within a population that follow similar patterns of recovery. The measures determining each group's trajectory are the latent growth factors derived from maximum likelihood estimation (i.e., intercepts and slopes). The intercept refers to the initial score at baseline and the slope corresponds to the rate of change of the trajectory across assessments. Nonlinear trajectories are evaluated by introducing additional quadratic or cubic growth measures in the model. GBTM evaluates the probability of each patient belonging to the identified trajectory subtypes and uses the highest probability to assign the patient to a single subtype. Within the GBTM framework, data imputation is performed under the missing at random (MAR) assumption, hence allowing for incorporating all available data in estimating measures and standard errors. To identify the optimal number of trajectory subtypes, we evaluated censored normal models (applied to normally distributed data with truncation at both ends) having 2 to 6 trajectories and selected a best-fitting model on the basis of clinical plausibility and statistical fit measures. It has been recommended that a model with the best fit should have the following statistical properties: (1) the least Bayesian information criterion (BIC); (2) each trajectory subgroup should include at least 5% of study population; (3) posterior probability >0.70; (4) odds of correct classification >5; and (5) concordance between estimated and actual proportion of patients assigned to the subgroup.[11]

For the present analysis, a 3-step procedure was applied in choosing the optimal model. In the first step, we started with the 6-trajectory model, decreasing the number of trajectories in a stepwise manner while using the BIC as test statistic in choosing the model that best represents the heterogeneity in trajectories. In this first step, we defined all trajectories as following a cubic polynomial based on prior literature suggesting recovery following SCI is nonlinear. In the second step, we evaluated the possibility that the shapes of the recovery trajectories are better described by a linear or quadratic function using BIC and a test of statistical significance. In a third step, having identified the model with the optimal number of trajectories and shapes, we assessed its adequacy using aforementioned recommended criteria. Finally, using a similar 3-step procedure, we evaluated multitrajectory models to examine the joint probability of recovery across the 3 neurologic endpoints. Here, we compared multitrajectory models with 3 to 6 trajectories, as described above.

To investigate factors that are predictive of recovery trajectories, descriptive statistics were applied comparing baseline covariates according to trajectory subgroups using analysis of variance for continuous variables and χ^2 for categorical variables. Next, association analyses were performed using multinomial logistic regression, with risk adjustment for the fixed effect of study, and baseline covariates as specified. The association between trajectory subtypes and the ZPP was analyzed using 2 approaches: (1) we examined the effect of the number of spinal segmental levels below the ASIA motor or sensory level with some preserved sensory or motor activity (extent of ZPP); (2) we further examined the effect of the degree of preserved sensory or motor activity measured as cumulative sensory or motor scores within the ZPP. Within the GBTM framework, multinomial regression was applied to study the association of recovery trajectories with 12-month functional outcome. Independent variables were the 3 trajectories and dependent variable was the motor subscore of the FIM scale. Risk-adjusted analyses accounted for the effect of age, sex, mechanism of injury, injury level, and fixed effect of study. Results are reported as relative risk ratios (RRRs) with 95% confidence intervals (CIs).

We performed a number of sensitivity analyses. We estimated trajectories for patients with at least 3 assessments to

understand the influence of attrition on our results. We also estimated trajectories for the individual studies, comparing the results to the pooled dataset, to understand the potential influence of between-study heterogeneity. Finally, we imputed missing covariates under the MAR assumption using multiple imputation by chained equations, a technique for inputting multivariable data, to generate 20 datasets. We repeated the association analyses in imputed data and compared results with the complete case analyses to study the influence of missing data. Estimates were pooled across datasets using the Rubin technique. Significance level was set at 5%. The analyses were performed using the GBTM module *Traj* within Stata version 13.1 (Stata Corp, College Station, TX).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was duly approved by the Research Ethics Board of The University Health Network, Toronto, Canada. Written informed consent was obtained from all participants who were enrolled in the primary SCI studies. The reporting of this study is in compliance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data Availability

Data from this study including those of NASCIS III, the Sygen Multicenter Acute Spinal Cord Injury Study, NACTN, and STASCIS are available on request.

Results

Participants

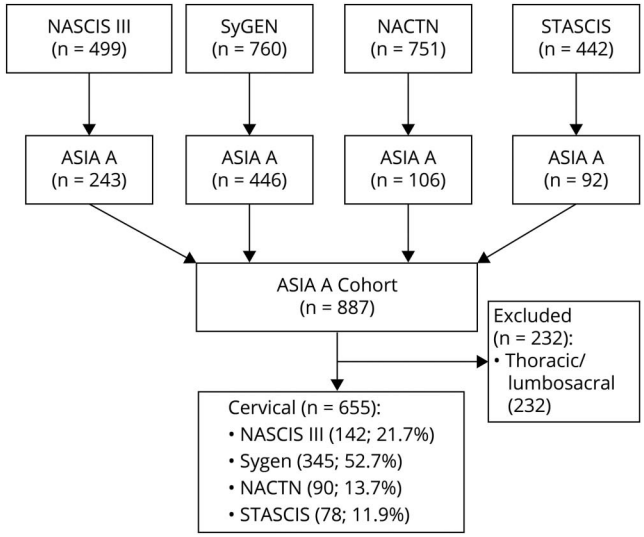
There were 2,452 patients across the 4 studies; among these, 655 (26.7%) were classified as having cervical level AIS grade A injury at baseline assessment performed within 1 week postinjury. Figure 1 shows a flowchart of the analysis. Baseline neurologic data were available for 93.3% (611/655) of patients. Follow-up was 66.6% (n = 436) at 3 months, 76.9% (n = 504) at 6 months, and 71.0% (n = 465) at 12 months. The average age was 35.5 ± 15.5 years, and most were men (81.4%; n = 533). MVC was the most common cause of injury (50.0%; n = 326) followed by falls (22.9%; n = 149), and others (27.2%; n = 177). Surgery was performed within 24 hours of the injury in 36.0% (n = 196) of patients, whereas 70.1% (n = 458) had methylprednisolone administration.

Trajectory Characteristics

The models with increasing trajectory subgroups had better fit statistics for all neurologic endpoints. To illustrate: BIC values for 2- to 6-trajectory models of the UEMS were −7,088.6, −6,731.2, −6,565.7, −6,483.5, and −6,473.0, respectively. Inspection of the trajectory plots indicated additional trajectories largely replicated the patterns of the 3-trajectory model but with smaller group sizes for all endpoints. Furthermore, models including more than 3 trajectories had one or more trajectories intersecting, hence complicating their interpretability. We therefore settled for the 3-trajectory model with all shapes specified by cubic function as having the optimal balance between heterogeneity, parsimony, and interpretation of recovery patterns. The models with 3 trajectories had posterior probabilities ranging from 0.87 to 0.98, and similarity between estimated and actual proportion of patients assigned to the subgroups, irrespective of neurologic endpoint, suggesting good statistical fit. The odds of correct classification ranged from 6 to 296, indicating adequate group assignment. For the joint probability models, the BIC improved as the trajectory groups increased. Visual inspection indicated that the 3- or 4-trajectory models were the most useful in terms of parsimony (see supplementary file, datadryad.org/stash/share/NwNMZVawfA7-cUdRtOj51LTyT6f-zGHYHKJ9B8YlP22g). We preferred the 3- over the 4-trajectory model since the group shapes and proportions of assigned subjects were comparable, except for a small group with especially good prognosis among the 4-trajectory model. We also considered descriptive consistency with the individual endpoint trajectories. Model diagnostic metrics indicated the 3-group multitrajectory model had excellent separation of groups based on established metrics (see supplementary file, datadryad.org/stash/share/NwNMZVawfA7-cUdRtOj51LTyT6f-zGHYHKJ9B8YlP22g).[11]

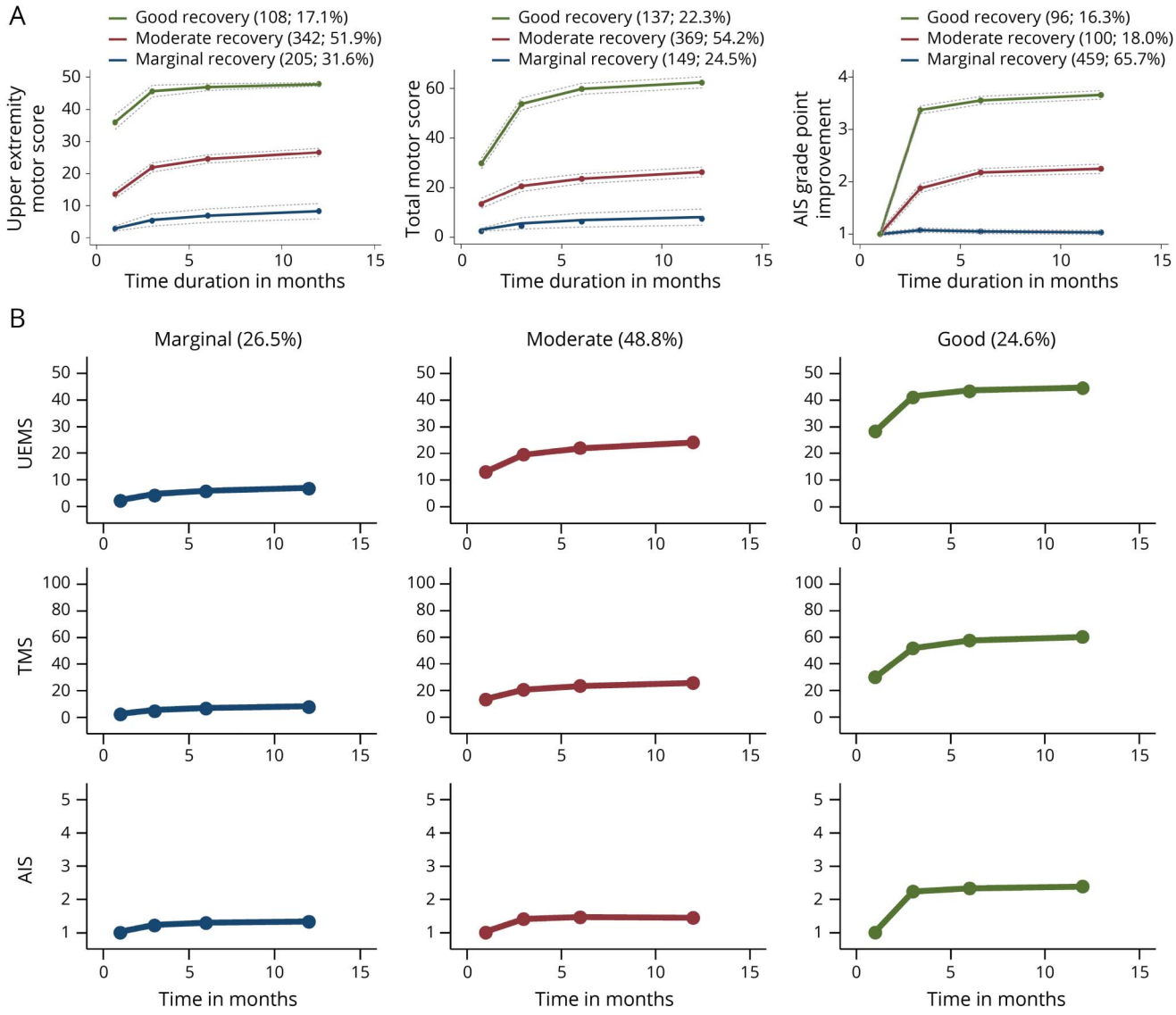
Figure 2A shows the 3 recovery trajectories for the different neurologic endpoints. Figure 2B presents the trajectories as joint probabilities of recovery across the neurologic

Figure 1 Flowchart of Participants in the Analysis



National Acute Spinal Cord Injury Study III (NASCIS III) is a double-blind, randomized multicenter study conducted between 1991 and 1995 to compare the efficacy of methylprednisolone administered for 24 hours with methylprednisolone administered for 48 hours or tirilazad mesylate administered for 48 hours in patients with acute spinal cord injury (SCI). Sygen is a double-blinded randomized multicenter study to determine efficacy and safety of Sygen (GM-1 ganglioside) in acute SCI. The Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) prospective cohort was conducted between 2002 and 2009 to evaluate the relative effectiveness of early (24 hours before injury) versus late (24 hours after injury) decompressive surgery after traumatic cervical SCI. The North American Clinical Trials Network (NACTN) prospective nonrandomized study enrolls patients from 11 centers to investigate the natural history of acute SCI. Enrolment commenced in 2005 and is ongoing. ASIA = American Spinal Injury Association.

Figure 2 Trajectories of Natural Recovery in Neurologic Function Following Complete Cervical Spinal Cord Injury



(A) Trajectories for each neurologic endpoint; each trajectory subgroup is defined by 1 trajectory. (B) Trajectories for the joint probability of recovery across the endpoints; each trajectory subgroup is defined by 3 trajectories: one for upper extremity motor score (UEMS), a second for total motor score (TMS), and a third for American Spinal Injury Association Impairment Scale (AIS) improvement. Note that the percentages provided in the legends are weighted in terms of the average posterior probabilities of group membership and therefore the numbers per group do not have to add up to whole counts. Some cases cannot be attributed unambiguously to one group or another.

endpoints. Table 1 displays the patients' characteristics according to trajectory pattern subtypes. For descriptive purposes, we applied the following labels to the trajectory subgroups:

Marginal recovery trajectory: patients who were deemed to follow this trajectory made minimal or no improvement in motor strength or had no change in AIS grade status (remained grade A) 12 months after the injury. When recovery was assessed as improvement in UEMS, 31.6% of patients were identified under this trajectory subgroup. The proportion was smaller with respect to TMS (24.5%). When recovery was assessed as improvement in AIS grade, 65.7% of patients followed this trajectory pattern. As shown in figure 2B, the joint probability of belonging to the marginal recovery group was 26.5%.

Moderate recovery trajectory: patients who were identified within this trajectory subgroup made modest progressive improvement in motor score or experienced, on average, a 1-point improvement in AIS grade (i.e., converted from AIS A at baseline to AIS B at 12 months postinjury). They had predicted mean UEMS of 14/50 points at baseline, which improved to 27/50 points at 12 months follow-up, indicating an average gain of 13 motor points over that time period. The moderate recovery trajectory was the most prevalent pattern subtype for motor function (UEMS, 54.2%; TMS, 55.2%). When recovery was assessed as improvement in AIS grade,

Table 1 Distribution of Patients' Baseline Characteristics According to Trajectory Subgroups for the Different Neurologic Endpoints

	Upper motor extremity score			Total motor score			American Spinal Injury Association Impairment Scale conversion		
Variable	Marginal	Moderate	Good	Marginal	Moderate	Good	Marginal	Moderate	Good
Baseline score	2.5 ± 3.3	13.9 ± 7.4	36.3 ± 10.5	1.7 ± 2.9	13.3 ± 7.8	30.6 ± 16.4	—	—	—
Age, y	38.8 ± 16.3	34.9 ± 15.2	31.2 ± 13.7	39.0 ± 16.1	34.9 ± 15.2	33.1 ± 15.1	35.2 ± 15.2	34.6 ± 15.7	37.9 ± 16.7
Male	172 (83.9)	277 (81.0)	84 (77.8))	124 (83.3)	305 (82.6)	104 (75.9)	380 (82.8)	80 (80.0)	73 (76.0)
Etiology: MVC	99 (49.0)	172 (50.3)	55 (50.9)	69 (49.4)	194 (52.7)	63 (45.9)	230 (50.4)	57 (57.0)	39 (40.6)
Fall	50 (24.7)	72 (21.0)	27 (25.0)	38 (25.9)	72 (19.6)	39 (28.5)	98 (21.5)	21 (21.0)	30 (31.3)
Others	53 (26.2)	98 (28.7)	26 (24.1)	40 (27.2)	102 (27.7)	35 (25.5)	128 (28.1)	22 (22.0)	27 (28.1)
SBP	115.5 ± 25.2	112.2 ± 22.4	114.5 ± 24.3	116.1 ± 25.2	112.7 ± 23.4	113.7 ± 22.8	113.5 ± 23.3	110.7 ± 27.1	117.3 ± 21.3
Levels									
C1–C4	170 (82.9)	117 (34.2)	8 (7.4)	130 (87.2)	138 (37.4)	27 (19.7)	213 (46.4)	34 (34.0)	48 (50.0)
C5–C6	35 (17.1)	224 (65.5)	68 (63.0)	19 (12.8)	228 (61.8)	80 (58.4)	221 (48.2)	62 (62.0)	44 (45.8)
C7–C8	0 (0)	1 (0.5)	32 (29.6)	0 (0)	0 (0.8)	30 (21.9)	25 (5.4)	4 (4.0)	4 (4.2)
Light touch	14.5 ± 6.8	22.4 ± 9.7	37.2 ± 14.8	13.4 ± 6.2	22.0 ± 9.5	32.8 ± 15.8	21.5 ± 11.9	24.3 ± 11.2	23.2 ± 15.3
Pinprick	14.1 ± 6.7	20.9 ± 8.0	35.5 ± 15.4	13.0 ± 6.4	20.5 ± 7.4	31.6 ± 16.4	20.5 ± 11.7	22.8 ± 10.3	21.6 ± 12.2
Sensory score	28.5 ± 13.1	43.4 ± 16.5	72.5 ± 29.3	26.4 ± 12.5	42.5 ± 15.9	64.1 ± 31.4	42.0 ± 23.1	47.2 ± 21.1	44.9 ± 25.7
Early surgery	54 (32.0)	112 (38.5)	30 (35.7)	42 (34.4)	115 (36.4)	39 (36.8)	134 (35.1)	30 (34.9)	32 (42.1)
Steroid	140 (69.0)	242 (70.8)	76 (70.4)	103 (69.6)	255 (69.3)	100 (73.0)	323 (70.7)	66 (66.0)	69 (71.9)

Abbreviations: MVC = motor vehicular collision; SBP = systolic blood pressure.
Missing data excluded.

18.0% of patients were classified as belonging to this trajectory subgroup. When recovery was modeled as a joint function of all 3 endpoints, 48.8% of patients mapped to this recovery pattern type (figure 2B).

Good recovery trajectory: patients following this trajectory experienced rapid recovery in motor strength or improved on average 2 grade points on the AIS (converting from AIS grade A to at least a grade C) within 3 months of injury. The predicted mean UEMS increased from 36/50 at baseline to 48/50 at 12 months, indicating full recovery potential in upper extremity motor function. The smallest proportion of patients followed this trajectory when the 3 neurologic endpoints were examined individually (UEMS, 17.1%; TMS, 22.3%; AIS, 16.0%) or as a joint function (24.7%).

Association With Clinical and Treatment Variables

We present the results of association analysis for individual recovery endpoints rather than their joint probabilities. The trajectory subgroups demonstrated differential clinical and treatment characteristics. As shown in table 1, the marginal recovery group had a high preponderance of C1–C4 injuries, lowest scores for sensory modalities (light touch, pinprick, and total sensory score), and a high proportion of patients without a zone of partial injury. In contrast, the good recovery group had high preponderance of C7–C8 injuries, the highest scores for sensory modalities, and a high proportion of patients with some preservation of sensory and motor activity at lower neurologic levels beyond the injury level (that is, ZPP). Association analyses indicated that, compared to the marginal recovery group, patients following the moderate or good recovery trajectories were of a younger age, had more caudally located cervical injuries, and had a higher degree of preserved motor and sensory function at baseline examination (tables 2–4). The good recovery group in particular was characterized by the presence of a ZPP ≥3 sensory levels or ≥2 motor segmental levels and also by a higher degree of motor preservation (cumulative motor score) within the ZPP. Patients who had early surgery were more likely to be classified as belonging to the good recovery trajectory of UEMS, relative to those who had late surgery (adjusted RRR, 2.91, 95% CI, 1.05–8.14; $p = 0.04$). Less robust associations were noted between clinical and treatment characteristics and AIS grade improvement trajectories.

Association With Functional Outcome

Trajectories with better prognosis for neurologic recovery had significantly higher mean FIM motor scores at 12 months.

Table 2 Association of Clinical and Treatment Characteristics With Upper Extremity Motor Score Trajectories

	Unadjusted RRR (95% CI)		Adjusted RRR (95% CI)	
Variables	**Moderate recovery**	**Good recovery**	**Moderate recovery**	**Good recovery**
Age	0.98 (0.97–0.99)	0.97 (0.95–0.98)	0.98 (0.97–0.99)	0.97 (0.95–0.99)
Sex: female	Ref	Ref	Ref	Ref
Male	0.82 (0.52–1.30)	0.67 (0.37–1.21)	0.76 (0.48–1.21)	0.60 (0.33–1.09)
Etiology: MVC	Ref	Ref	Ref	Ref
Fall	0.83 (0.54–1.28)	0.97 (0.55–1.72)	1.18 (0.57–2.43)	1.88 (0.71–5.00)
Others	1.06 (0.70–1.61)	0.88 (0.50–1.57)	1.56 (0.84–2.91)	0.85 (0.34–2.15)
SBP	0.99 (0.98–1.00)	0.99 (0.99–1.01)	0.99 (0.98–1.00)	1.00 (0.98–1.01)
Levels: C1–C4	Ref	Ref	Ref	Ref
C5–C6	9.30 (6.07–14.25)	626,181.4	10.85 (6.16–19.11)	31.29 (12.19–80.33)
C7–C8	41.29 (18.22–93.56)	2.93e+08	408,049.4	9.85e+07
Light touch	1.19 (1.14–1.23)	1.30 (1.25–1.36)	1.11 (1.05–1.17)	1.21 (1.14–1.29)
Pinprick	1.37 (1.13–1.22)	1.31 (1.25–1.37)	1.06 (1.01–1.11)	1.18 (1.11–1.24)
Sensory score	1.09 (1.07–1.12)	1.15 (1.13–1.18)	1.05 (1.02–1.07)	1.10 (1.07–1.13)
ZPP left sensory: 0	Ref	Ref	Ref	Ref
1	1.30 (0.82–2.07	1.40 (0.65–2.99)	1.89 (0.94–3.81)	1.88 (0.61 5.83)
2	2.33 (1.15–4.73)	1.93 (0.64–5.87)	3.12 (1.16–8.47)	2.60 (0.47–14.45)
≥3	2.05 (1.23–3.44)	2.54 (1.17–5.53)	2.32 (1.10–4.88)	3.74 (1.19–11.76)
ZPP right sensory: 0	Ref	Ref	Ref	Ref
1	1.10 (0.69–1.76)	1.60 (0.75–3.42)	1.35 (0.68–2.69)	2.95 (0.94–9.28)
2	2.40 (1.24–4.67)	1.17 (0.34–4.04)	1.78 (0.71–4.43)	8.83e-07
≥3	1.88 (1.13–3.10)	2.81 (1.31–6.05)	2.17 (1.03–4.55)	5.52 (1.69–18.01)
ZPP left motor: 0	Ref	Ref	Ref	Ref
1	1.79 (1.17–2.72)	2.00 (0.91–4.40)	1.89 (1.01–3.56)	7.80 (1.92–31.61)
≥2	5.78 (2.91–11.48)	19.54 (8.144–46.89)	6.09 (2.18–17.01)	57.28 (2.18–259.71)
ZPP right motor: 0	Ref	Ref	Ref	Ref
1	2.18 (1.43–3.34)	1.74 (0.78–3.88)	1.80 (0.95–3.40)	4.94 (1.26–19.40)
≥2	5.33 (2.92–9.72)	12.79 (5.68–28.80)	4.52 (1.85–11.02)	30.79 (7.55–125.55)
Surgery: late	Ref	Ref	Ref	Ref
Early	1.33 (0.89–1.99)	1.18 (0.68–2.05)	1.83 (0.87–3.87)	2.91 (1.05–8.14)
MP: no	Ref	Ref	Ref	Ref
Yes	1.09 (0.75–1.59)	1.07 (0.64–1.78)	0.81 (0.42–1.58)	0.70 (0.27–1.79)

Abbreviations: CI = confidence interval; MP = methylprednisolone; MVC = motor vehicular collision; RRR = relative risk ratio; SBP = systolic blood pressure; ZPP = zone of partial preservation.

Predicted mean FIM motor score approximately doubled when considering patients exhibiting moderate as compared to marginal recovery trajectories and doubles again when considering patients exhibiting good as compared to moderate recovery trajectories. To illustrate, predicted mean FIM motor score for the 3 UEMS trajectories were as follows: marginal recovery subtype: 20.7, 95% CI 14.8–26.6 points; moderate recovery: 44.4, 95% CI: 39.8–48.9 points; and good recovery: 71.5, 95% CI: 63.4–79.6 points ($p < 0.001$). Similar trends were observed with respect to the other endpoints (TMS and AIS).

Table 3 Association of Demographic, Clinical, and Treatment Characteristics With Total Motor Score Trajectories

	Unadjusted RRR (95% CI)		Adjusted RRR (95% CI)	
Variables	**Moderate recovery**	**Good recovery**	**Moderate recovery**	**Good recovery**
Age	0.98 (0.97–0.99)	0.98 (0.96–0.99)	0.98 (0.97–1.00)	0.97 (0.96–0.99)
Sex: female	Ref	Ref	Ref	Ref
Male	0.96 (0.57–1.60)	0.64 (0.36–1.13)	0.93 (0.56–1.56)	0.57 (0.31–1.03)
Etiology: MVC	Ref	Ref	Ref	Ref
Fall	0.63 (0.42–1.09)	1.12 (0.64–1.97)	1.04 (0.48–2.27)	2.12 (0.84–5.36)
Others	0.91 (0.57–1.43)	0.96 (0.54–1.69)	1.39 (0.71–2.72)	1.26 (0.54–2.96)
SBP	0.99 (0.98–1.00 0	1.00 (0.98–1.01)	0.99 (0.98–1.01)	0.99 (0.98–1.01)
Levels: C1–C4	Ref	Ref	Ref	Ref
C5–C6	11.31 (6.68–19.12	3,477,034	11.74 (5.90–23.37)	19.41 (8.47–44.52)
C7–C8	20.27 (10.59–38.82)	1.78e+08	875,934.2	3.11e+07
Light touch	1.23 (1.16–1.29)	1.31 (1.25–1.38)	1.12 (1.05–1.19)	1.21 (1.13–1.29)
Pinprick	1.21 (1.16–1.27)	1.32 (1.25–1.39)	1.04 (1.02–1.16)	1.21 ((1.12–1.29)
Sensory score	1.11 (1.10–1.14)	1.16 (1.13–1.19)	1.05 (1.02–1.09)	1.11 (1.07–1.15)
ZPP left sensory: 0	Ref	Ref	Ref	Ref
1	1.24 (0.75–2.05)	1.43 (0.69–2.96)	2.43 (1.14–5.15)	3.23 (1.16–9.00)
2	1.97 (0.90–4.27)	2.55 (0.92–7.06)	2.60 (0.90–7.49)	2.64 (0.60–11.66)
≥3	2.44 (1.35–4.41)	3.31 (1.52–7.22)	4.11 (1.71–9.90)	7.50 (2.47–22.80)
ZPP right sensory: 0	Ref	Ref	Ref	Ref
1	1.28 (0.77–2.12)	1.60 (0.77–3.30)	1.70 (0.82–3.55)	3.17 (1.15–8.74)
2	2.34 (1.12–4.89)	1.89 (0.66–5.39)	1.68 (0.63–4.48)	0.55 (0.09–3.41)
≥3	2.28 (1.30–4.03)	3.17 (1.49–6.73)	3.44 (1.46–8.14)	8.13 (2.68–24.71)
ZPP left motor: 0	Ref	Ref	Ref	Ref
1	2.74 (1.67–4.48)	3.47 (1.64–7.34)	3.98 (1.89–8.38)	9.54 (3.09–29.45)
≥2	4.57 (2.16–9.63)	19.65 (8.17–47.28)	3.56 (1.13–11.23)	29.43 (7.65–113.20)
ZPP right motor: 0	Ref	Ref	Ref	Ref
1	4.34 (2.60–7.25)	3.40 (1.62–7.13)	4.84 (2.29–10.25)	6.01 (2.06–17.53)
≥2	6.85 (3.36–13.98)	14.30 (6.16–33.16)	5.75 (1.98–16.70)	20.29 (5.83–70.58)
Surgery: late	Ref	Ref	Ref	Ref
Early	1.09 (0.70–1.69)	1.11 (0.64–1.91)	1.06 (0.48–2.34)	1.11 (0.42–2.96)
MP: no	Ref	Ref	Ref	Ref
Yes	0.99 (0.65–1.49)	1.18 (0.71–1.98)	0.76 (0.37–1.57)	0.65 (0.26–1.64)

Abbreviations: CI = confidence interval; MP = methylprednisolone; MVC = motor vehicular collision; RRR = relative risk ratio; SBP = systolic blood pressure; ZPP = zone of partial preservation.

Sensitivity Analysis

To understand the possible influence of attrition, we compared the 495 (76%) patients for whom at least 3 of the 4 neurologic assessments are available to the 160 (24%) patients who had 2 or fewer follow-up assessments. A notable difference was that the former were younger than the latter group with fewer assessments (33.5 ± 14.3 vs 42.2 ± 17.5 years, $p = 0.001$). However, restricting the analysis to only the patients for whom 3 or 4 neurologic assessment time points were available demonstrated the 3-group model remained optimal and the shape of trajectories and patient assignment to trajectory subtypes were largely comparable to the primary

Table 4 Association of Demographic, Clinical, and Treatment Characteristics With American Spinal Injury Association Impairment Scale Conversion Trajectories

	Unadjusted RRR (95% CI)		Adjusted RRR (95% CI)	
Variables	**Moderate recovery**	**Good recovery**	**Moderate recovery**	**Good recovery**
Age	1.00 (0.98–1.01)	1.01 (1.00–1.02)	1.00 (0.98–1.01)	1.01 (0.99–1.02)
Sex: female	Ref	Ref	Ref	Ref
Male	0.83 (0.48–1.44)	0.66 (0.39–1.11)	0.83 (0.48–1.45)	0.56 (0.38–1.11)
Etiology: MVC	Ref	Ref	Ref	Ref
Fall	0.87 (0.50–1.50)	1.81 (1.06–3.07)	0.78 (0.35–1.75)	1.99 (0.94–4.21)
Others	0.69 (0.41–1.19)	1.24 (0.73–2.13)	0.66 (0.34–1.31)	1.62 (0.79–3.34)
SBP	1.00 (0.98–1.01)	1.01 (1.00–1.02)	1.00 (0.98–1.01)	1.00 (0.99–1.02)
Levels: C1–C4	Ref	Ref	Ref	Ref
C5–C6	1.76 (1.11–2.78)	0.88 (0.56–1.39)	1.74 (0.95–3.18)	1.01 (0.55–1.84)
C7–C8	1.00 (0.33–3.06)	0.71 (0.24–2.13)	1.01 (0.27–3.82)	0.84 (0.22–3.17)
Light touch	1.02 (1.00–1.03)	1.01 (0.99–1.03)	1.01 (0.99–1.04)	1.03 (1.00–1.06)
Pinprick	1.02 (1.00–1.03)	1.01 (0.99–1.03)	1.01 (0.98–1.04)	1.02 (0.99–1.05)
Sensory score	1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.01 (0.99–1.02)	1.02 (1.00–1.03)
ZPP left sensory: 0	Ref	Ref	Ref	Ref
1	1.42 (0.79–2.56)	1.34 (0.68–2.65)	1.11 (0.53–2.35)	1.70 (0.73–3.99)
2	0.55 (0.20–1.53)	1.07 (0.42–2.74)	0.61 (0.18–2.00)	0.64 (0.16–2.58)
≥3	1.47 (0.79–2.71)	1.88 (0.96–3.67)	1.47 (0.68–3.20)	2.36 (0.98–5.68)
ZPP right sensory: 0	Ref	Ref	Ref	Ref
1	1.27 (0.71–2.29)	1.08 (0.54–2.16)	0.95 (0.45–2.01)	1.13 (0.48–2.71)
2	0.77 (0.33–1.81)	1.18 (0.50–2.79)	0.80 (0.30–2.22)	0.61 (0.15–2.42)
≥3	1.37 (0.75–2.4)	1.54 (0.79–2.99)	1.51 (0.71–3.22)	2.44 (1.04–5.73)
ZPP left motor: 0	Ref	Ref	Ref	Ref
1	2.15 (1.28–3.62)	1.76 (0.95–3.26)	1.63 (0.83–3.21)	2.10 (0.90–4.92)
≥2	1.41 (0.74–2.66)	2.61 (1.39–4.91)	1.26 (0.56–2.79)	4.11 (1.74–9.68)
ZPP right motor: 0	Ref	Ref	Ref	Ref
1	1.38 (0.81–2.33)	1.26 (0.68–2.35)	1.15 (0.58–2.27)	1.02 (0.44–2.36)
≥2	1.34 (0.74–2.42)	2.33 (1.27–4.30)	1.37 (0.63–2.96)	2.13 (0.95–4.76)
Surgery: late	Ref	Ref	Ref	Ref
Early	0.99 (0.61–1.62)	1.35 (0.82–2.22)	0.93 (0.43–1.98)	0.55 (0.24–1.25)
MP: no	Ref	Ref	Ref	Ref
Yes	0.81 (0.51–1.28)	1.06 (0.65–1.73)	0.90 (0.45–1.81)	0.71 (0.31–1.65)

Abbreviations: CI = confidence interval; MP = methylprednisolone; MVC = motor vehicular collision; RRR = relative risk ratio; SBP = systolic blood pressure; ZPP = zone of partial preservation.

analysis incorporating all available data. Association analysis led to the same conclusions.

With respect to the influence of between-study heterogeneity, we noted the NASCIS III and Sygen cohorts were generally younger and had higher proportions of injuries due to MVC, C7–C8 injuries, and most of these patients were administered methylprednisolone, compared to the NACTN and STASCIS groups. A relatively smaller proportion of the NASCIS III (n = 26 [24%]) and Sygen (n = 60 [22%]) patients had early

surgery (within 24 hours postinjury) when compared to the NACTN (n = 60 [70%]) and STASCIS (n = 50 [71%]) study patients ($p = 0.008$) (see supplementary file, datadryad.org/stash/share/NwNMZVawfA7cUdRtOj51LTyT6f-zGHYHKJ9B8YlP22g). Despite these differences, patient assignment to trajectory subgroups in the pooled analysis did not statistically differ between studies for the UEMS and TMS endpoints. However, for the AIS endpoint, more patients were assigned to the marginal recovery subgroup and lower proportions assigned to the good recovery trajectory among the Sygen cohort than the other studies. When we stratified analysis by studies, the 3-trajectory model remained robust across constituent studies, although the proportion of patients mapping to each trajectory subtype differed across studies. Finally, data imputation was performed for 1,108 of 11,790 (9.4%) data points needed for the association analyses. Results of analyses in imputed data were similar to those from complete case analyses, and the conclusions remained the same.

Discussion

This study provides a unique approach to assess recovery trajectories in the SCI population. This novel approach suggests that patients with traumatic cervical complete SCI follow 3 unique pathways of neurologic recovery during the initial 12 months postinjury. These distinctive trajectories may be interpreted as denoting relatively similar subpopulations with variable innate potential for neurologic improvement over time. The variable potential for recovery could be related to differences in injury mechanism, pathologic expression, or postinjury neuroanatomic and pathophysiologic adaptations.[12,13]

Natural history studies have demonstrated that majority of individuals who sustain sensorimotor complete SCI will experience no improvement in neurologic grade and minimal motor recovery at 1 year.[5,7-9,14] The marginal recovery trajectory most likely mirrors the prognosis of this cohort, since the members presumably sustained an extremely severe primary cord injury, hence were inherently incapable of recovery.

Based on studies assessing cumulative mean change in motor or sensory scores, it is recognized that in a variable proportion of patients, spontaneous improvement in neurologic function can occur, with the bulk of recovery occurring in the first 6 months, though some residual incremental improvement can occur up to, and infrequently after, 12 months postinjury.[5,9,14] While our results are consistent with this overall pattern, they further demonstrate that among those who experience recovery following a sensorimotor complete SCI, 2 broad categories of patients are recognizable (i.e., moderate and good recovery trajectories). Patients belonging to a moderate recovery trajectory will make progressive but partial improvements. This trajectory represents the majority of patients who improved with time. Prognosis for improvement was greatest among the good recovery trajectory cohort, who could achieve functionally meaningful recovery in neurologic function. It is possible that, to some degree, this group reflects apparent recovery due to grade misclassification from early neurologic assessment in some patients.[15,16] According to the literature, the potential for grade misclassification is higher when neurologic assessment is performed within 24 hours of the injury, or when adequate measures have not been taken to exclude patients in whom early assessment might prove unreliable; for example, those with attenuated cognitive function due to comorbid head injury, drug use, neuropsychiatric comorbidity, ventilator support, or language difficulties, among others.[15,17] Although our analysis included a significant proportion of patients who had neurologic assessment within 24 hours of injury, specifically those from the NACTN study and the STASCIS, it is noteworthy that patient recruitment in the studies followed standardized protocols designed to minimize confounding due to unreliable early examination. Previous studies have found that a residual proportion of patients with neurologically complete SCI will still achieve functionally meaningful recovery in neurologic function, even after factors leading to unreliable assessment are excluded.[16,18,19]

From the perspective of AIS change, identified trajectories essentially correspond to degrees of grade conversion over time. The proportion of patients mapping to the different AIS recovery trajectories are similar to reported conversion rates in the literature.[5,9] A relatively higher proportion of patients mapped to motor trajectories with improved prognosis for recovery compared to AIS trajectories, possibly because of greater sensitivity of the ASIA motor score to change in neurologic status compared to the AIS classification.[9] This finding is in line with the common clinical finding that while the majority of patients will remain AIS grade A at follow-up, many will experience recovery of one level of motor neurologic function (i.e., no improvement in AIS grade but some recovery in motor score).

The zone of partial preservation is critical in understanding the prognosis for neurologic recovery after a sensorimotor complete SCI.[9] In evaluating the significance of the ZPP, previous studies demonstrate that a higher motor power within the zone predicts a higher possibility of functionally meaningful recovery, particularly if a partially innervated myotome also exhibits sensory preservation in the corresponding dermatome.[7,9,20] Our present study highlights the effect of cumulative motor and sensory activity within the ZPP, showing that the neurologic extent of the zone and the magnitude of preserved motor or sensory function within it differentially characterize longitudinal recovery trajectories. Furthermore, the association between trajectories with improved prognosis for recovery and younger age could be explained by the degree of cord resilience to injury, differential aptitude for recovery, or the extent of comorbid burden.

Our finding that patients with sensorimotor complete SCI follow fundamentally different longitudinal recovery paths has

considerable implications. First, it contributes to a refined understanding of longitudinal dynamic trends of recovery in SCI, thereby providing supplementary insight into the history of natural recovery following SCI. In this regard, the evidence from our study may contribute to improving our understanding of reasons for heterogeneity in natural recovery observed in the literature. According to a recent review evaluating AIS grade A patients, reported rates of conversion varied widely from 10% to 70%.[6] Possibly, this heterogeneity reflects subpopulations at varying recovery trajectories at the reference time point. Second, the finding that recovery trajectories are differentially associated with clinical and treatment characteristics indicates the feasibility of developing trajectory-based practical prediction tools to inform prognosis or predict treatment response. The need for such a tool is further underscored by the current quest for improvement in the design of translational studies of novel therapies, and the application of precision medicine for SCI.[3,15,21] Third, it is possible trajectory pattern subtypes have unique clinicopathologic identities. Hence, examining their correlation with molecular, genetic, electrophysiologic, and neuroimaging biomarkers could shed greater light on SCI heterogeneity and serve as a framework for a nuanced classification of the disease phenotype. Our study, therefore, provides the starting point to define unique clinical phenotypes based on potential for recovery, rather than baseline severity of injury alone.

The main strength of this study is the use of longitudinal data from large prospective multicenter cohort studies of SCI. Follow-up assessments were repeated at documented points in the natural history of SCI recovery. The trajectory patterns were robust to multiple metrics of neurologic function and between-study heterogeneity. Of importance also is the fact that the current analysis covered the critical first year postinjury when recovery, if feasible, would mostly occur.[5,9] Furthermore, the observed temporal patterns most likely reflect real-world trends considering that group-based trajectory modeling makes no a priori assumptions about the shape of trajectory patterns, allows for identification of inherent trends in the distribution of longitudinal data, and is useful to calibrate whether individual changes are indicative of real or random variations in behavior.[11] Other analysts of large SCI datasets have used recursive partitioning to split patients into recovery-based classes and especially identify those with floor and ceiling effects.[22] This methodology is compatible with group-based trajectory modeling, which has the advantage to disclose latent factors that may not be considered in recursive partitioning trees.

From a limitations perspective, stricter eligibility and exclusion of patients with very poor prognosis from the prospective studies and clinical trials may have artificially inflated the proportion of patients mapping to trajectory pattern subtypes with improved prognosis for recovery limiting generalizability. In spite of this, the high quality of data and follow-up arising from such studies helps to ensure the internal validity of this analysis. There are elements of chronological bias related to variability in initial timing of assessment between patients and across studies or related to the eligibility period of the included studies, which covered a broad time frame, or since the present study provides no insight beyond the first year postinjury. Nonetheless, it is well recognized that neurologic recovery occurs mostly within the time frame covered by our study.[5,9,19] We are unable to exclude intangible elements of treatment selection bias resulting from between-center variations in acute care and rehabilitation protocols. It should be noted that variability in treatment protocols is recognized within current clinical guidelines, considering limited evidence in support of the efficacy of many treatment options.[23-25] Perhaps, in accommodating between-center variability, we have enhanced the translation of our study findings to broader care settings. The drop-off rate in the present study is not insignificant, though comparable to those of previous prospective studies evaluating long-term outcomes of SCI.[5,26] Presumably, patients lost to follow-up experienced relatively worse prognosis, and, given that scenario, would have hypothetically followed the marginal recovery trajectory. Hence, their inclusion in the analysis would be unlikely to alter trajectory numbers or shapes, as we showed in sensitivity analysis, although it would have changed the proportion of patients following individual trajectory subtypes. To minimize the effect of data loss, we applied multiple imputations assuming a MAR mechanism. Whereas the ideal situation would have been to have all data points available, the practical realities of registry-based data analysis precluded this possibility. The MAR assumption is reasonable given prior literature that missing values in medical science often occur on a MAR mechanism.[27] Furthermore, sensitivity analysis demonstrated no major change in study findings between complete cases and imputed datasets, reinforcing the suitability of this assumption. It should also be acknowledged that inclusion of additional trajectories may have led to increased model fit, however, this also would have diminished clinical utility and interpretability as discussed above; our final models were weighted in preference of substantive usefulness over fit statistics. Although our choice to model trajectory shape using cubic functions was based on a priori information on SCI recovery and expert recommendations,[11] the cubic function less accurately described the marginal trajectory subgroups, given its smaller variability in recovery with time. However, this function likely remains the best option for modeling this clinical situation based on the data available at the time. Finally, we studied a limited number of time invariant characteristics. An important next step would be to consider modifiable risk factors and time-variant factors to assess how well risk factors classify individuals into trajectory subgroups. Future work will also be required to validate the trajectory models we have developed in this article.

This study shows that patients with sensorimotor complete traumatic cervical SCI can be classified into distinct subgroups based on their temporal patterns of neurologic recovery. The subgroups demonstrated differential clinical and treatment characteristics and potential for subsequent long-term functional outcome. Our findings demonstrate the utility of a

novel approach to describing with greater granularity the history of natural recovery following SCI. In addition, this work defines unique clinical phenotypes based on potential for recovery, rather than baseline severity of injury alone. This approach may prove beneficial in clinical prognostication and in the design and interpretation of clinical trials in acute SCI.

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References

1. NSCIS Center. *Spinal Cord Injury (SCI) Facts and Figures at a Glance*. University of Alabama at Birmingham; 2016.
2. Ackery A, Tator C, Krassioukov A. A global perspective on spinal cord injury epidemiology. *J Neurotrauma*. 2004;21(10):1355-1370.
3. Ahuja CS, Wilson JR, Nori S, et al. Traumatic spinal cord injury. *Nat Rev Dis Primers*. 2017;3:17018.
4. Marino RJ, Barros T, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury. *J Spinal Cord Med*. 2003;26(suppl 1): S50-S56.
5. Marino RJ, Ditunno JF Jr, Donovan WH, Maynard F Jr. Neurologic recovery after traumatic spinal cord injury: data from the Model Spinal Cord Injury Systems. *Arch Phys Med Rehabil*. 1999;80(11):1391-1396.
6. El Tecle NE, Dahdaleh NS, Bydon M, Ray WZ, Torner JC, Hitchon PW. The natural history of complete spinal cord injury: a pooled analysis of 1162 patients and a meta-analysis of modern data. *J Neurosurg Spine*. 2018;28(4):436-443.
7. Waters RL, Adkins RH, Yakura JS, Sie I. Motor and sensory recovery following complete tetraplegia. *Arch Phys Med Rehabil*. 1993;74(3):242-247.
8. Waters RL, Yakura JS, Adkins RH, Sie I. Recovery following complete paraplegia. *Arch Phys Med Rehabil*. 1992;73(9):784-789.
9. Fawcett JW, Curt A, Steeves JD, et al. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord*. 2007;45(3):190-205.
10. Wang M, Vaez M, Dorner TE, et al. Trajectories and characteristics of work disability before and after acute myocardial infarction. *Heart*. 2018;104(4):340-348.
11. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6:109-138.
12. Rossignol S, Frigon A. Recovery of locomotion after spinal cord injury: some facts and mechanisms. *Annu Rev Neurosci*. 2011;34:413-440.

13. Curt A, Van Hedel HJ, Klaus D, Dietz V. Recovery from a spinal cord injury: significance of compensation, neural plasticity, and repair. *J Neurotrauma.* 2008;25(6):677-685.
14. Burns AS, Marino RJ, Flanders AE, Flett H. Clinical diagnosis and prognosis following spinal cord injury. *Handb Clin Neurol.* 2012;109:47-62.
15. Tator CH. Review of treatment trials in human spinal cord injury: issues, difficulties, and recommendations. *Neurosurgery.* 2006;59(6):957-987.
16. Marino RJ, Burns S, Graves DE, Leiby BE, Kirshblum S, Lammertse DP. Upper- and lower-extremity motor recovery after traumatic cervical spinal cord injury: an update from the national spinal cord injury database. *Arch Phys Med Rehabil.* 2011;92(3):369-375.
17. Burns AS, Lee BS, Ditunno JF Jr, Tessler A. Patient selection for clinical trials: the reliability of the early spinal cord injury examination. *J Neurotrauma.* 2003;20(5):477-482.
18. Brown PJ, Marino RJ, Herbison GJ, Ditunno JF Jr. The 72-hour examination as a predictor of recovery in motor complete quadriplegia. *Arch Phys Med Rehabil.* 1991;72(8):546-548.
19. Kirshblum S, Millis S, McKinley W, Tulsky D. Late neurologic recovery after traumatic spinal cord injury. *Arch Phys Med Rehabil.* 2004;85(11):1811-1817.
20. Wilson JR, Cadotte DW, Fehlings MG. Clinical predictors of neurological outcome, functional status, and survival after traumatic spinal cord injury: a systematic review. *J Neurosurg Spine.* 2012;17(1 suppl):11-26.
21. Piazza M, Schuster J. Timing of surgery after spinal cord injury. *Neurosurg Clin N Am.* 2017;28(1):31-39.
22. Evaniew N, Fallah N, Rivers CS, et al. Unbiased recursive partitioning to stratify patients with acute traumatic spinal cord injuries: external validity in an observational cohort study. *J Neurotrauma.* 2019;36(18):2732-2742.
23. Fehlings MG, Tetreault LA, Wilson JR, et al. A clinical practice guideline for the management of patients with acute spinal cord injury and central cord syndrome: recommendations on the timing (</=24 hours versus >24 hours) of decompressive surgery. *Glob Spine J.* 2017;7(3 suppl):195s-202s.
24. Fehlings MG, Tetreault LA, Aarabi B, et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the type and timing of rehabilitation. *Glob Spine J.* 2017;7(3 suppl):231s-238s.
25. Fehlings MG, Martin AR, Tetreault LA, et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the role of baseline magnetic resonance imaging in clinical decision making and outcome prediction. *Glob Spine J.* 2017;7(3 suppl):221s-230s.
26. Kopp MA, Watzlawick R, Martus P, et al. Long-term functional outcome in patients with acquired infections after acute spinal cord injury. *Neurology.* 2017;88(9):892-900.
27. Rubin DB. Multiple imputation for nonresponse in surveys. Hoboken, NJ: John Wiley & Sons; 1987.