Prognostic value of tissue bridges in cervical spinal cord injury: a longitudinal, multicentre, retrospective cohort study

Dario Pfyffer, Andrew C Smith, Kenneth A Weber II, Andreas Grillhoesl, Orpheus Mach, Christina Draganich, Jeffrey C Berliner, Candace Tefertiller, Iris Leister, Doris Maier, Jan M Schwab, Alan Thompson, Armin Curt, Patrick Freund

Summary

Background The accuracy of prognostication in patients with cervical spinal cord injury (SCI) needs to be improved. We aimed to explore the prognostic value of preserved spinal tissue bridges—injury-spared neural tissue adjacent to the lesion—for prediction of sensorimotor recovery in a large, multicentre cohort of people with SCI.

Methods For this longitudinal study, we included patients with acute cervical SCI (vertebrae C1–C7) admitted to one of three trauma or rehabilitation centres: Murnau, Germany (March 18, 2010–March 1, 2021); Zurich, Switzerland (May 12, 2002–March 2, 2019); and Denver, CO, USA (Jan 12, 2010–Feb 16, 2017). Patients were clinically assessed at admission (baseline), at discharge (3 months), and at 12 months post SCI. Midsagittal tissue bridges were quantified from T2-weighted images assessed at 3–4 weeks post SCI. Fractional regression and unbiased recursive partitioning models, adjusted for age, sex, centre, and neurological level of injury, were used to assess associations between tissue bridge width and baseline-adjusted total motor score, pinprick score, and light touch scores at 3 months and 12 months. Patients were stratified into subgroups according to whether they showed better or worse predicted recovery.

Findings The cohort included 227 patients: 93 patients from Murnau (22 [24%] female); 43 patients from Zurich (four [9%] female); and 91 patients from Denver (14 [15%] female). 136 of these participants (from Murnau and Zurich) were followed up for up to 12 months. At 3 months, per preserved 1 mm of tissue bridge at baseline, patients recovered a mean of 9·3% (SD 0·9) of maximal total motor score (95% CI 7·5–11.2), 8·6% (0·8) of maximal pinprick score (7·0–10·1), and 10·9% (0·8) of maximal light touch score (9·4–12·5). At 12 months post SCI, per preserved 1 mm of tissue bridge at baseline, patients recovered a mean of 10·9% (1·3) of maximal total motor score (8·4–13·4), 5·7% (1·3) of maximal pinprick score (3·3–8·2), and 6·9% (1·4) of maximal light touch score (4·1–9·7). Partitioning models identified a tissue bridge cutoff width of 2·0 mm to be indicative of higher or lower 3-month total motor, pinprick, and light touch scores, and a cutoff of 4·0 mm to be indicative of higher and lower 12-month scores. Compared with models that contained clinical predictors only, models additionally including tissue bridges had significantly improved prediction accuracy across all three centres.

Interpretation Tissue bridges, measured in the first few weeks after SCI, are associated with short-term and long-term clinical improvement. Thus, tissue bridges could potentially be used to guide rehabilitation decision making and to stratify patients into more homogeneous subgroups of recovery in regenerative and neuroprotective clinical trials.

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Introduction

Patients with spinal cord injury (SCI) usually have sensorimotor and autonomic dysfunction and the extent of recovery after an SCI depends on the degree of spinal cord tissue damage.[1] Accurate outcome prediction is of utmost importance for patients, treating therapists, and attending physicians.[2] The gold standard in predicting the extent of recovery is to use neurological characteristics assessed at hospital admission, according to the International Standards for the Neurological Classification of SCI (ISNCSCI)[3] and the American Spinal Injury Association Impairment Scale (AIS) grade.[4,5] However, patients with SCI with similar baseline clinical scores can show different recovery trajectories.[6] This variability can be attributed, in part, to limitations of the clinical assessments (eg, lack of proper inter-rater reliability and susceptibility to examination confounds), which cannot directly capture the neurological heterogeneity owing to the complexity of the different neuropathological processes that influence recovery.[6]

Early prediction-based stratification of patients could guide more specific and individualised rehabilitation programmes post SCI and help identify more homogeneous subgroups. This approach could help to distinguish treatment-induced effects from spontaneous recovery and to improve the efficiency of interventional trials.[7,8] Injury-spared spinal tissue bridges—as measured on sagittal T2-weighted MRI scans—are an emerging quantitative predictor of clinical outcome

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Spinal Cord Injury Center, Balgrist University Hospital, University of Zurich, Zurich, Switzerland (D Pfyffer PhD, Prof A Curt MD, Prof P Freund MD); **Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Palo Alto, CA, USA** (D Pfyffer, K A Weber II PhD); **Craig Hospital, Englewood, CO, USA** (A C Smith PhD, C Draganich DO, J C Berliner DO, C Tefertiller PhD); **Department of Physical Medicine and Rehabilitation, Physical Therapy Program, University of Colorado School of Medicine, Aurora, CO, USA** (A C Smith); **Spinal Cord Injury Center, BG Trauma Center Murnau, Murnau, Germany** (A Grillhoesl MD, O Mach MA, I Leister PhD, D Maier MD); **Paramove, SCI Research Unit, BG Trauma Center Murnau, Murnau, Germany** (I Leister); **Institute of Molecular Regenerative Medicine and Spinal Cord Injury and Tissue Regeneration Center Salzburg, Paracelsus Medical University, Salzburg, Austria** (I Leister); **Department of Neurology, Department of Physical Medicine and Rehabilitation, and Department of Neuroscience, Belford Center for Spinal Cord Injury, Wexner Medical School, The Ohio State University, Columbus, OH, USA** (Prof J M Schwab MD); **Department of Neurology and Experimental Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany** (Prof J M Schwab); **Department of Brain Repair and Rehabilitation** (Prof A Thompson, Prof P Freund) **and Wellcome**

Trust Centre for Neuroimaging (Prof P Freund), **UCL Institute of Neurology, London, UK; Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany** (Prof P Freund)

Correspondence to: Prof Patrick Freund, Spinal Cord Injury Center, Balgrist University Hospital, Zurich 8008, Switzerland
patrick.freund@balgrist.ch

Research in context

Evidence before this study

We searched PubMed for relevant articles from database inception to May 22, 2024, using the terms "spinal cord injury", "neurologic recovery", "multicentre study", and "conditional inference tree". We did not restrict the search by language or article type. Three articles were identified: one prospective longitudinal observational multicentre study and two retrospective longitudinal observational multicentre studies. These studies found that, in patients with complete or incomplete cervical spinal cord injury (SCI), clinical assessments within the first month after hospital admission can predict changes to upper limb function and self-care outcomes at 6–12 months post SCI. However, they used non-representative patient cohorts (complete SCI *vs* incomplete SCI), a small number of follow-up timepoints and clinical endpoints, or only clinical predictor variables. Neuroimaging studies have shown that MRI biomarkers at the injury level, such as the extent of the intramedullary lesion, have prognostic value for neurological and functional recovery after SCI. These studies highlighted the value that MRI biomarkers add to baseline clinical scores for long-term outcome prediction, particularly using combined radiological–clinical models to guide decision making. Furthermore, composite MRI and CSF biomarker models outperform models based on MRI or CSF markers alone in classifying SCI severity. Injury-spared neural tissue adjacent to the lesion—spinal cord tissue bridges—can be quantitatively assessed from conventional MRI and represent an emerging powerful predictor of clinical outcome. There is an urgent need for neuroimaging parameters to increase the power of clinical trials to detect effects of interventions and reduce sample sizes in SCI research.

Added value of this study

Our longitudinal, multicentre imaging study provides compelling evidence that early conventional MRI-derived tissue bridges can predict baseline-adjusted neurological recovery from hospital admission to discharge at 3 months and 12 months follow-up after acute cervical SCI. We highlight the crucial value of individually quantified tissue bridges and their corresponding cut-offs, in addition to baseline clinical scores, for improved prediction-based stratification of patients into homogeneous subgroups. We show that baseline tissue bridges are even more powerful predictors than clinical measures for assigning patients into subgroups of similar clinical outcome distributions across three international centres and extend these findings by externally validating our models, reinforcing a generalisable multivariable radiological–clinical approach. Whereas previous studies primarily used upper limb motor function at chronic stages as clinical endpoints, we investigated combined upper and lower limb motor scores as well as sensory scores (ie, pinprick and light touch scores) as clinical outcomes at both 3 months and 12 months after SCI, which represent clinically meaningful timepoints of recovery. Moreover, our study included patients with both complete SCI and incomplete SCI and implemented statistical models that can adjust for different baseline clinical scores of patients in that heterogeneous SCI cohort.

Implications of all the available evidence

Spared tissue bridges are associated with neurological recovery at both hospital discharge at 3 months and at 12 months of follow-up, and enhance stratification of patients with SCI into homogeneous subgroups of distinct recovery profiles. Similar radiological–clinical relationships for both 3 month and 12 months outcomes highlight a broad clinical applicability of our approach. Spared tissue bridges have the potential to be implemented as neuroimaging biomarkers for improved accuracy of prognostication after SCI and to guide rehabilitation decision making. Tissue bridges also hold great promise for informing outcome prediction, planning of future interventional, multicentre trials, and reducing sample sizes. The ability to reduce patient numbers in SCI trials while still maintaining enough statistical power could address the difficulty in enrolling participants to clinical trials and increase study feasibility, and ultimately optimise individualised treatment after SCI.

after SCI.[9–13] In a monocentric study, tissue bridges showed great value in predicting baseline-adjusted recovery rates and stratifying patients with SCI into recovery-specific subgroups.[14] Although midsagittal tissue bridges were shown to be reliably measurable across raters[9–11] and to hold the potential to improve planning of clinical trials,[15,16] their reproducibility and generalisability across multiple centres have yet to be demonstrated.

We aimed to assess the value of MRI-derived tissue bridges for the prediction of 3-month baseline-adjusted neurological recovery after cervical SCI, using datasets from three international centres, with follow-up investigation of 12-month recovery for two of the datasets.

Methods

Study design and participants

This longitudinal, multicentre, retrospective study included patients with cervical SCI admitted to the BG Trauma Center, Murnau, Germany (March 18, 2010–March 1, 2021), Balgrist University Hospital, Zurich, Switzerland (May 12, 2002–March 2, 2019), and Craig Hospital, Denver, CO, USA (Jan 12, 2010–Feb 16, 2017). Patients with SCI admitted to the BG Trauma Center and Balgrist University Hospital were included in the European Multicenter Study about Spinal Cord Injury (EMSCI), which was approved by the local ethics committee (EK-03/2004). Patients with SCI admitted to Craig Hospital were involved with research approved by the local institutional review board (HealthONE 1182575).

The research was conducted in accordance with the Declaration of Helsinki. All study participants gave written, informed consent at hospital admission for their data to be used for research purposes.

Inclusion criteria were acute cervical SCI (vertebrae C1–C7), imaging assessment between 3 weeks and 4 weeks post SCI, and clinical assessments at hospital admission (baseline), discharge (around 3 months), and 12 months of follow-up (with the exception of Denver participants, for whom 12 months of follow-up was not available due to differences in US and European care strategies). We excluded patients who at the date of SCI had: concomitant diagnosed neurological or psychiatric disorders; brain injuries or lesions; a thoracic, lumbar, or sacral injury (eg, cauda equina syndrome); clinical trial enrolment; or MRI contraindications or insufficient image quality (eg, spinal metal artifacts). The study protocol is available in appendix 1.

Procedures

Patients with SCI were neurologically examined at baseline, at 3 months, and at 12 months by physicians or physical or occupational therapists using the ISNCSCI protocol.[3] The ISNCSCI protocol comprises bilateral sensorimotor testing of 20 key muscle groups graded 0–5 (total motor score 0–100 points, consisting of an upper extremity motor score [UEMS; 0–50 points] plus lower extremity motor score [LEMS; 0–50 points]) and 28 dermatomes graded 0–2 on each side of the body (pinprick tests and light touch tests, 112 points each). According to the degree of neurological function at baseline (admission) and at 3 months (discharge), patients were classified into AIS grades A (complete sensorimotor impairment), B (complete motor impairment and incomplete sensory impairment), C (incomplete motor impairment with lower muscle ratings), D (incomplete motor impairment with higher muscle ratings), or E (no functional impairment).

Participants were scanned at 3–4 weeks post SCI at 1·5 T or 3·0 T in a supine head-first position using a Philips scanner (Philips Healthcare, Best, Netherlands) in Murnau, a Siemens scanner (Siemens Healthcare, Erlangen, Germany) in Zurich, and a GE scanner (GE Medical Systems, Waukesha, WI, USA) in Denver, with 8-channel, 16-channel, or 32-channel receive spine coils integrated in the table. The conventional clinical MRI protocol consisted of anatomical sequences, including sagittal T1-weighted, sagittal T2-weighted, and axial T2-weighted scans of the cervical spinal cord, and was centred to the lesion level. From all sagittal T2-weighted images, the midsagittal slice was identified for segmentation of spared neural tissue.

Injury-spared spinal tissue bridges are defined as the relatively hypointense regions between the intramedullary cyst and the spinal canal around the cord, both appearing with an increased signal intensity on T2-weighted images.[9,11] Hyperintense oedema resolves within the first 2–3 weeks post SCI and the cystic cavity becomes demarcated, allowing a reliable quantification of tissue bridges (even in the proximity of metal artifacts) which do not undergo further substantial changes.[9,11] Initial widespread oedema potentially covering the cyst had resolved for everyone at the time of the baseline scan and no patients were excluded on the basis of unresolved oedema.

Preserved tissue bridges were manually segmented by trained raters on midsagittal T2-weighted images covering the lesion site (appendix 2 p 6). The narrowest distances between the hyperintense intramedullary cyst and the spinal canal were quantified perpendicularly to alignment of the spinal cord in the head–feet direction and summed to the total width of tissue bridges. Raters were masked to patient identity (DP in Murnau and Zurich, with use of MERLIN [version 5.8.1, Phönix-PACS, Freiburg, Germany] and Jim [version 7.0, Xinapse Systems, Aldwincle, UK] software; ACS and a member of his research team in Denver, with use of OsiriX [version 14.0.1, Pixmeo, Geneva, Switzerland]). Previous studies demonstrated high intra-rater reliability (coefficient of variation: 4·3–5·3%)[9,11] and inter-rater reliability (intraclass correlation coefficient: 0·9)[10] for the manual segmentation of midsagittal tissue bridges, irrespective of scanner model, supported by the excellent reliability reported in this study. Segmentation of midsagittal tissue bridge widths of ten patients from Denver was compared between raters DP and ACS by calculating the intraclass correlation coefficient using a two-way random-effects model.

See Online for appendix 2

See Online for appendix 1

Outcome measures in this study were neurological recovery rates in ISNCSCI-derived[3] total motor score, UEMS, LEMS, pinprick score, and light touch score at 3 months and 12 months. Although fractional outcome regression models included all of these outcomes, conditional inference tree models were limited to total motor score, pinprick score, and light touch score.

Statistical analysis

Changes in sensorimotor scores (ie, total motor score, UEMS, LEMS, pinprick score, and light touch score) from baseline to follow-up were calculated and normalised by dividing them by the maximal score improvable, thereby accounting for the neurological heterogeneity of the SCI cohort at hospitalisation. Normalised sensorimotor recovery rates were scaled using the min-max scaling method:[17] $x\square = x - \min(x) / \max(x) - \min(x)$. Changes in neurological scores are represented as means, with SD and 95% CIs used to describe the variability and certainty around these recovery rates, extracted from regression models.

We used fractional outcome logistic regression models to explore relationships between the width of injury-spared tissue bridges and baseline-adjusted neurological recovery rates assessed with sensorimotor scores at

3 months and 12 months. After model fitting, we calculated the corresponding conditional means of percentage change in the dependent outcome variable (ie, neurological recovery) for a given change in the independent predictor covariate (ie, tissue bridge width). To account for the dependency of covariates of no interest, models were adjusted for age, sex, centre, and neurological level of injury. Wald χ^2 parametrical measures, extracted from logistic regressions, determined the collective power of independent variables for the model, with higher values indicating better predictive power. The α threshold was set at $p \leq 0 \cdot 05$.

We applied unbiased recursive partitioning conditional inference tree (URP-CTREE)[7,18,19] models implemented in the *party* package within R (version 3.4.3) for prediction-based stratification of the neurologically heterogeneous patient population into subgroups of specific recovery profiles, by identifying predictors splitting patients into subgroups with maximised difference in preselected clinical endpoints. This technique has been described in detail previously.[20]

Based on previous literature[11,14,21] and our experience, we used a combination of baseline imaging and clinical outcome measures, age, and centre as predictors, and follow-up clinical scores as endpoints in our URP-CTREE models. Sex was not used because we did not find any association between sex and clinical outcomes. The imaging measure was represented by tissue bridge width; clinical outcome measures comprised ISNCSCI-derived scores (total motor score, pinprick score, and light touch score), AIS grade, and neurological level of injury.[3] Total motor, pinprick, and light touch scores at 3 months and 12 months of follow-up were defined as clinical endpoints, as previously suggested for clinical trials.[22] The maximum number of URP-CTREE levels was set to two, the first level consisting of inner nodes and the second level of terminal nodes (ie, resulting subgroups). In a first analysis, trees were modelled based on the combined dataset. In a subsequent analysis, trees were modelled based on the largest dataset from Murnau and validated by applying the inner node decision rules on independent datasets from Zurich and Denver to assess the performance and generalisability of the URP-CTREE model, as previously applied.[7,18] We used Kruskal-Wallis tests followed by pair-wise Mann-Whitney *U* tests to investigate centre differences in clinical outcome distribution at 3 months and 12 months of follow-up. Non-parametric tests were applied for all subgroup comparisons to account for the non-normally distributed data. The statistical analysis was done using R (version 3.4.3) and Stata (version 17.0).

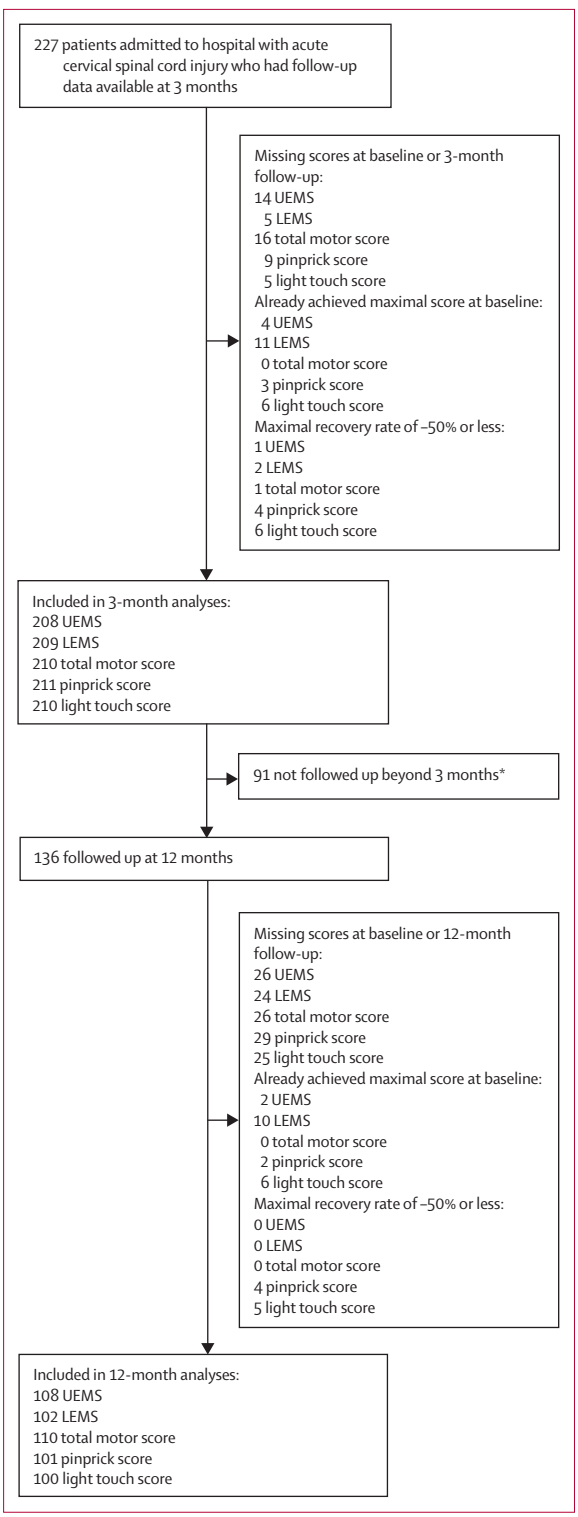

Figure 1: **Study profile**
Inclusion and exclusion of patients in the 3-month and 12-month analyses was specific to the distinct sensorimotor scores analysed. Reasons for dropouts included missing scores at baseline or follow-up, maximal scores at baseline, or a normalised recovery rate of –50% or less, attributable to the subjective nature of the neurological assessment and its susceptibility to comorbidities.[3] LEMS=lower extremity motor score. UEMS=upper extremity motor score. *Patients at the Craig Hospital, Denver (CO, USA) were not followed up to 12 months owing to differences between US and European care strategies.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The multicentre SCI cohort consisted of 227 patients: 93 from BG Trauma Center, Murnau, Germany (22 [24%] female); 43 from Balgrist University Hospital, Zurich, Switzerland (four [9%] female); and 91 from Craig Hospital, Denver, CO, USA (14 [15%] female). Overall, the mean age of patients with SCI was 46·6 years (SD 18·0). The flow of patients through the study and the number of patients included at each analysis stage are shown in figure 1. Timepoints of MRI and clinical assessments at baseline and at 3 months are reported in table 1. From baseline to 3 months post SCI, mean improvement in UEMS was 9·0 points (SD 9·0; 95% CI 7·8–10·3, p<0·0001), in LEMS was 7·8 points (10·6; 6·4–9·2, p<0·0001), in total motor score was 16·7 points (17·2; 14·3–19·0, p<0·0001), in pinprick score was 14·8 points (21·6; 11·9–17·7, p<0·0001), and in light touch score was 13·7 points (19·0; 11·2–16·3, p<0·0001). 67 (30%) patients at baseline and 55 (24%) patients at 3 months had a complete sensorimotor lesion (ie, AIS grade A; table 1). Midsagittal tissue bridges measured a mean width of 2·4 mm (SD 1·8) for patients with AIS grades B–D. Of 227 patients, 80 (35%) had positive AIS grade changes after 3 months. Among these 80 patients, 73 (91%) had midsagittal tissue bridges. 61 (27%) of 227 patients had no midsagittal tissue bridges, and 54 (89%) of these patients showed no improvement in AIS grade (table 1). The calculated intraclass correlation coefficient of 0·96 (95% CI 0·87–0·99) indicated an excellent inter-rater reliability for tissue bridge segmentation between different raters.

The width of preserved tissue bridges was positively associated with baseline-adjusted 3-month improvement in total motor score, UEMS, LEMS, pinprick score, and light touch score (table 2). Tissue bridges represented the most significant independent variable contributing to 3-month models, which also included the covariates of age, sex, centre, and lesion level. These models demonstrated predicted 3-month increases in all sensorimotor scores. Per preserved 1 mm of tissue bridge at baseline, patients recovered a mean of 9·3% (SD 0·9) of maximal total motor score (95% CI 7·5–11·2), 8·6% (0·8) of maximal pinprick score (7·0–10·1), and 10·9% (0·8) of maximal light touch score (9·4–12·5) at 3 months (figure 2, appendix 2 p2)

In patients from Murnau and Zurich (n=136) with 12-month follow-up data, midsagittal tissue bridge width was positively associated with baseline-adjusted recovery in UEMS, LEMS, total motor score, pinprick score, and light touch score (table 2). Of all variables fed into 12-month outcome models, tissue bridges added the most predictive power as compared with age, sex, centre, and lesion level. From baseline to 12 months, mean improvement in UEMS was 2·5 points (SD 0·4; 8·7% [SD 1·3] of maximal recovery, 95% CI 6·1–11·3, p<0·0001), in LEMS was 3·7 points (0·4; 12·6% [1·5], 9·7–15·5, p<0·0001), in total motor score was 6·3 points (0·7; 10·9% [1·3], 8·4–13·4,

	Murnau participants (n=93)	Zurich participants (n=43)	Denver participants (n=91)	Combined cohort (n=227)
Age, years	50·9 (18·7)	48·5 (16·8)	41·4 (16·8)	46·6 (18·0)
Sex				
Female	22 (24%)	4 (9%)	14 (15%)	40 (18%)
Male	71 (76%)	39 (91%)	77 (85%)	187 (82%)
Clinical assessment, days after injury				
Baseline	11 (8–13)	7 (6–11)	21 (14–28)	12 (9–19)
3 months	76 (74–84)	86 (80–89)	95 (78–114)	83 (75–95)
AIS grade at baseline*				
A	28 (30%)	8 (19%)	31 (34%)	67 (30%)
B	9 (10%)	8 (19%)	18 (20%)	35 (15%)
C	25 (27%)	8 (19%)	23 (25%)	56 (25%)
D	29 (31%)	19 (44%)	19 (21%)	67 (30%)
E	0	0	0	0
AIS grade at 3 months				
A	20 (22%)	5 (12%)	30 (33%)	55 (24%)
B	9 (10%)	5 (12%)	10 (11%)	24 (11%)
C	9 (10%)	4 (9%)	18 (20%)	31 (14%)
D	53 (57%)	28 (65%)	33 (36%)	114 (50%)
E	2 (2%)	1 (2%)	0	3 (1%)
Lesion level according to neurological level of injury†				
C1	2 (2%)	3 (7%)	8 (9%)	13 (6%)
C2	9 (10%)	2 (5%)	13 (14%)	24 (11%)
C3	18 (19%)	10 (23%)	13 (14%)	41 (18%)
C4	42 (45%)	15 (35%)	32 (35%)	89 (39%)
C5	14 (15%)	4 (9%)	11 (12%)	29 (13%)
C6	5 (5%)	3 (7%)	9 (10%)	17 (7%)
C7	3 (3%)	3 (7%)	4 (4%)	10 (4%)
C8	0	2 (5%)	1 (1%)	3 (1%)
UEMS				
Baseline	18·2 (14·1)	29·0 (12·9)	18·2 (14·0)	20·3 (14·4)
3 months	30·5 (15·3)	36·4 (10·9)	25·3 (15·4)	29·5 (15·1)
LEMS				
Baseline	17·8 (18·1)	26·3 (19·6)	11·1 (16·4)	16·8 (18·6)
3 months	27·6 (21·2)	32·6 (21·1)	17·8 (20·1)	24·6 (21·5)
Total motor score				
Baseline	35·5 (26·4)	55·3 (27·9)	29·2 (26·9)	37·1 (28·4)
3 months	58·2 (33·4)	69·0 (28·9)	43·1 (32·0)	54·1 (33·4)
Pinprick score				
Baseline	38·6 (29·1)	53·6 (28·0)	37·1 (27·6)	40·9 (28·9)
3 months	62·0 (32·4)	70·1 (32·6)	43·3 (30·9)	55·9 (33·5)
Light touch score				
Baseline	55·9 (29·8)	65·8 (28·6)	48·7 (32·8)	54·9 (31·3)
3 months	74·5 (32·0)	77·8 (27·6)	57·5 (35·5)	68·3 (33·8)
MRI assessment, days	35 (16–83)	33 (23–48)	21 (14–35)	28 (16–42)

(Table 1 continues on next page)

	Murnau participants (n=93)	Zurich participants (n=43)	Denver participants (n=91)	Combined cohort (n=227)
(Continued from previous page)				
Tissue bridge width in mm, mean (SD)				
AIS grade A	0·5 (0·9)	0·2 (0·5)	0·2 (0·3)	0·3 (0·7)
AIS grade B	2·0 (1·4)	2·2 (2·0)	1·0 (0·9)	1·5 (1·4)
AIS grade C	2·6 (1·7)	2·9 (1·3)	0·9 (0·9)	1·9 (1·6)
AIS grade D	3·5 (1·9)	3·9 (1·9)	1·7 (1·3)	3·1 (1·9)
AIS grade B–D	2·8 (1·7)	3·1 (1·9)	1·4 (1·0)	2·4 (1·8)
All patients	2·2 (1·9)	2·7 (2·1)	0·9 (1·0)	1·7 (1·8)
Patients with AIS grade improvement, all patients	37 (40%)	18 (42%)	25 (27%)	80 (35%)
With tissue bridge	34/37 (92%)	17/18 (94%)	22/25 (88%)	73/80 (91%)
Patients with AIS grade improvement, AIS grade A	9 (10%)	3 (7%)	3 (3%)	15 (7%)
With tissue bridge	6/9 (67%)	2/3 (67%)	2/3 (67%)	10/15 (67%)
Patients without AIS grade improvement	56 (60%)	25 (58%)	66 (73%)	147 (65%)
Patients with tissue bridge	71 (76%)	37 (86%)	58 (64%)	166 (73%)
Patients without tissue bridge	22 (24%)	6 (14%)	33 (36%)	61 (27%)
AIS grade A at baseline	19/22 (86%)	6/6 (100%)	21/33 (64%)	46/61 (75%)
AIS grade A at 3 months	17/22 (77%)	5/6 (83%)	22/33 (67%)	44/61 (72%)
With no AIS grade improvement	19/22 (86%)	5/6 (83%)	30/33 (91%)	54/61 (89%)
Patients with AIS grade A at 3 months	20 (22%)	5 (12%)	30 (33%)	55 (24%)
Without tissue bridge	17/20 (85%)	5/5 (100%)	22/30 (73%)	44/55 (80%)

Data are mean (SD), n (%), median (IQR), or n/N (%). Centre-wise average tissue bridge width is given for all patients and for only patients with tissue bridges present. Although patients of all centres were followed up at hospital discharge at around 3 months post SCI, Murnau and Zurich patients had an additional follow-up at 12 months. Data were not collected on ethnicity because this is not reported as standard of care data. SCI=spinal cord injury. AIS=American Spinal Injury Association Impairment Scale. UEMS=upper extremity motor score. LEMS=lower extremity motor score. *AIS grade at baseline was not available for two patients from Murnau. †Lesion level was not available for one patient from Zurich.

Table 1: **Demographic, clinical, and structural neuroimaging data, and tissue bridge characteristics of patients with cervical SCI**

p<0·0001), in pinprick score was 3·9 points (0·9; 5·7% [1·3], 3·3–8·2, p<0·0001), and in light touch score was 3·7 (0·8) points (0·8; 6·9% [1·4], 4·1–9·7, p<0·0001) per mm of tissue bridge width (figure 2). Patients with no midsagittal tissue bridges showed improvement to only around 30% of maximal recovery in sensorimotor scores. Recovery rates were greater in patients with more extensive tissue bridges and reached a plateau of more than 70% of maximal recovery in patients with tissue bridges larger than 5–6 mm.

We applied URP-CTREE models to the dataset from all three centres to identify baseline clinical and imaging parameters and respective cutoffs, splitting the heterogeneous patient population into recovery-specific subgroups. Baseline total motor, pinprick, and light touch scores, tissue bridges (1·6–2·0 mm), and AIS grade separated patients into more homogeneous terminal subgroups of lower and higher 3-month total motor score, pinprick score, and light touch score (appendix 2 pp 7–9). URP-CTREEs were generated based on the dataset from Murnau, as a first step in assessing the generalisability of these models; similar to the multicentre dataset, baseline clinical scores and tissue bridges were identified as predictors splitting patients into subgroups according to 3-month sensorimotor scores (appendix 2 pp 7–9). These models were validated by applying the inner node decision rules (ie, identified predictors and cutoffs) to the independent datasets from Zurich and Denver and comparing the distribution of clinical outcomes of terminal subgroups across all centres. The distribution of 3-month total motor score was similar for two terminal subgroups (nodes 3 and 4), of pinprick score for three terminal subgroups (nodes 3, 4, and 6), and of light touch score for one terminal subgroup (node 3), indicating general

	Murnau participants (n=93)			Zurich participants (n=43)			Denver participants (n=91)			Combined cohort (n=227)		
	Data available, n (%)	Wald χ^2	p value	Data available, n (%)	Wald χ^2	p value	Data available, n (%)	Wald χ^2	p value	Data available, n/N (%)	Wald χ^2	p value
3-month scores												
UEMS	88 (95%)	47·92	<0·0001	40 (93%)	11·41	0·0024	80 (88%)	22·57	0·0032	208/227 (92%)	84·25	<0·0001
LEMS	90 (97%)	105·09	<0·0001	35 (81%)	52·25	0·011	84 (92%)	52·75	0·0002	209/227 (92%)	111·27	<0·0001
Total motor score	90 (97%)	78·37	<0·0001	41 (95%)	23·42	0·0008	79 (87%)	44·94	0·0002	210/227 (93%)	117·24	<0·0001
Pinprick score	85 (91%)	87·15	<0·0001	39 (91%)	41·89	<0·0001	87 (96%)	4·32	0·063	211/227 (93%)	116·30	<0·0001
Light touch score	87 (94%)	130·26	<0·0001	38 (88%)	44·05	<0·0001	85 (93%)	32·10	<0·0001	210/227 (93%)	185·11	<0·0001
12-month scores												
UEMS	66 (71%)	22·53	<0·0001	42 (98%)	31·93	0·0023	NA	NA	NA	108/136 (79%)	43·31	<0·0001
LEMS	66 (71%)	25·86	<0·0001	36 (84%)	31·46	0·0045	NA	NA	NA	102/136 (75%)	45·01	<0·0001
Total motor score	67 (72%)	30·05	<0·0001	43 (100%)	40·51	0·0006	NA	NA	NA	110/136 (81%)	52·43	<0·0001
Pinprick score	61 (66%)	25·13	0·0008	40 (93%)	35·51	0·012	NA	NA	NA	101/136 (74%)	38·29	<0·0001
Light touch score	61 (66%)	11·22	0·0092	39 (91%)	25·71	<0·0001	NA	NA	NA	100/136 (74%)	24·55	<0·0001

3-month follow-up clinical scores were available for the entire SCI cohort (n=227) and 12-month follow-up scores were available for patients from Murnau and Zurich (n=136). The exact number of patients included for each neurological score and reasons for dropout are shown in figure 1. Statistical models were corrected for covariates of no interest, including age, sex, centre (for the combined cohort), and neurological level of injury. UEMS=upper extremity motor score. LEMS=lower extremity motor score. NA=not available. SCI=spinal cord injury.

Table 2: **Statistical outputs of fractional outcome regression models exploring associations between preserved tissue bridges and neurological recovery after cervical SCI**

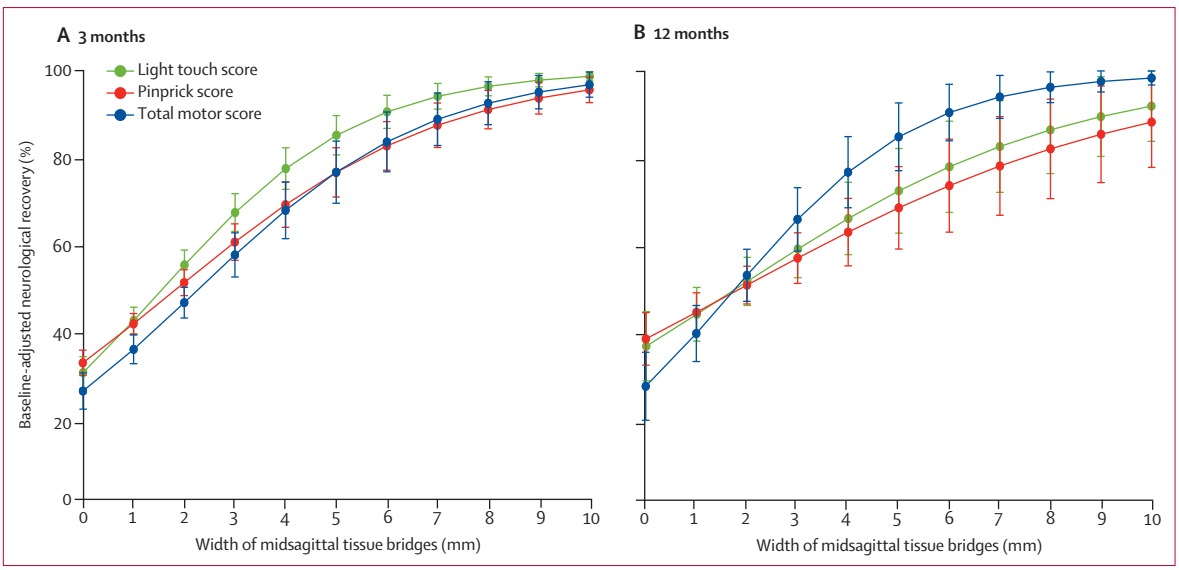

Figure 2: **Association between width of preserved tissue bridges and neurological recovery**
(A) 3-month baseline-adjusted neurological recovery in the complete cohort. (B) 12-month baseline-adjusted neurological recovery in the Murnau and Zurich cohorts. Each model fit indicates the increase in neurological recovery per additional mm in tissue bridge width. Midsagittal tissue bridge width on the x-axis represents the sum of ventral and dorsal tissue bridge widths. Error bars show 95% CIs.

external validity of prediction-based stratification among centres (appendix 2 pp 10–11). URP-CTREEs that included only clinical parameters showed distribution differences among centres for most subgroups, whereas models including only imaging parameters revealed only one subgroup (for the 3-month total motor score outcome only) that varied among centres. Centre-wise comparisons and statistics are presented in appendix 2 (pp 3–4).

Based on URP-CTREEs with 12-month clinical outcomes from Murnau and Zurich patients, AIS grade (A *vs* B–D) and initial total motor score (cutoffs of 15 points and 19 points) separated patients into subgroups of distinct motor recovery profiles (appendix 2 pp 12–14). AIS grade (A *vs* B–D) and tissue bridge width (0·0 mm for AIS grade A, 4·0 mm for grades B–D) stratified patients in terms of 12-month pinprick score, whereas baseline light touch score (48 points and 68 points) and tissue bridges (1·5 mm) split patients into subgroups of lower and higher 12-month light touch score (appendix 2 pp 12–14). URP-CTREEs derived from the Murnau dataset found the same predictors splitting patients into subgroups of lower and higher 12-month sensorimotor scores. Specifically, the algorithm identified: baseline AIS grade (A *vs* B–D) and total motor score (9 points and 19 points) predicting 12-month total motor score; baseline AIS grade (A *vs* B–D) and tissue bridges (0·5 mm) predicting 12-month pinprick score; and tissue bridges (0·5 mm) and initial light touch score (62 points) predicting 12-month light touch score (appendix 2 pp 12–14). Upon applying these decision rules with clinical and imaging parameters to the Zurich dataset for validation, comparison of clinical outcome distributions across the two centres (Murnau and Zurich) revealed no differences for 12-month total motor score, pinprick score, and light touch score subgroups. URP-CTREE model validation demonstrated similar centre-wise distribution of sensorimotor scores for all but one subgroup (node 3, 12-month pinprick score) using imaging parameters only and all subgroups using clinical parameters only (appendix 2 p 5).

Discussion

This longitudinal, multicentre imaging study provides evidence that the width of tissue bridges is predictive of baseline-adjusted sensorimotor recovery at 3 months and 12 months after cervical SCI and can also stratify patients into recovery-specific subgroups within days after injury. MRI-based, injury-spared tissue bridges have the potential to improve outcome prediction, clinical decision making, and individualised treatment approaches.

In monocentric studies, tissue bridge width was associated with improved outcome at chronic SCI stages (>6 months).[9–14,23] Our multicentre study demonstrates that tissue bridges can also be used to predict early clinical improvements (<3 months) and retain the power for 12-month follow-up outcome prediction, independent of the initial clinical status (ie, baseline-adjusted recovery). In 2021, Fouad and colleagues discussed the importance of looking at neurological recovery rates (in percentage) post SCI and highlighted that a certain amount of spared tissue is necessary for patients to show a clinically relevant recovery.[24] In support of this, we demonstrate that patients with SCI with wider tissue bridges show the largest recovery. For every preserved mm in tissue bridge width, patients with SCI gained an

average of 7·8–12·1% of their maximal sensorimotor recovery over 3 months and 5·7–12·6% over 12 months. For example, a patient with a baseline total motor score of 60 points (total of 100 and maximum improvement of 40 points) and 4 mm of preserved tissue bridges at baseline (corresponding to around 70% of maximal motor score improvement; figure 2) would improve total motor score by approximately 28 points within the first 3 months post SCI. Neurological recovery trajectories (ie, motor, pinprick, and light touch scores) are steepest for individuals who have midsagittal tissue bridges measuring up to 4 mm (from a 9–10 mm maximum[25]) and patients presenting with tissue bridges larger than 5–6 mm reach a plateau based on their extent of spared neural tissue (>70% of recovery). This observation indicates a potential crucial window of opportunity for interventions in patients with smaller tissue bridges to maximise their recovery potential.[24] Compared with recovery at 3 months, 12-month sensory recovery trajectories seem more linearly dependent on the tissue bridge width, with a higher intercept at 0 mm (around 40%), potentially due to more time having elapsed (figure 2). Whether disease-modifying interventions might induce macrostructural changes in tissue bridge width, as seen with slowed brain atrophy after administration of neuroprotective agents in multiple sclerosis, for example, remains to be explored. Nevertheless, they are crucial for any regenerative agent that aims to promote axonal sprouting or regeneration to bypass the lesion site.

To improve the specificity and individualisation of therapies, early subgrouping of patients based on their neurological function is crucial.[14] Prediction-based stratification of patients according to subacute, in addition to chronic, outcomes is of utmost importance for the planning and evaluation of rehabilitation strategies in clinics. This subgrouping also allows time-efficient and cost-efficient clinical trial design, with the possibility to review potential treatment success and predict outcomes soon after SCI. Baseline tissue bridge width—together with clinical scores—was identified as a predictor of 3-month and 12-month total motor, pinprick, and light touch scores, improving separation of patients with SCI into specific subgroups of worse and better outcomes. Specifically, patients that were initially divided into subgroups (ie, inner nodes) according to their baseline tissue bridge widths or sensorimotor score were further separated into more homogeneous subgroups, based on additional distinct baseline sensorimotor scores or tissue bridge widths and respective cutoffs. Stratification of patients based on a combination of their baseline clinical and imaging parameters also improved distinction between neurologically more similar subgroups (eg, intermediate terminal nodes 4 and 6 in appendix 2 pp 7–9) where predictive distinctions are most challenging. Crucially, smaller cutoff widths (around 2·0 mm) seem to be indicative of better or worse neurological recovery at 3 months, especially in patients who are more severely injured. A broader range of tissue bridge width cutoffs appeared to improve patient stratification regarding 12-month recovery, with higher cutoffs (ie, 4·0 mm) subgrouping patients with less impairment (ie, incomplete lesion). The crucial radiological–clinical relationship highlighted in our study for both 3-month and 12-month outcomes also demonstrates a global clinical applicability of our approach.

Previous studies used only clinical predictor variables, a small number of clinical endpoints, or selected cohorts of patients (complete SCI *vs* incomplete SCI), limiting generalisability.[7,18,19,26] Moreover, prediction models need to be reproducible and generalisable to new patients and thus need to be externally validated.[7,18,27] Our multicentre study, including three independent datasets for 3-month follow-up and two for 12-month follow-up, compared clinical outcome distributions of recovery-specific subgroups across centres and found that URP-CTREE models including imaging and clinical measures outperformed models with clinical measures only, thereby highlighting the potential of combining clinical and imaging metrics and the benefits of using objective imaging biomarkers in clinical decision making, patient counselling, and trial planning. Our findings are valid across SCI centres, MRI scanners (vendors and field strength), and tissue bridge raters, supported by the high inter-rater reliability for tissue bridge segmentation,[9–11] fulfilling the reproducibility aspect for multicentre trials.

This study had limitations. Conventional human MRI does not allow for the retrieval of molecular information underlying tissue bridges, such as axonal and myelin preservation, which might affect recovery post SCI. Diffusion tensor imaging could add value but is challenging at the lesion site, mainly due to metal-induced artefacts and low resolution, and needs further technical development. Future studies should assess parasagittal slices for a better understanding of the total amount and localisation of preserved tissue. Despite accounting for most variables of no interest in our models, other factors that were not systematically available might have affected recovery trajectories, such as socioeconomic background, rehabilitation programmes, comorbidities, or medication. We found some differences in age, sex, and lesion level and severity distribution among centres. We adjusted our models for these covariates, demonstrating that tissue bridges are valid biomarkers for prediction-based patient stratification in multicentre SCI trials, independent of cohort differences. Although scanner models varied between centres, previous studies combining scans acquired at 1·5 T and 3 T and from different vendors did not detect differences when quantifying tissue bridges.[9,11,14,28,29] We also corrected our models for centre. Our analyses show that intermediate node subgroups (the ones in the middle at the bottom of URP-CTREEs) differ across centres for a few 3-month outcomes, especially for

models with clinical predictors only, potentially attributable to lower subgroup sizes. Future studies would benefit from even larger datasets. Assessment timepoints slightly varied between centres, which reinforces the generalisability of our models and highlights the need to complementarily acquire early conventional neuroimaging data in addition to neurological measures in the clinical workup, even if timepoints of clinical assessments are different across centres and from neuroimaging timepoints.

In conclusion, this study shows the predictive potential of preserved tissue bridges for baseline clinical score-adjusted recovery both over the first 3 months and in the longer term (12 months) after cervical SCI in patients across multiple sites. Tissue bridges are a powerful neuroimaging biomarker that can divide patients into subgroups with specific recovery profiles and add value to multiparametric prediction-based stratification models, compared with clinical scores when comparing outcome distributions across centres. Tissue bridge widths could be assessed as part of the clinical care standards to counsel patients and guide rehabilitation decision making, and they have potential to improve design of future interventional, multicentre trials.[15,16] This approach could help to address the difficulty in enrolling participants to clinical trials, including specific inclusion criteria, and comply with the current need in SCI research to increase the feasibility and efficiency of clinical studies, such as through the use of smaller sample sizes.

Contributors

Authors DP and PF directly accessed and verified the underlying raw data. All authors had full access to all the data in the study, have seen and approved of the final text, and accept responsibility to submit for publication. DP designed and conceptualised the study, did the literature search, curated data, acquired, analysed, and interpreted the data, created figures, and drafted the manuscript for intellectual content. ACS designed and conceptualised the study, analysed the data, and revised the manuscript for intellectual content. KAW designed and conceptualised the study and revised the manuscript for intellectual content. AG and OM analysed the data and revised the manuscript for intellectual content. CD, JCB, CT, IL, and DM revised the manuscript for intellectual content. JMS designed and conceptualised the study and revised the manuscript for intellectual content. AT and AC revised the manuscript for intellectual content. PF designed and conceptualised the study, supervised the study, and revised the manuscript for intellectual content.

Declaration of interests

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Data sharing

After publication and upon reasonable request, de-identified participant data, the data dictionary, and the study protocol will be made available to qualified scientific and medical researchers providing valid research questions and a methodologically sound proposal. Inquiries can be sent via email to the corresponding author of the study and data requestors will need to sign a data access agreement.

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