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Clinical study

Injury volume extracted from MRI predicts neurologic outcome in acute spinal cord injury: A prospective TRACK-SCI pilot study

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ABSTRACT

Conventional MRI measures of traumatic spinal cord injury severity largely rely on 2-dimensional injury characteristics such as intramedullary lesion length and cord compression. Recent advances in spinal cord (SC) analysis have led to the development of a robust anatomic atlas incorporated into an open-source platform called the Spinal Cord Toolbox (SCT) that allows for quantitative volumetric injury analysis. In the current study, we evaluate the prognostic value of volumetric measures of spinal cord injury on MRI following registration of T2-weighted (T2w) images and segmented lesions from acute SCI patients with a standardized atlas. This IRB-approved prospective cohort study involved the image analysis of 60 blunt cervical SCI patients enrolled in the TRACK-SCI clinical research protocol. Axial T2w MRI data obtained within 24 h of injury were processed using the SCT. Briefly, SC MRIs were automatically segmented using the *sct_deepseg_sc* tool in the SCT and segmentations were manually corrected by a neuro-radiologist. Lesion volume data were used as predictor variables for correlation with lower extremity motor scores at discharge. Volumetric MRI measures of T2w signal abnormality comprising the SCI lesion accurately predict lower extremity motor scores at time of patient discharge. Similarly, MRI measures of injury volume significantly correlated with motor scores to a greater degree than conventional 2-D metrics of lesion size. The volume of total injury and of injured spinal cord motor regions on T2w MRI is significantly and independently associated with neurologic outcome at discharge after injury.

1. Introduction

Spinal cord injury (SCI) is a common condition that affects up to 16,000 people per year [1]. The cervical region is the most common area injured after SCI and can lead to severe neurological injury [2]. Currently, treatment of cervical SCI is focused on early surgery [3], blood pressure management [4], and other interventions aimed at preventing secondary injury after the initial trauma [5]. As early and aggressive treatments for SCI become standard of care [6], it has led to increasing reliance on the clinical examination very early after injury to triage patients. However, the clinical examination early after SCI is unreliable, and confounded by spinal shock and

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the presence of polytrauma [7]. Thus, other diagnostic modalities have been used to classify SCI early after injury, including magnetic resonance imaging (MRI) [8].

There are several ordinal and categorical 2-dimensional MRI features that have been shown to correlate with the initial injury severity and outcome in SCI [8]. For example, the intramedullary lesion length (IMLL) [9] and the brain and spinal injury center (BASIC) score [10] reflect the degree of T2 signal abnormality in the sagittal and axial MRI planes, respectively. Both of these related measures have shown strong correlations with overall spinal injury severity and have demonstrated diagnostic and prognostic value after SCI [11]. However, such metrics are limited in that they are primarily based on a single two-dimensional (2-D) image and thus are, at best, proxies for the true 3-D size and distribution of the injured spinal cord. It remains to be determined if the 3-D volume of the lesion after SCI would be a more accurate measure of SCI severity.

Here, we test this hypothesis by leveraging the Spinal Cord Toolbox (SCT) [12], an open source anatomic atlas to allow for quantitative volumetric injury analysis. The goal of this study was to (1) investigate if volume information correlates with injury severity and (2) whether volume information predicts injury severity to a greater degree than two dimensional markers such as BASIC or IMLL.

2. Methods

2.1. Patient selection

Patients who were enrolled in the Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI) patient registry and diagnosed with blunt cervical traumatic SCI at the Zuckerberg San Francisco General Hospital (ZSFGH), a level 1 trauma center, were included in this study (Fig. 1) [2]. Inclusion criteria for the TRACK-SCI patient registry consists of (1) all consecutive traumatic SCI patients who presented to the emergency room of a single level I trauma center, (2) documented neurological deficit with an associated spinal fracture or ligamentous injury based on MRI or computed tomography (CT) scans, and (3) ability to consent to the study. Exclusion criteria were (1) patients<18-years old, (2) patients in custody or prisoners, (3) patients who were pregnant, or (4) patients on a on medically indicated psychiatric hold or otherwise unable to consent to the study. For the current study, we further excluded patients who (1) did not have an MRI after the injury, (2) did not require a surgical intervention, and (3) did not have a an adequate MRI study based on a fellowship-trained neuroradiologist identifying clear, motion-induced distortion in the axial view or sagittal reconstruction of the T2 weighted MRI images.

3. Outcome evaluation

The International Standard for Neurological Classification of Spinal Cord Injury (ISNCSCI) is published by ASIA and was used to assess motor function and sensory impairment and group patients by injury severity. Specifically, this examination provides a measure of spinal cord severity based on the ASIA impairment scale (AIS; see ref 19 for a review), and ranges from A (most severe) to E (not impaired). ISNCSCI examinations were conducted by physicians, nurse practitioners, physician assistants, and ICU nurses who completed the ASIA International Standards Training E Program (InSTEP) and in-person training. ISNCSCI exams were performed for all patients during the initial admission, either as part of clinical care if the treating provider completed InSTEP training, or separately for the research study if the ISNCSCI was not performed for clinical purposes. Occasionally, an ISNCSCI was not performed during the admission, usually because the patient was excessively sedated and could not participate in the exam. The major outcome in the current paper was the lower motor score from the ISNCSCI exam. All data were housed in a Research Electronic Data Capture (REDCap) database. included reviewing CDEs, assembling the data dictionary, and setting up the database. REDCap is in full compliance with Health Insurance Portability and Accountability Act (HIPAA) security standards for protection of personal health information (PHI).

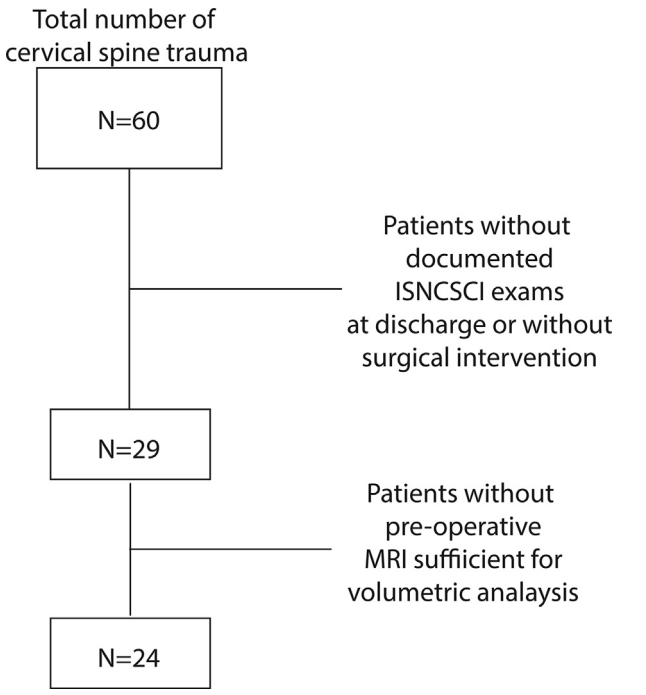

Fig. 1. Inclusion criteria. Of the 60 patients included in the analysis, 29 had sufficient clinical data (including ISNCSCI examinations at discharge) to be included in the analysis. Of the 29 patients, a further 5 were not included based on the absence or insufficiency of pre-operative MR imaging.

4. MRI acquisition and image processing

All imaging was completed within 24 h of injury on a 3-Tesla Siemens Skyra scanner with software version E11 (Siemens Healthcare, Erlangen, Germany). As part of a conventional clinical imaging protocol for spine trauma, axial T2w imaging was completed with the following parameters: time to repetition (TR) = 3800 ms, time to echo (TE) = 102 ms, average echo train length (ETL) of 18, section thickness = 3–4 mm with a phase encoding direction of left to right. T2w Axial MRI DICOM images were downloaded from PACS and converted to NIfTI format using the DICOM to NIfTI conversion software available at www.nitrc.org. FSLeyes version 0.30.1 viewer module obtained at https://git.fmrib.ox.ac.uk/fsl/fsleyes/fsleyes was used to manually mark two vertebral levels as part of the 'labels' file creation for registration in the SCT. Image files were processed using a deep learning [13] segmentation algorithm (*sct_deepseg_sc*) within the SCT platform that automates spinal cord segmentation from the axial T2-W images. Automated segmentation results were examined by a neuroradiologist (JFT) and confirmed for accuracy. Manual adjustments to the initial automated spinal cord segmentation were performed by a neuroradiologist (JFT) using FSLeyes. Segmented spinal cords were then registered to the PAM50 [12] template in the SCT, consisting of a probabilistic atlas for gray matter, white matter, and white matter tracts. A lesion mask was manually created for each patient's injury using ITKsnap software

obtained from www.itksnap.org (Fig. 2) [14]. For segmentation purposes, injuries were defined as any regions of abnormal hyperintensity or hypointensity within the spinal cord related to the patient's contusion injury. PAM50 registration in conjunction with manual masks of lesions on each axial slice were used to run the extract-metric function in the SCT. The resulting probabilistic lesion volumes of each axial slice were used to calculate total lesion volumes (Fig. 2). Intramedullary lesion length and BASIC score were derived as previously described (Fig. 2) [10].

4.1. Statistical analysis

Statistical analyses assessing the prognostic value of lesion volume metrics were executed with custom scripts in MATLAB. Univariate analyses were conducted using two tailed t-tests with significant thresholds of 0.05. The relation between the volume of the lesion and the injury severity was performed using a Pearson's correlation statistic, and the combined effect of volume, BASIC score, and IMLL on injury severity was assessed using a multiple linear with regression lower extremity motor score as the output variable and Correlation of lesion volume with intramedullary lesion length (IMLL).

5. Results

Overall, 60 patients were included in the study. After applying the inclusion and exclusion criteria, 24 patients were included in the final analysis. Fig. 1 shows the application of the main exclusion criteria of the study. Demographic data from these 24 patients is given in Table 1. Of note, there were more males than females in our final database (75% compared to 25%), and also there were more AIS D injuries compared to other injury patterns. To assess whether the demographic data had any correlation with the volumes of the lesions, we calculated the Pearson's coefficient and the associated p-value of the demographic data with the volumes of the lesions based on the pre-operative MRI. There were no significant associations with the volume of the lesion and the age of the patient (Pearson's coefficient: −0.083, p-value: 0.70), the injury severity score (Pearson's coefficient: 0.145, p-value: 0.50), or the time from injury to surgical decompression (Pearson's coefficient: 0.277, p-value: 0.191).

We next calculated the volume of the T2 lesion for all patients and found the median volume for all patients. In this group, lesion volumes ranged from 34.21386856 mm^3 to 3533.749738 mm^3. The distribution of all volumes of lesions is given in Fig. 3. The median volume was 404.6 cc.

We next correlated the MRI features with the severity of the injury. In particular, we correlated the BASIC score (Fig. 4A), the IMLL (Fig. 4B), and the volume data (Fig. 4C) with the lower extremity motor score at discharge. The lower extremity score was used in order to capture the effect of the cervical injury on the descending motor tracts, which should be independent of the level of the cervical lesion. We calculated Pearson's correlation for each metric with the lower extremity motor (LEM) score to determine if there was a relation between the MRI metric and the injury severity. The BASIC score (Pearson's coefficient: 0.240, p-value: 0.26), the IMLL (Pearson's coefficient: −0.405, p-value:

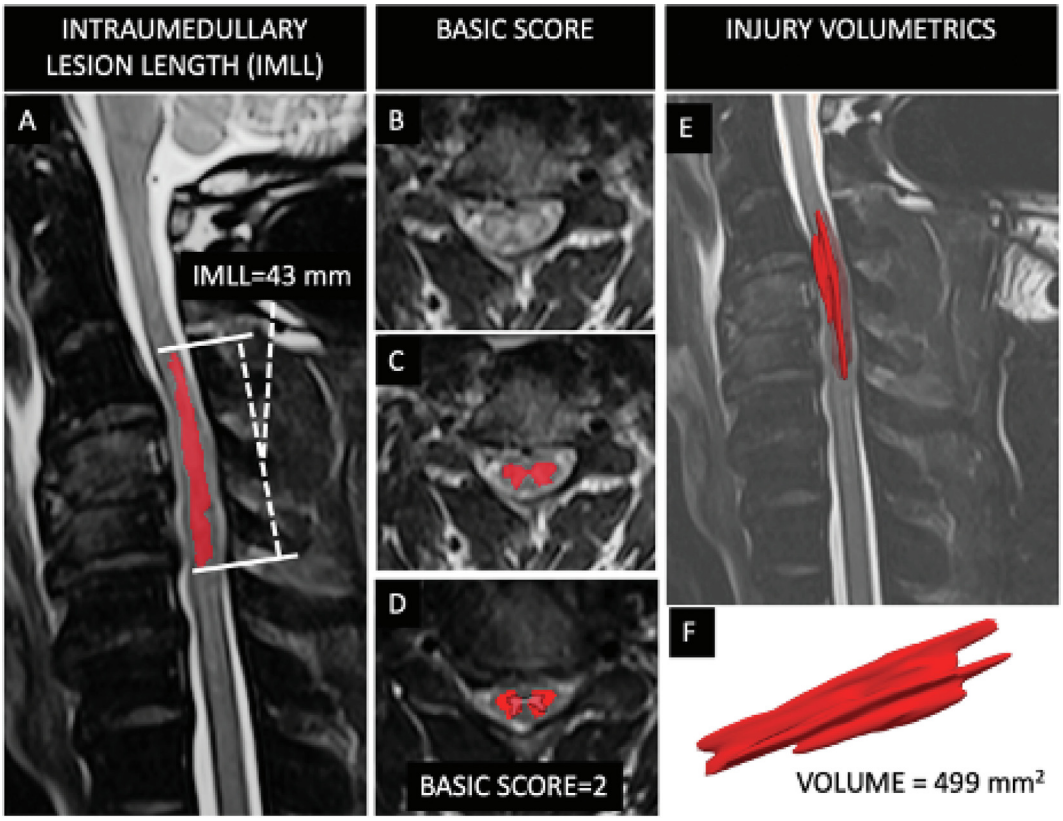

Fig. 2. MRI injury characteristics. A) Sagittal T2w MRI image from a representative patient with the intramedullary lesion segmentation delineated by red mask. IMLL represents the length of T2 signal abnormality on the sagittal image delimited by the horizontal white lines in *A*. BASIC score was assessed on axial T2w image at the injury epicenter (B-D). The T2-hyperintense injury shown in *B* is segmented in *C* (red segmentation mask). Overlay of the probabilistic gray matter template from the SCT (D) on the segmented injury mask shows that the injury involves both central gray matter and adjacent white matter with relative preservation of peripheral white matter, consistent with BASIC score of 2. Volumetric injury segmentation (E) is superimposed on midline sagittal T2w image. F) Isolated volumetric injury segmentation mask with calculated volume measurement.

Table 1
Demographic information. The age, gender, injury severity scale (ISS), time from injury to surgery, and the AISA impairment scale (AIS) at discharge are shown for the 24 patients in the study. The average and the standard errors on the mean (SEM) are shown for continue variables. The correlation of the continuous variables with the volume of the lesion was calculated with Pearson's correlation coefficient (Pearson's C) and the p-value (p) is shown.

		Pearson's C	p
Age	51.8 years (SEM 3.71)	−0.083	0.700
Gender (% male)	75%	–	–
ISS	20.5 (SEM 1.56)	0.145	0.499
Time to surgery	16.1 h (SEM 3.14)	0.277	0.191
AIS at discharge			
A	12.5%	–	–
B	8.3%	–	–
C	25.0%	–	–
D	54.2%	–	–

0.50), and the volume data (Pearson's coefficient: −0.499, p-value: 0.01) all correlated with the LEM, however only the volume data correlated statistically significantly with the LEM data after correcting for multiple comparisons using a false discovery rate method.

Finally, we tested whether the volume data predicted LEM to a greater degree than either the BASIC score or the IMLL data. Specifically, we used a multiple regression with the LEM as the output variable and IMLL and the volume data as predictors. The beta value for the volume data was −0.017 (95% CI: −0.031 to −0.003) which was significant after controlling for the IMLL data (p = 0.0497). The same regression using the BASIC score and the volume data as a regressor yielded a beta value for the volume data of −0.0188 (95% CI: −0.0399 to 0.0022), which did not reach statistical significance (p = 0.0945).

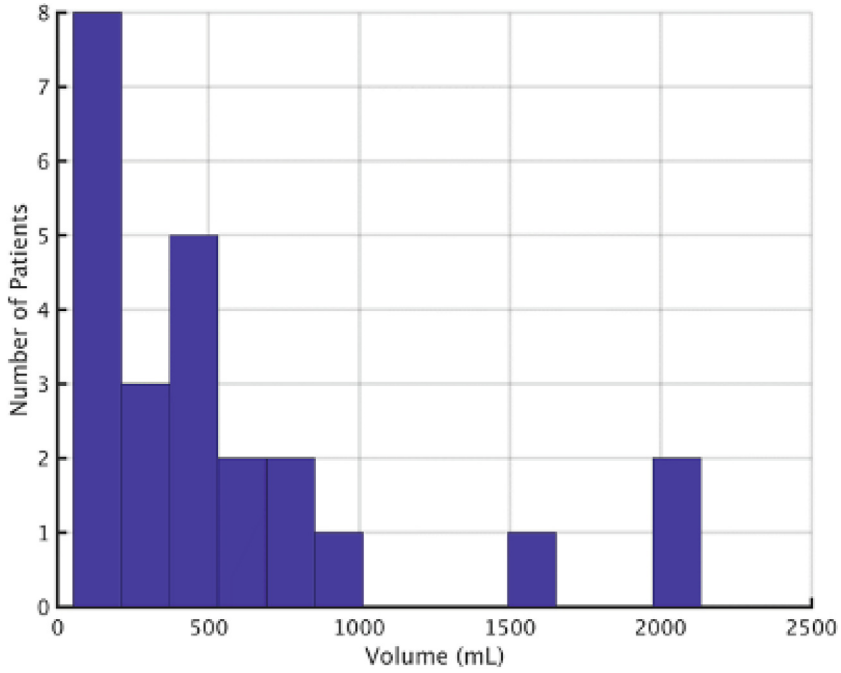

Fig. 3. Distribution of volume data across patients.

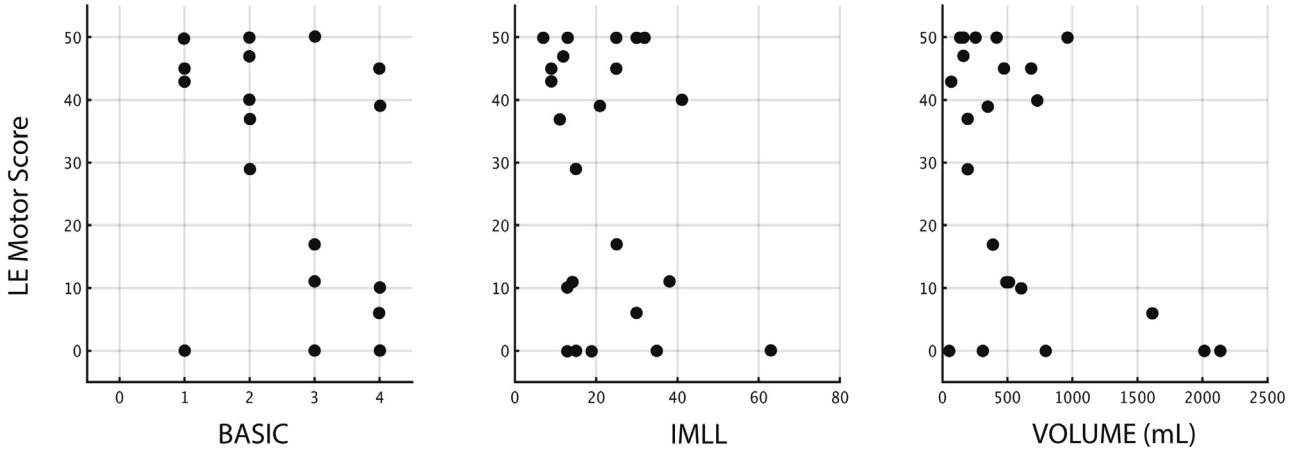

Fig. 4. Correlation of of MRI scores with motor function. The BASIC score (A), the IMLL (B), and the volume data (C) are shown as a function of the lower extremity motor score at discharge.

6. Discussion

The primary purpose of this study was to determine if the volume of the intramedullary SCI lesion on MRI predicted the severity of the injury. We secondarily sought to determine if the 3-D volume of the lesion was more or less predictive than more conventional 2-D MRI measures of injury severity, namely IMLL and the BASIC score. We found that the volume of lesions based on segmented regions of T2 signal abnormality correlated with injury severity to a greater degree than either of the 2-D metrics evaluated in this study. When the multivariate models were used to directly compare volume vs. IML and volume vs. BASIC score, the volume of the lesion outperformed the IMLL but not the BASIC score. Together, these data suggest that volume data is valid tool to determine the severity of SCI and directly outperforms IMLL ($p < 0.05$), and trends to outperform the BASIC score ($p < 0.10$).

There is need to identify improved noninvasive biomarkers of injury severity after SCI aside from the clinical examination. Specifically, the clinical examination, as summarized by the AIS score, has been specifically shown to be a poor correlate of motor strength at discharge, as well as follow up visits. The reason for this discrepancy is likely related to the confounding factor of spinal shock as well the polytrauma. As the field moves to earlier interventions for spinal cord injury, the lack of a reliable predictor of injury severity confounds prognosis, decision making, as well as inclusion in clinical trials, where injury severity stratification is critical. Thus, there is a push to look for alternative diagnostic tools for SCI that can be used early after injury, such as pre-operative MRI. This has led to standardized metrics of MRI lesion characteristics, such as the IMLL and the BASIC score among many others [8,15,16]. However, most conventional MR biomarkers of SCI are 2-dimensionals measures or ordinal classification scores based on a single image slice, and it is an open question whether three dimensional volumetric measures of injury measures may enhance assessment of injury severity and prognosis. In this respect, this study represents the first attempt to apply such volumetric lesion metrics to prospective SCI data in order to characterize injury severity.

The principle conclusion of this study is that the volume of a spinal lesion as measured with T2w MRI is correlated with severity to a greater degree than IMLL and BASIC score. This finding is predicated by a number of pre-clinical studies dating back more than 4 decades that have evaluated the utility of 3-dimensional morphometric features of spinal cord injury in a variety of animal models [17,18,19]. For example, Bresnahan et al showed that three-dimensional interactive representations of lesions provide a more complete picture of lesion characteristics than what is usually provided with 2-dimensional representations of injury [19]. Despite this strong pre-clinical foundation of literature favoring a volumetric approach to injury analysis, volumetric techniques demonstrated to be advantageous in animal models of SCI have not been previously applied in clinical SCI evaluation. This in part relates to a lack of tools readily available for clinical injury segmentation and morphometric feature extraction. The recently developed SCT now enables such analysis with clinical MRI data. The strong correlations observed between T2-based injury volume and lower extremity motor impairment in the current study provides a translational link between many early pre-clinical studies and modern clinical spinal MR analytic tools.

In addition to providing a more holistic view of the spinal cord injury on MRI, volumetric analysis is conducive to automated analysis. Many of the steps in our image processing pipeline are automated as part of the SCT platform of integrated tools, including spinal cord segmentation, template registrations, and volumetric injury feature extraction. Translating this approach more broadly in a busy clinical practice would require full, or near-full automation of the image processing steps given the time required for manual injury segmentation. Deep learning-based injury segmentation tools have been developed which show great promise for advancing automated morphometric injury analysis [20,21]. Future efforts aimed at fully automating the steps outlined in this manuscript as an end-to-end pipeline and examining additional morphometric features of spinal cord injury and subregional cord involvement are ongoing.

As a pilot proof-of-principle study, several limitations are recognized. Most notably, the small sample size limits extrapolation of our results to a larger and more diverse SCI population. However, despite the small sample size, we were able to show that the volumetric data correlates with motor impairment in the lower extremities to a greater degree than 2-D metrics analyzed. Further, this statistically significant result persisted after direct multivariate analysis for the IMLL variable. Another limitation is that most of the injuries were biased towards milder injury severity, with a relatively large percentage of AIS D injuries. Further analysis is needed to show whether the correlation of lesion volume and injury severity generalizes across a wider range of injury severity presentations. Longer term outcome data and correlation with other functional and neurologic outcome measures are also needed. Finally, the manual injury segmentation steps introduce potential error and bias in analysis.

7. Conclusion

Using a semi-automated image-processing pipeline incorporating many tools available freely as part of the open-source SCT, volumetric injury measures can be extracted from pre-operative MRI for SCI patients. These measures predict lower extremity motor function at discharge from the hospital more strongly than standard two-dimensional radiographic parameters including the BASIC score and IMLL. The volume of the T2 lesion after SCI thus holds great promise as a more accurate imaging biomarker of injury severity than conventional 2-D MRI measures of injury.

8. Disclosure of funding

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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