Determining the short-term neurological prognosis for acute cervical spinal cord injury using machine learning

（機械学習を用いた急性期頚髄損傷の機能予後予測）

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Abstract

It is challenging to predict neurological outcomes of acute spinal cord injury (SCI) considering issues such as spinal shock and injury heterogeneity. Deep learning-based radiomics (DLR) were developed to quantify the radiographic characteristics automatically using a convolutional neural network (CNN), and to potentially allow the prognostic stratification of patients. We aimed to determine the functional prognosis of patients with cervical SCI using machine learning approach based on MRI and to assess the ability to predict the neurological undergone MRI and had an American Spinal cord Injury Association Impairment Scale (AIS) assessment at 1 month after injury, enrolled with a total of 294 MR images. Sagittal T2-weighted MR images were used for the CNN training and validation. The deep learning framework TensorFlow was used to construct the CNN architecture. After we calculated the probability of the AIS grade using the DLR, we built the identification model based upon the random forest using 3 features: the probability of each AIS grade obtained by the DLR method, age, and the initial AIS grade at admission. We performed a statistical evaluation between the actual and predicted AIS. The accuracy, precision, recall and f1 score of the ensemble model based on the DLR and RF were 0.714, 0.590, 0.565 and 0.567, respectively. The present study demonstrates

that prediction of the short-term neurological outcomes for acute cervical spinal cord injury based on MRI using machine learning is feasible.

Keywords:

spinal cord injury; prognosis; ASIA impairment scale; trauma; cervical

Introduction

Acute spinal cord injury (SCI) affects approximately 200,000 people globally each year and has a devastating impact on quality of life (QOL).[1] Accurate prediction of neurological outcomes for acute cervical SCI facilitates estimations for independence in activities of daily living (ADL). Furthermore, with knowledge of the neurological prognosis, we can set rehabilitation goals and can more readily assess the therapeutic effect in clinical trials for SCI treatments. Although there is a great need for early biomarkers of SCI in the acute phase, it is challenging to predict neurological outcomes due to spinal shock and injury heterogeneity.

Magnetic Resonance Imaging (MRI) is the gold standard to visualize soft tissue injury, as well as spinal cord compression and internal structures. Several studies have suggested the usefulness of early MRI as a prognostic tool. [2][3][4] Previous conventional MRI studies have demonstrated that the extent of the intramedullary hemorrhage and the canal diameter at the location of the maximum spinal canal compression (MSCC) are important predictors of neurologic outcome[5][6]. It is inconclusive, however, if these MRI characteristics can determine the prognosis for SCI because these studies had few subjects and limited evidence.

Deep learning-based radiomics (DLR) have been developed to quantify radiographic characteristics automatically using a convolutional neural network (CNN), and to potentially allow the prognostic stratification of patients. DLR is superior to conventional methods, which require the extraction of pre-designed and hand-crafted features from segmented regions of interest, in that a prognosis by DLR can be determined using automatic image feature extraction. Currently there are reliable DLR-based studies to determine cancer phenotypes or survival prognosis[7][8]. A Random Forest (RF) is a well-established method of machine learning based on decision trees.[9] A decision tree is a model that represents laws in classification and regression in a tree-like structure. By combining various decision trees, it enables us to create a highly accurate classification model by majority voting.

There are few previous studies using machine learning to predict functional outcomes in the spine region, thus we sought to apply this promising technique to predict outcomes after acute SCI. The purpose of this study was to assess the ability of machine learning to determine the neurological prognosis of patients with cervical SCI using MRI.

Materials & Methods

Patients

This study was approved by the IRB of four institutions (Chiba University Graduate School of Medicine, Kimitsu Chuo Hospital, Asahi General Hospital, Chiba Emergency Medical Center) and informed consent was waived due to the retrospective analysis. We retrospectively reviewed the medical records at 5 institutions and enrolled patients with cervical spinal cord injury who had undergone MRI within 24 hours after injury and had completed an American Spinal cord Injury Association [ASIA] Impairment Scale (AIS) assessment at both admission and 1 month after injury. Patients with pre-existing or comorbid conditions that could modify neurological symptoms were excluded such as patients with a history of cerebral infraction, thoracolumbar SCI, or impaired consciousness from causes such as head injury or dementia.

Two hundred and thirty-six patients met the inclusion criteria, and 21 patients (2 with dementia, 6 with brain injury, 2 with history of cerebral infarction, 1 with previous history of cervical SCI, 1 with pre-existing paralysis due to cervical spondylotic myelopathy, 3 with thoracolumbar SCI and 6 with low MRI quality) were excluded and 215 patients were enrolled. Surgical indications and surgical procedure selection were not standardized due to the multicenter nature of the study. Basically, spinal cord injuries without radiographic abnormality (SCIWORA) were treated non-operatively in most cases, and unstable spinal injuries with fractures or discoligamentous injuries were treated with fusion surgery. Fifty-nine of the 215 patients underwent surgical treatment

AIS Measurement

The AIS, which is considered to be a reference standard for the neurologic examination of patients with SCI, and a reliable measurement with discriminative and evaluative values[10], was used as the neurologic measurement tool and outcome measure at admission and at 4 (range 3 to 5) weeks after injury. The following scale is used to classify the degree of impairment.[11]

A: Complete. No sensory or motor function is preserved in the sacral segments.

B: Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments.

C: Incomplete. Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a manual muscle test (MMT) grade less than 3.

D: Incomplete. Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a MMT grade greater than or equal to 3.

E: Normal.

MRI Dataset

All patients underwent urgent MRI within 24 hours after injury. We collected the mid-sagittal plane of the T2-weighted image (T2WI) of the cervical spinal cord for the CNN training and validation. Previous studies using MRI images have primarily used indicators extracted from T2-weighted sagittal images[12], thus we also used T2-weighted sagittal images in this study. The MRIs were labeled with the patient's AIS at 4 weeks after injury. The MRIs were performed using either a 1.5 T or 3.0 T MR scanner. Although the T2WI of MRI acquisition protocol was not standardized across the institutions, the following parameters were generally used; repetition time/echo time=3000-5000/100-110ms; flip angle=180°; slice thickness=3.0mm; field-of-view=240 × 240mm^2; matrix size=224-288 × 224-288.

Image Preprocessing

The MRIs of the cervical spinal cord were acquired as digital imaging and communications in medicine (DICOM) files and were exported in jpeg format from the picture archiving and communication system (PACS) in each hospital. A board certified orthopaedic surgeon (SO, 7 years of experience) performed the image preprocessing using a Photo application (Apple Inc., Cupertino, CA) to create the image for CNN training. The region of interest (ROI) was applied to crop a region containing the injured zone and the anteroposterior border of the spinal canal at the level of injury, which had an aspect ratio of 1:1 (Fig.1).

Machine Learning Algorithms

The CNN architecture was constructed using Python programming language, version 3.6.7 (https://www.python.org) and Keras, version 2.2.4 with TensorFlow, version 1.14.0 (https://www.tensorflow.org) at the backend. In this study, we used the Xception architectural model, which had been trained previously using images with ImageNet.[13] The input images were resized to 299 × 299 pixels. We then fine-tuned the model with the dataset of MR images from patients with an AIS of A, B, C, D or E. The weights of the first 108 out of 135 layers were frozen and the weights in the other layers were retrained with our data. The network was trained for 100 epochs with a learning rate of 0.1, which was reduced if no improvement was seen. Convergence of the model training was monitored using cross-entropy loss. All images were randomly augmented using the ImageDataGenerator (https://keras.io/preprocessing/image/) by a rotation angle range of 20°, width shift range of 0.2, height shift range of 0.2, brightness range of 0.3–1.0, and a horizontal flip of 50%.

The performance of the CNN model for predicting the AIS was evaluated with five-fold cross-validation. Then, the concordance rate between the actual and predicted AIS was measured. The MR images of SCI were randomly divided into five equal-sized independent subgroups. Data of the four subgroups were designated as the training dataset and the remaining independent subgroup served as the validation dataset. The prediction was made based upon the highest probability of the five grades: A, B, C, D or E. This cross-validation process was repeated five times. After calculating the probability of the AIS grade using the DLR, we built the identification model based on random forest model using three features; the probability of each AIS grade obtained by the DLR, age, and the initial AIS grade at admission (Fig.2). The performance of the random forest was also evaluated using cross-validation in the same method that was used for the evaluation of the DLR. The CNN and random forest were trained and validated on a computer with a GeForce RTX 2060 graphics processing unit (NVIDIA, Santa Clara, CA), a Core i7-9750 central processing unit (Intel, Santa Clara, CA), and 16 GB of random access memory.

Statistical and Data Analysis

Accuracy is a percentage of the correct predictions out of the total prediction made. Recall is a measure of the number of correct positive predictions from all positives in a dataset, also known as sensitivity. Precision is a measure for the correctness of a positive prediction and is also known as positive prediction value. F score is the weighted average of precision and recall. To calculate the accuracy, precision, recall and F score, we obtained the true positive (TP), true negative (TN), false positive (FP) and false negative (FN). The accuracy, recall, precision and F score were defined as follows; accuracy = (TP + TN)/ (TP + FP + FP + FN + TN); recall = TP/ (TP + FN); precision = TP/ (TP + FP); F1 score = 2 × recall × precision/ (recall + precision).

All computations were done using the statistical package JMP (version 13.2.0.; SAS Institute Inc., Cary, NC). Comparisons were made between the five groups: patients with AIS grade A, grade B, grade C, grade D or grade E. Parametric variables were evaluated using a one-way analysis of variance (ANOVA). A Student t test was used to compare the potential covariates (sex and age, time to the MRI and days to discharge). A P-value of < 0.05 was considered significant in two-sided tests of statistical inference.

Results

Patient Characteristics

The baseline demographic data are shown in Table 1. The number of patients whose AIS at 1 month after injury was A, B, C, D, or E was 25, 4, 45, 91 and 50, respectively. The number of MRI slices with an AIS at 1 month after injury of A, B, C, D, or E was 35, 5, 62, 124 and 68, respectively. The average age of the AIS group E was significantly younger than that of the other groups. Males accounted for approximately 80% of all cases, which was consistent with previous studies.[14],[15],[16] Most patients underwent MRI within 5 hours of injury on average. The patients with more severe SCIs had a greater number of days to discharge. Table 2 shows the AIS at admission and 1 month after injury. The number of patients whose AIS at admission/AIS at 1 month after injury was A, B, C, D or E were 25/25, 19/4, 62/45, 82/91, and 27/50, respectively. After 1 month, 67.0% patients had the same AIS as at the time of admission.

Performance of the DLR

Tables 3 indicates the confusion matrix of the ground truth and predicted AIS using the MRIs. Table 3 indicates that 143 out of 294 (48.6%) of the MRI images correctly predicted the AIS, and 242 out of 294 (82.3%) of the image predictions were within one off the correct AIS. The accuracy of the DLR was 0.486. The precision, recall, and F1 were not available because the DLR did not predict any AIS of B.

Performance of The DLR and RF

Tables 4 indicates the confusion matrix of the ground truth and predicted AIS using the DLR and RF. Two hundred and ten out of 294 (71.4%) of the MR images correctly predicted the AIS, and 277 out of 294 (94.2%) of the image predictions were within one of the correct AIS. The accuracy, precision, recall and F1 score were 0.714, 0.590, 0.565 and 0.567, respectively.

Feature Importance

Among the three parameters (AIS probabilities, age and initial AIS at admission), the importance of the factors predicting the AIS from the random forest was calculated. The feature importance of the probability of an AIS of A, B, C, D and E predicted by the DLR were 0.1115, 0.0708, 0.126, 0.128 and 0.1132, respectively. The feature importance of age and the initial AIS were 0.1311 and 0.297, respectively.

Discussion

The present study demonstrates that DLR, which uses only MR images, could predict the short-term neurological outcomes of acute cervical SCI based on an MRI taken 24 hours after injury with accuracy of 0.486. Moreover, the combination of the DLR and RF could more accurately determine the prognosis than the DLR-only method with accuracy of 0.714.

Our study revealed that using DLR, the accuracy of prediction of AIS at one month after injury was 0.486, which was a moderate agreement. Recently, DLR research has received increasing interest from the medical field and the effectiveness of radiomics has been demonstrated. A previous report suggested that radiomics identified a prognostic phenotype existing both in lung and head-and-neck cancers using data from computed tomography[17]. Another report also concluded that imaging radiomics could predict the tumor regression grade of patients with rectal cancer who were receiving neoadjuvant chemo-radiation therapy[18]. CNNs have an advantage over standard MRI analyses because they automatically extract features and classify images using back-propagation, and do not require manual feature extraction. Unlike the DLR method, which automatically determines neurological prognosis simply by the image input, conventional methods require manual effort to measure injury characteristics. According to previous reports, a longer intramedullary hemorrhage was independently predictive of worse neurologic outcomes, particularly in patients with complete injuries.[5][19] Several papers have also concluded that the presence of hemorrhage was associated with worse neurological outcomes. However, the main limitation of these studies is that the timing of the baseline MRI varied greatly, ranging from hours after hospital admission to 14 days post-injury. The present study, in which the timing of the baseline MRI was limited to within 24 hours after injury, suggests that MR images in this study were not limited by the time-dependent traumatic changes which may have influenced the previous studies. Another report suggested that a smaller spinal canal diameter at the MSCC was associated with worse neurologic recovery.[12] A systematic review indicated that other MRI characteristics might be good prognostic factors, such as a more extensive SCI lesion size, the presence of soft-tissue injuries and disc herniations, and more cord swelling. However, these findings need to be confirmed in larger prospective studies.

The present study demonstrated that the combination of the DLR and RF could more accurately determine the prognosis of acute cervical SCI. The RF is one of the well-known ensemble tree-algorithms to increase the prediction accuracy, decrease the variance between datasets, and avoid overfitting. The ensemble trees are simply the junction of several models used to perform a classification task based on the prediction made by every single tree.[20] Furthermore, this study also demonstrates that the probabilities predicted by the DLR and the initial AIS were more efficient information for the final prediction. A previous report also concluded that the strongest predictors of long-term motor score recovery were the admission AIS motor score[21], supporting the present study.

There are few studies applying machine learning to determine neurological prognosis of cervical SCI using MRI. A recent report used 43 features extracted from the MRI and patients' information such as Brain and Spinal Cord Injury Center (BASIC) score, Maximum Canal Compromise (MCC), length measurement of T2 hyperintensity on the sagittal plane, age, sex, body weight and mechanism of injury. They applied a 2-class discrimination model using XGBoost, which is an ensemble learning algorithm based on decision tree, to predict the AIS (A, B, C or D, E) of cervical SCI at 6 months after the injury and obtained an accuracy of 81.1%. [22] Deep learning-based segmentation of the spinal cord was applied to patients with acute spinal cord injury. Volumes of injury derived from automated lesion segmentation correlated with measures of motor score in the acute phase but not with motor score at discharge.[2] The machine learning model for predicting in-hospital mortality and one-year mortality was developed. The Spinal Cord Injury Risk Score (SCIRS) consists of age, complete injury or not, cervical level of injury or not, AOSpine classification of spinal column injury morphology, and abbreviated injury scale scores. For SCIRS, the values for the area under the receiver operating characteristics curve for one-year mortality prediction was 0.86, for in-hospital mortality was 0.85. [23]

There are several limitations in the present study. First, the images need to be manually cropped prior to the DLR assessment, which may increase the bias. Our future research will construct an object detection model to identify the center of the injury and address this limitation. Second, the number of patients and MR images included in this study was small. Although we applied fine-tuning and data augmentation, a larger data set is needed to improve the accuracy for determining neurological prognosis after SCI. Third, the potential modifiers such as surgical interventions or blood pressure management were not considered in this analysis. However, despite increasing acceptance of early surgery after SCI, the timing of surgery and which patient population will benefit from surgery are not definitive.[24] In addition, no blood pressure management was performed in this study.[25] Lastly, we focused on the neurological prognosis at one month after the injury, and not on the long-term neurological prognosis. Patients with severe paralysis have greater difficulty in follow up hospital visits compared to patients with mild or no symptoms, so long-term follow up can be challenging after severe injuries.

Conclusion

Our study suggests that the combination of the DLR and RF can robustly determine the neurological prognosis of acute cervical SCI using MRI taken within 24 hours. This method could be a novel imaging biomarker for SCI patients, which facilitates better patient care and estimations for future independence in ADL and QOL.

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Figure Legends

Figure 1.

The region of interest was applied to crop a region containing the injured zone and the anteroposterior border of the spinal canal at the level of injury, which had an aspect ratio of 1:1

Figure 2.

Final prediction was made based on random forest using three parameters;

the probability of each AIS grade obtained by deep learning-based radiomics model, the initial AIS grade at admission and age.

jpg, joint photographic experts group; AIS, American spinal cord injury association Impairment Scale

Table 1
Demographic data of the patients.

AIS	A	B	C	D	E
Number of patients(at admission/1 month after injury)	25/25	19/4	62/45	82/91	27/50
Number of MRI slices	35	5	62	124	68
Age ± SD	67 ± 12	67 ± 8	69 ± 14	64 ± 14	56 ± 21
Sex (Male/Female)	22 / 3	4 / 0	36 / 9	77 / 14	39 / 11
Time to MRI(hours ± SD)	4.0 ± 1.8	3.0 ± 0.8	5.4 ± 4.5	5.2 ± 4.4	7.5 ± 6.8
Days to discharge (days ± SD)	76 ± 43	52 ± 11	42 ± 16	33 ± 12	14 ± 12

AIS, American spinal cord injury association Impairment Scale; MRI, magnetic resonance imaging; SD, standard deviation.

Table 2
AIS at admission and 1 month after injury.

		AIS at 1 month after injury				
		A	**B**	**C**	**D**	**E**
AIS at admission	**A**	22	0	2	1	0
	B	2	3	12	2	0
	C	1	1	31	27	2
	D	0	0	0	61	21
	E	0	0	0	0	27

AIS, American spinal cord injury association Impairment Scale.

Table 3
The relationship between the actual AIS and the predicted AIS with the DLR only.

		Predicted AIS with DLR				
		A	**B**	**C**	**D**	**E**
Actual AIS	**A**	**10**	0	11	11	3
	B	2	**0**	2	0	1
	C	6	0	**22**	23	11
	D	5	0	19	**67**	33
	E	4	0	2	18	**44**

AIS, American spinal cord injury association Impairment Scale; DLR, deep learning-based radiomics

Table 4
The relationship between the actual AIS and the predicted AIS with the DLR and RF.

		Predicted AIS with DLR and RF				
		A	**B**	**C**	**D**	**E**
Actual AIS	**A**	**27**	0	6	2	0
	B	1	**0**	4	0	0
	C	6	2	**35**	19	0
	D	2	0	11	**104**	7
	E	0	0	1	12	**44**

AIS, American spinal cord injury association Impairment Scale; DLR, deep learning-based radiomics; RF, random forest.

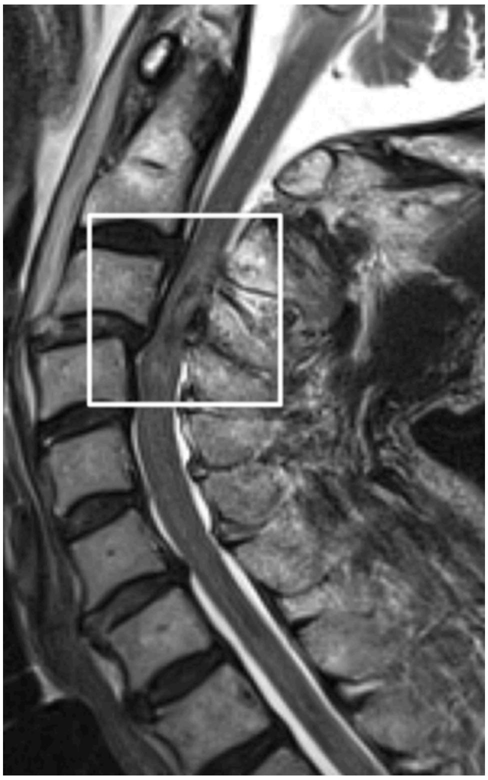

Figure 1

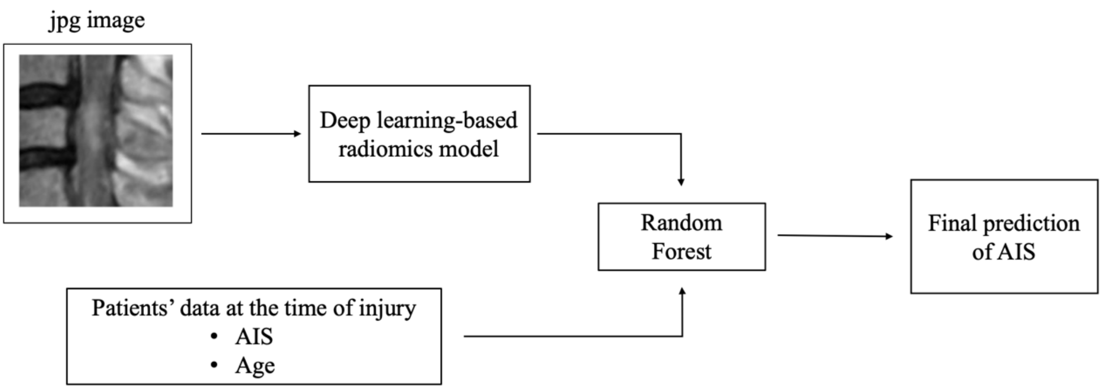

Figure 2

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