

Application of diffusion tensor imaging and neurophysiological monitoring in the quantitative and predictive evaluation of spinal cord function

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Abstract

Objective: To identify which the combination of diffusion tensor imaging (DTI) and neurophysiological monitoring (NM) is reliable in the quantitative and predictive evaluation of spinal cord function.

Methods: Data acquisition was collected in 12 patients who underwent spinal cord tumor surgery in our hospital. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) data of the regions of interest (ROIs) on DTI images were obtained. Preoperative NM and intraoperative neurophysiological monitoring (IONM) were performed. Patients were followed up 2 weeks later. European myelopathy score (EMS score) was recorded pre- and post-operatively. Correlation analysis was conducted to evaluate spinal cord function.

Results: The average value of ADC in the two ROIs before operation was higher than that in the area without spinal cord compression ($P=0.026$), while the average value of FA was the opposite ($p=0.018$). Preoperative FA value significantly decreased in the fiber-interrupted group and the moderate-to-severe-damage group ($P<0.05$). The preoperative FA value had more significant positive correlation with the postoperative EMS score ($R=0.853$, $P=0$), while the preoperative SEP amplitude had more significant positive correlation with the improvement rate ($R=0.826$, $P=0.001$).

Conclusion: For spinal cord tumor patients, the combination of preoperative DTI and NM could quantify the postoperative spinal cord function and predict the prognosis more comprehensively. Preoperative FA value is more valuable to reflect the postoperative subjective symptom, while preoperative SEP amplitude is more meaningful to predict the improvement degree of disease.

Introduction

Spinal cord injury (SCI) is a highly disabling disease. Motor, sensory and autonomous functions are inevitably affected after SCI, either transiently or permanently. Spinal cord tumor is the most common non traumatic spinal cord injury (NTSCI) with adequate indication for surgery. Most people focus on the innovation of examination and surgical techniques, but how to predict postoperative spinal cord function early and reasonably through preoperative examination for the psychological needs of patients and the future rehabilitation should also become a new requirement. Thus, precise and effective methods for early evaluation of spinal cord function are crucial.

Magnetic resonance imaging (MRI) is the most commonly used tool in the diagnosis of SCI for its better soft-tissue resolution. The limitation of traditional MRI is to describe the spinal cord as uniform tissue, although the spinal cord is composed of a series of complex and orderly nerve fiber bundles, thus limiting its application in the evaluation of spinal cord function[1]. Diffusion tensor imaging (DTI) is an emerging MRI technique with high spatial resolution, which can accurately assess the spinal cord structural integrity by depicting and reconstructing the directional diffusion of water molecules[2]. Researchers have stated that DTI can identify the spinal cord injury, even in the regions that were apparently normal on T2W images[3, 4]. For patients with spinal cord compression, whether acute injury or chronic injury, DTI showed higher specificity and sensitivity than T2-weighted image[5]. Many animal models have suggested the correlation between DTI and pathophysiological changes during the recovery of spinal cord injury[6–10]. DTI parameters, ADC (apparent diffusion coefficient) and FA (fractional anisotropy), were associated with the clinical symptoms of patients with SCI[11]. Neurophysiological monitoring (NM) is another excellent monitoring equipment which can reflect the real-time transformation of spinal function for its high time resolution. Intraoperative neurophysiological monitoring (IONM), as an important application branch of NM in neurosurgery, has been employed to estimate the integrity of conduction pathways and the boundary of surgical resection during spinal tumor removal[12]. Continuous IONM can effectively predict and reduce the incidence of postoperative complications[13]. SEP (somatosensory evoked potential) and MEP (motor evoked potential) were two important monitoring indicators, the changes of which were related to the changes of spinal cord structure and postoperative recovery[14].

Any single assessment exhibits particular deficiencies, a systematic and comprehensive evaluation system that assesses spinal cord function is lacking and so is urgently required. A previous report observed that the decrease of FA value was correlated with the amplitude of SEP, and they all reflected the degree of clinical SCI. Demyelination and degeneration of spinal cord fiber bundle can influence DTI, which led to abnormal clinical symptoms and various changes of electrophysiological signals[15]. There were few studies to explore the correlation between DTI, NM and existing spinal cord function score. A recent study found that FA

values showed excellent correlation with the ASIA impairment scale motor scores in the patients with blunt spinal cord injury[16]. The combination of DTI and NM to assess spinal cord function and to predict interventional outcome has yet to be demonstrated. In this study, we have selected 12 spinal cord tumor patients with surgical indications for prospective study. This study attempted to correlate DTI and NM with clinical manifestation and functional score to quantify spinal cord function, which will assist diagnosis, guide treatment, predict prognosis, and provide reference for future research.

Materials And Methods

1.1 Subjects

Between October 2018 and August 2019, we conducted conventional MRI, DTI and NM preoperatively on 12 spinal cord tumor patients, and recorded intraoperative SEPs. T1 and T2 weighted phase and DTI of spine were included in the examination sequence. Patients were followed up 2 weeks later. European myelopathy score (EMS score) was recorded pre- and post-operatively.

1.2 DTI Techniques

All MRI data were available on a 3.0T scanner (Siemens Verio, Siemens, Munich, Germany) respectively. The patients were placed in the coil in a supine position to reduce the influence of respiratory movement on magnetic resonance artifacts of the spinal cord. The scanning sequences include T1-weighted image (TR: 1500ms, TE: 9ms), T2-weighted image (TR: 6000ms, TE: 95ms) and sequentially the thin contrast-enhanced T1-weighted image by intravenous injection gadodiamide on sagittal, axial and coronal plane. Other parameters were as follows: slice thickness 5ms, slice interval 1.5mm, FOV 230mm*230mm, matrix size 307*384. Single-shot Echo-planar Image (EPI) was used in DTI with 25 directions of encoding. All DTI data were acquired in sagittal view with 4mm slice interval and a 128 × 128 matrix, b value of 700 msec, TE of 92.5msec and TR of 3100msec.

The relevant parameters were transferred to a separate work - station (Syngo.via, Siemens, Munich, Germany) and the corresponding photographic images were then synthesized using DTI MR Neuro3D package. Data acquisition was carried out on two ROIs on sagittal view (central gray region): the plane at the junction of the superior and lower margin of the tumor between the normal spinal cord, and normal value was acquired on the area without spinal cord compression which was one vertebra away from the lesion. The average of measurements on two ROIs (ADC_{mean}/FA_{mean}) was collected for statistical analysis. (Fig. 1)

1.3 IONM Techniques

A single technician performed and analyzed NM (including IONM) using the XLTEK Protektor32 (Natus Medical Incorporated, San Carlos, Calif.). Both SEPs and MEPs were monitored in all patients. SEPs were elicited by stimulating the median nerve at the wrist and the posterior tibial nerve at the ankle. We recorded SEPs amplitude of N20 and P40 before starting the surgical procedure. MEPs were obtained from peripheral nerve and muscle responses which triggered by stimulating the motor cortex. We defined the prolongation of latencies of more than 10% or reduction in amplitude of more than 50% as the alarm criteria for evoked potentials. According to this standard, the patients were divided into 2 groups of moderate to severe impairment and mild to no impairment.

1.4 Classification of spinal cord function

European myelopathy score (EMS score) was applied to classify clinical symptoms of patients. Improvement rate (%) = $(\text{postoperative scores} - \text{preoperative score}) / (18 - \text{preoperative score}) * 100\%$.

1.5 Statistical Analysis

The ADC and FA values of compression and non-compression area were tested by normality test and variance homogeneity test. T-test was used in the difference analysis and spearman-test was conducted for correlation analysis. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS v25 software (SPSS Inc., Chicago, IL, USA).

Results

In our study, there were 7 females (58%) and 5 males (42%), with an average age of 49.3 years old. Symptoms on admission were primarily dyskinesia, dysesthesia and pain. There were 4 cases of dyskinesia (33.3%), 10 cases of dysesthesia (83.3%) and 6 cases of pain (50%), including 4 cases of neck pain ,1 case of shoulder pain and 1 case of upper limb pain. All patients achieved gross total tumor resection microscopically. (Table 1a)

Table 1
Clinical information of patients.

Table 1a. Basic information of patients.					
Patient	Gender	Age	Symptom	Site	Pathology
1	M	49	Dysesthesia, neck pain	C2-3	Neurinoma
2	F	63	Dysesthesia, neck pain	C4-5	Meningioma
3	M	28	Dysesthesia	C2-3	Neurinoma
4	M	60	Dysesthesia, dyskinesia	T6-10	Ependymoma, II
5	F	70	Dysesthesia, dyskinesia	T1	Ependymoma, II
6	F	67	neck pain	C1	Meningioma, I-II
7	F	52	Dysesthesia, upper limb pain	C7-T1	Neurinoma
8	M	20	Dysesthesia, dyskinesia	T4-7	Hemangioblastoma
9	F	46	Dysesthesia, neck pain	C4-5	Neurinoma
10	M	53	Dysesthesia	C7-T1	Meningioma
11	F	39	Dysesthesia, shoulder pain	C3-4	Neurinoma
12	F	45	Dyskinesia	T2-3	Meningioma

Table 1b. DTI data of patients.									
Patient	ROI1-ADC (*10 ⁻³ mm ² /s)	ROI2-ADC (*10 ⁻³ mm ² /s)	N-ADC (*10 ⁻³ mm ² /s)	ROI-ADC _{mean} (*10 ⁻³ mm ² /s)	ROI1-FA (*10 ⁻³ mm ² /s)	ROI2-FA (*10 ⁻³ mm ² /s)	N-FA (*10 ⁻³ mm ² /s)	ROI-FA _{mean} (*10 ⁻³ mm ² /s)	Shape
1	1786	1771	779	1778.5	608	317	830	462.5	intact
2	1454	945	607	1199.5	186	764	803	475	intact
3	2095	1715	1026	1905	424	523	767	473.5	intact
4	1496	2663	1023	2079.5	71	350	593	210.5	disruptive
5	2355	2004	1966	2179.5	487	362	684	424.5	disruptive
6	1635	1523	1085	1579	497	323	754	410	intact
7	1578	1023	830	1300.5	576	363	798	469.5	intact
8	2130	1789	1624	1959.5	134	421	693	277.5	disruptive
9	1563	1326	987	1444.5	523	398	816	460.5	intact
10	1752	1711	758	1731.5	588	497	812	542.5	intact
11	1903	1674	1124	1788.5	619	541	728	580	intact
12	1601	1723	1524	1662	498	336	841	417	intact

Table 1c. NM data of patients.		
Patient	Preoperative SEP amplitude(uV)	IONM
1	2.1	mild to no impairment
2	2.2	mild to no impairment

Table 1a. Basic information of patients.					
Patient	Gender	Age	Symptom	Site	Pathology
3	1.1				mild to no impairment
4	0				moderate to severe impairment
5	0.5				moderate to severe impairment
6	1.5				moderate to severe impairment
7	2.2				mild to no impairment
8	0				moderate to severe impairment
9	2.1				mild to no impairment
10	2				mild to no impairment
11	2.2				mild to no impairment
12	1.2				moderate to severe impairment
Table 1d. Clinical manifestations and prognosis.					
Patient		Preoperative JOA score	Postoperative JOA score	Improvement rate (%)	
1		17	18	100	
2		17	18	100	
3		15	18	100	
4		11	8	-42.9	
5		15	16	33.4	
6		14	16	50	
7		15	18	100	
8		15	15	0	
9		14	17	75	
10		15	17	66.7	
11		16	18	100	
12		14	16	50	

2.1 DTI

DTI scans were successfully obtained in all 12 patients, and the data were transferred to a workstation for postprocessing. Diffusion tensor tractography (DTT) was successfully performed, and the reconstructed images showed the spinal nerve fiber tracts clearly without obvious distortion. In the 12 patients, 9 patients (75%) with intact spinal fiber bundles and 3 patients (25%) with disruptive spinal fiber bundles from preoperative DTI. The average value of ADC in the two regions of interest before operation was higher than that in the area without spinal cord compression, and the average value of FA was lower than that in the area without spinal cord compression. (Table 1b)

2.2 NM

All patients underwent pre-operative NM and SEPs amplitude were recorded. IONM indicated moderate to severe impairment in 5 patients (42%) and mild to no impairment in 7 patients (58%). (Table 1c)

2.3 Clinical Manifestations and Prognosis

Only 1 patient had decreased EMS score after the surgery, and the other patients had improved symptoms in different extent. (Table 1d)

2.4 Statistical Analysis

The ADC_{mean} and FA_{mean} were tested for normality, and the results showed that the distribution was normal. ADC_{mean} value of compression area was $1717.3 \pm 299.4 \times 10^{-3} \text{ mm}^2/\text{s}$, ADC_{mean} value of non-compression area was $1111.1 \pm 400.4 \times 10^{-3} \text{ mm}^2/\text{s}$. FA_{mean} value of compression area was $433.6 \pm 102.0 \times 10^{-3} \text{ mm}^2/\text{s}$, FA_{mean} value of non-compression area was $759.9 \pm 73.8 \times 10^{-3} \text{ mm}^2/\text{s}$. (Fig. 2A and 2B)

ADC and FA values had statistical difference between ROIs and the areas without spinal cord compression, and the difference of FA values between spinal cord compression area and non-compression area was more significant ($P = 0.018$) (Fig. 2C and 2D). The preoperative FA values significantly decreased in the fiber-interrupted group ($P = 0.04$) and the moderate-to-severe-damage group ($P = 0.024$) (Table 2).

Table 2
Correlation of DTT and IONM between preoperative FA value.

Group		FA value	P value
DTT	intact	9	0.004
	disruptive	3	
IONM	mild to no impairment	7	0.024
	moderate to severe impairment	5	

The preoperative FA value had more significant positive correlation with the postoperative EMS score ($R = 0.853$, $P = 0$), while the preoperative SEP amplitude had more significant positive correlation with the improvement rate ($R = 0.826$, $P = 0.001$) (Table 3). In addition, in this study, preoperative FA values of ROI of intramedullary tumors were significantly lower than that of extramedullary tumors ($P = 0.004$).

Table 3
Correlation between preoperative FA value or preoperative SEP amplitude and preoperative EMS score, postoperative EMS score or improvement rate as calculated using Spearman rank correlation coefficient (R) with $P < 0.05$ being considered as statistically significant.

	Preoperative FA value		Preoperative SEP amplitude	
	R	P value	R	P value
Preoperative EMS score	0.684	0.014	0.538	0.071
Postoperative EMS score	0.853	0	0.808	0.001
Improvement rate	0.817	0.001	0.826	0.001

Discussion

To investigate morphologic and functional alterations of nerves in spinal injury patients, changes in anatomical structure and neural conduction are measured. DT displays high spatial resolution but only low temporal resolution compared with neurophysiological monitoring. Through variations in quantitative parameter values and fiber tract morphology, DTI can sensitively and intuitively reflect structural and orientational damage of nerve fibers in SCI, serving as an important addition to routine MRI. NM can transform the neural signaling into the waveforms and quantitative data. For its high temporal resolution, NM is regarded as an objective measure – the gold standard of evaluation of the functional integrity of spinal pathways.

In our study, we firstly discussed the significance of FA value and the difference of FA value among different groups before surgery, which provided a basis for further exploration of their relationship with clinical symptoms and prognosis. We believe that the demyelination and axonal degeneration of spinal tracts were likely to reduce DTI signal, thereby leading to clinical symptoms and various changes in electrophysiological measures. Ker'kovský et al.[11] and Yoo et al.[17] have confirmed that DTI values were associated with clinical symptoms. Compared with asymptomatic patients with spinal cord injury, patients with clinical symptoms usually show more significant changes in FA value. Facon et al.[5] have tentatively proposed that the recovery of patients can be predicted by FA value: slightly lower FA value means a better prognosis, while significantly lower FA value indicates a poor prognosis. Low FA value indicated that the shape, structure or function of white matter fiber tracts was damaged. When FA value was lower, it indicated that the more likely the spinal cord was infiltrated rather than simply compressed, the more likely the fiber tracts were interrupted, the worse the integrity of the spinal cord was damaged, the more functions were lost, and the more serious the clinical symptoms and prognosis would be. So, FA value can be used as a quantitative indicator to predict the clinical outcome of patients after therapy. DTI is an important tool to reflect the anatomic integrity of white matter tracts in microstructure, while NM is an important tool to reflect the integrity of nerve cells and the connection between cells. NM can monitor the neural pathway timely and the decrease in amplitude, the extension of latency or the decrease of waveform complexity can indicate that the spinal cord nerve cells were disturbed or injured. The fluctuation of electrophysiological signal is always earlier than changes in vital signs. Siller et al.[18] proposed that multimodal IONM is a powerful signal to predict temporary and lasting postoperative results. Furthermore, Petersen et al.[15] observed that the decrease in FA was correlated with SEPs amplitude, both of which reflected the clinical completeness of spinal cord.

Our study found that compared with the preoperative EMS score, the postoperative EMS score and improvement rate had a stronger positive correlation with the preoperative FA value and SEP amplitude. The larger the preoperative FA value and the higher the SEP amplitude indicated that the integrity of the white matter fiber tracts was better preserved, which suggested that the spinal cord function was in good condition, the injury has a certain degree of reversibility, the surgical effect and long-term recovery were also favorable, and the clinical symptoms could be relatively improved after the disease was relieved. Furthermore, the preoperative FA value had more significant positive correlation with the postoperative EMS score ($R = 0.853$, $P = 0$), while the preoperative SEP amplitude had more significant positive correlation with the improvement rate ($R = 0.826$, $P = 0.001$). The symptom score focuses more on the subjective feeling of the patient, and the improvement rate pays more attention to the aggravation or relief of the symptom. Therefore, we believed that the preoperative FA value can better reflect the postoperative subjective symptom, while the preoperative SEP amplitude can better predict the improvement degree of the disease. Preoperative FA value and SEP amplitude can quantitatively grade the postoperative spinal cord function from two perspectives. Evaluating spinal cord function early and predicting the long-term recovery of patients' nervous system function are new demands and important concerns.

Conclusion

Precise and effective evaluation of spinal cord function is a prerequisite for the diagnosis and treatment of SCI, which further ensures a better and more predictable prognosis. DTI offers a unique perspective into the pathophysiology and microstructural alterations of spinal cord disorders with good spatial resolution, while IONM reflects the integrity of neural signaling with high temporal resolution. The combination of FA value and SEP amplitude before operation can quantify and predict the postoperative function of spinal cord from two aspects: subjective feeling and disease outcome. The number of patients in this study is small, but it can provide reference for the update and improvement of spinal cord function grading standard.

Declarations

Informed Consent Statement

Informed written consent was obtained from the patients for publication of this research.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author Contributions

Yue Cao, Xin-Rui Liu, and Hong-Mei Song designed the research, conducted the data analysis, interpreted the data, and wrote the main manuscript. Yu-He Cui, Qi Huang and Ming-Xin Yu supervised the data analysis and interpreted the data. Gang Zhao critically revised the article. All other co-authors helped to interpret the data and critically reviewed the article. All authors approved the final article for submission.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval

This prospective study was approved by our Ethics Committee of the first hospital of Jilin university, and the requirement for informed consent was waived due to its retrospective nature.

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Figures

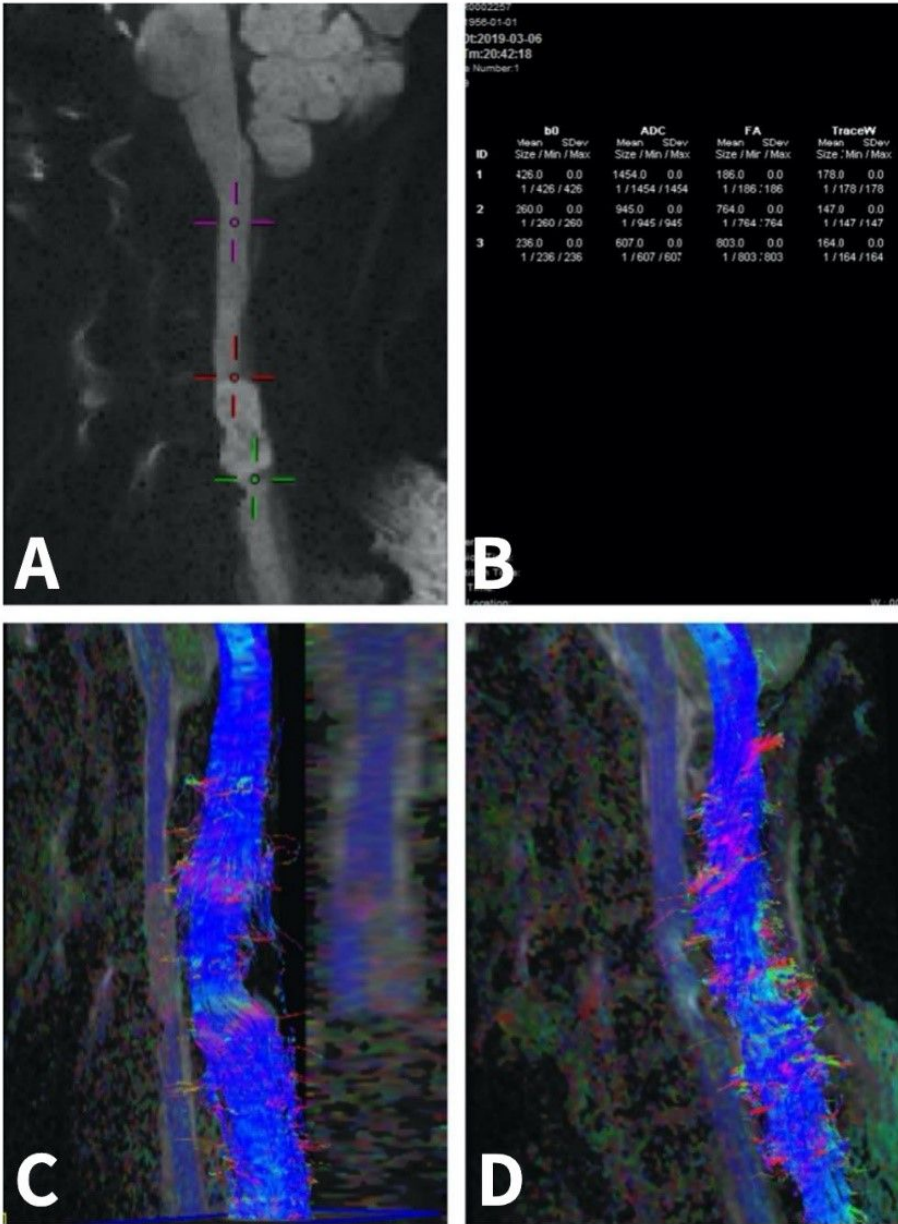


Figure 1

A) and B) The preoperative ROIs and the corresponding FA and ADC values of a C4-5 meningioma patient. **C) and D)** DTI and DTT images of spinal cord before and after operation.

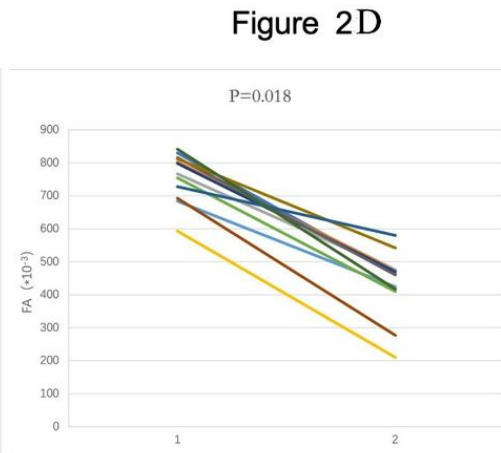
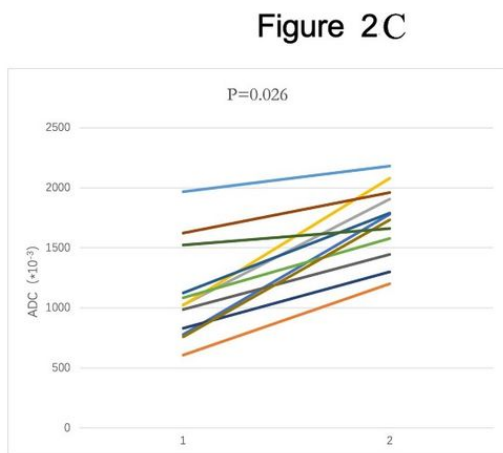
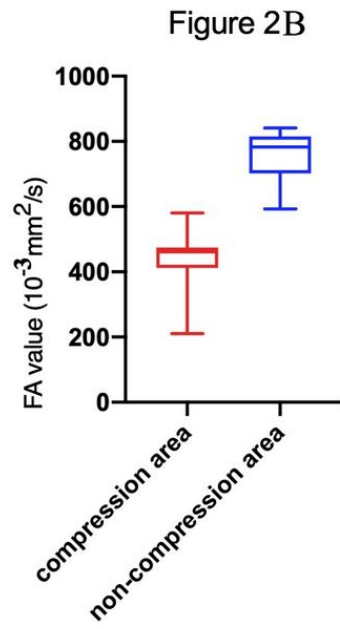
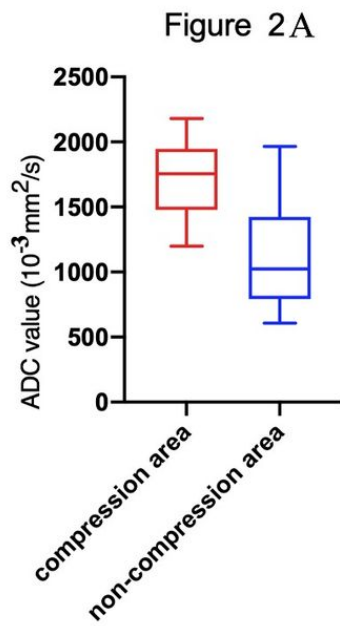


Figure 2

A) and B) Box plots of ADC and FA value. **C) and D)** Difference analysis between spinal cord compression area (1) and non-compression area (2) of ADC and FA.