

## RESEARCH ARTICLE

# Application of Neurite Orientation Dispersion and Density Imaging to Evaluate and Predict the Surgical Outcome for Degenerative Cervical Myelopathy

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## Abstract

**Objectives:** Although the neurite orientation dispersion and density imaging (NODDI) has been shown useful to evaluate the spinal cord dysfunction, there are few prospective studies on analyzing the operation recovery of degenerative cervical myelopathy (DCM) disease using NODDI. This study aims to investigate the preoperative evaluation and predictive ability of NODDI in DCM patients who received posterior cervical laminoplasty.

**Methods:** This prospective study included 55 patients with DCM from January to December 2017. NODDI metrics, including intracellular volume fraction (Vic), isotropic volume fraction (Viso), and orientation dispersion index (ODI) were measured at the maximally compressed (MC) level and the non-compressed C2 level in each patient at the preoperative and the 3- and 6-month postoperative follow-up stages. Neurological function was assessed using the modified Japanese Orthopaedic Association (mJOA) scoring system at each stage. Spearman's correlation and Kendall's tau-b correlation were used to analyze the relationship between NODDI metrics and mJOA scores. Wilcoxon signed rank test was used to examine the changes in the NODDI and mJOA scores between the preoperative and 6-month follow-up stages. ROC analysis was used to further evaluate the predictive capability.

**Results:** Preoperative Vic at the level of C2 has a significant correlation with the preoperative mJOA score ( $r = 0.278$ ,  $p = 0.048$ ). Vic and Viso at the MC level were significantly different between the preoperative period and 6-month follow-up. Viso at the MC level was correlated with the mJOA score at 6-month follow-up ( $r = -0.302$ ,  $p = 0.044$ ). Vic and ODI at the C2 level predicted the surgical prognosis, with areas under the receiver-operating characteristic curve of 0.663 ( $p = 0.042$ ) and 0.716 ( $p = 0.014$ ).

**Conclusions:** The preoperative NODDI metrics at the C2 level are capable of evaluating the severity of spinal cord dysfunction and predict the surgical outcome.

**Key words:** cervical degenerative disease; cervical myelopathy; diffusion tensor imaging; neurite orientation dispersion and density imaging; prognostic assessment

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## Introduction

Degenerative cervical myelopathy (DCM) is a term representing various age-related degenerative conditions of the cervical spine that result in spinal cord damage.<sup>1</sup> It is the most common cause of non-traumatic spinal cord dysfunction in adults. The anterior or posterior decompression surgery is an effective therapy for DCM. Conventional T1- and T2-weighted magnetic resonance imaging (MRI) is the most commonly used imaging method for evaluating DCM. However, anatomical images have a relatively low sensitivity for early diagnosis of spinal cord dysfunction caused by chronic spinal cord compression, and they often underestimate the progress of myelopathy.<sup>2</sup> The value of conventional MRI in the prognosis of DCM surgery is also controversial.<sup>3</sup> Currently, there is still a lack of imaging indicators that can quantitatively reflect the degree of myelopathy and predict the surgical outcome.<sup>2,4</sup>

In recent years, diffusion MRI has been widely used to evaluate the severity of spinal cord dysfunction.<sup>5</sup> By acquiring diffusion-weighted images along multiple directions, diffusion tensor imaging (DTI)<sup>6</sup> models the diffusion property of water molecules with a tensor and measures the diffusion anisotropy accordingly. It provides various diffusion metrics, including fractional anisotropy (FA), axial diffusivity, radial diffusivity, and mean diffusivity. Previous studies have shown that DTI metrics, especially FA, are correlated with the clinical assessment of DCM patients and are valuable for predicting the outcome after decompression surgery.<sup>6–12</sup> Compared with the metrics obtained from conventional MRI, such as intramedullary signal changes in T2-weighted images, DTI has higher sensitivity in the diagnosis of DCM.

In spite of its high sensitivity, DTI is inherently limited by low specificity in microstructures, because only a single tensor is used in characterizing the diffusion of all molecules in each voxel.<sup>13</sup> For example, it cannot determine whether the decreased FA is caused by a decrease in neurite density or by an increase in neurite orientation dispersion.<sup>14</sup> To better reveal tissue microstructures, more advanced diffusion models have been proposed. Among these models, neurite orientation dispersion and density imaging (NODDI)<sup>14</sup> is a practical choice in clinical applications due to its relatively short scan time. In the NODDI model, three types of water molecules are distinguished based on their microstructural environments: intracellular water, extracellular water, and cerebrospinal fluid (CSF), corresponding to restricted, hindered, and free diffusion properties, respectively. Three metrics, intracellular volume fraction (Vic, denoting neurite density), isotropic volume fraction (Viso, denoting free water fraction), and orientation dispersion index (ODI), are then calculated.

Previous studies have shown that the NODDI model is useful in evaluating spinal cord function at the microstructural scale, and the NODDI metrics are potentially valuable for evaluating and predicting the surgical outcome for DCM.<sup>15–18</sup> Ma *et al.*<sup>18</sup> showed that Vic is correlated with the

modified Japanese Orthopaedic Association (mJOA) score in postoperative DCM patients while ODI is not, indicating that the spinal cord dysfunction in DCM is mostly due to the decreased neurite density, not the orientation dispersion. Several studies claimed that NODDI metrics can predict the surgical outcome of DCM, showing that preoperative Vic at the most compressed level,<sup>16</sup> or preoperative Viso at the most compressed level,<sup>19</sup> is significantly correlated with the mJOA recovery rate.

The aims of this study are: (1) to further explore the capability of NODDI in evaluating the spinal cord function; (2) to validate the ability of NODDI in predicting surgical outcome in DCM patients; and (3) to investigate how NODDI can evaluate the microstructural dysfunction in the spinal cord. Specifically, we acquired NODDI data from 55 patients before the surgery, and at 3 and 6 months after the surgery. Then we evaluated the relationship between NODDI metrics and neurological function, represented by the mJOA score<sup>20</sup> at each pre- and postoperative stages. We further explored the predictive capability of NODDI by examining the correlation between preoperative NODDI metrics and the postoperative mJOA recovery rate, and by carrying out receiver-operating characteristic (ROC) analysis.

## Materials and Methods

### Patients

We included 55 patients with DCM (21 females and 34 males, aged 35–72 years, with an average of  $58.6 \pm 6.8$  years) who underwent posterior cervical laminoplasty at the first author's hospital between January and December 2017. Coralline hydroxyapatite was used as the implant in the surgery, to avoid metal artifacts on MRI images. This study was approved by the Ethics Committee of Beijing Jishuitan Hospital, with the IRB No. 201606–03.

The inclusion criteria were as follows: (i) patients with spinal cord compression at more than three levels caused by disk herniation, ossification of the posterior longitudinal ligament, cervical spondylosis, or spinal canal stenosis; (ii) patients aged 18–80 years; (iii) patients without response to regular conservative treatment and on a schedule for posterior cervical laminoplasty; and (iv) patients who were fully informed and consented to participate in the study. The exclusion criteria were as follows: (i) patients unable to undergo MRI; (ii) patients with history of spine surgery; (iii) patients with surgery-related injury to the spinal cord or nerve roots, such as C5 palsy<sup>21</sup> and without sufficient recovery at the last follow-up; and (iv) patients with spinal cord compression at the C2 level.

### Clinical Assessment

Neurological function was assessed before surgery and at three follow-up stages (3, 6 months, and 1–2 years after surgery) using the mJOA scoring system. Among all patients, 49 completed 3-month follow-up, 45 completed 6-month follow-up, and 50 completed 1–2 year follow-up. The mJOA

recovery rate<sup>1</sup> was calculated by:  $(\text{last-time follow-up mJOA} - \text{preoperative mJOA}) / (17 - \text{preoperative mJOA}) \times 100\%$ . The number “17” refers to the full mJOA score.

### MRI Data Acquisition

All MRI data were acquired on a Philips Ingenia 3.0T scanner (Philips, Best, the Netherlands) with a 16-channel head-neck coil. For each patient, MRI scans were performed three times: at the preoperative stage, and at the 3 and 6 months follow-up stages. The single-shot echo-planar-imaging-based sequence was used to acquire the axial diffusion-weighted images with three  $b$  values ( $b = 0, 1000, \text{ and } 2000 \text{ s/mm}^2$ ) and 32 diffusion directions. The reduced field of view (FOV) technique, outer volume suppression, was used to reduce the image distortion along the phase-encoding direction. The imaging parameters were: FOV =  $160 \times 60 \text{ mm}^2$ , in-plane resolution =  $1.5 \times 1.5 \text{ mm}^2$ , SENSE factor = 2, partial Fourier factor = 0.75, and TE/TR = 77/4500 ms. Seventeen slices were acquired with 4-mm thickness and a 2-mm gap to cover the vertebral levels from C2 to C7, with the central slice located between C4 and C5. The total scan time for the DTI sequence was 5 min. In addition, conventional MRI images including sagittal T1-, T2-weighted, and axial T2-weighted images were obtained for structural imaging.

### Image Processing

The acquired diffusion data were processed using the motion correction function in the Spinal Cord Toolbox<sup>22</sup> to co-register the images of different  $b$  values and diffusion directions at each slice. Then, the NODDI MatLab toolbox<sup>14</sup> was used to calculate the NODDI metrics (Vic, Viso, and ODI). Region of interest (ROI) analysis was performed using DTI-Studio software.<sup>23</sup> ROIs were drawn manually following the contour of the spinal cord on the Viso maps at the maximally compressed (MC) level for each patient, the average of other compressed levels (OC, defined as all the compressed levels except the MC level), and the C2 level. Owing to scanning errors, the preoperative NODDI images at the C2 level of four patients were missing. Hence, we only obtained preoperative NODDI metrics at the C2 level from 51 patients. The ROIs were carefully drawn inside the spinal cord, so that voxels with CSF volume were excluded. The ROIs from the Vic map were applied to all other metric maps. The average value of all voxels in the ROIs were calculated.

NODDI metrics were measured independently by two trained surgeons, and the average results were used in the final analysis. To assess the variation of measurements from the surgeons, an intra-class correlation coefficient for each preoperative metric at the MC level was examined, defined as dividing inter-surgeon variance by the intra-surgeon variance. The calculated intra-class correlation coefficients of Vic, Viso, and ODI were 0.806, 0.927, and 0.939, respectively, suggesting that measurements by the two surgeons were consistent.

In addition to NODDI metrics, conventional MRI metrics were recorded at the MC level, including signal changes

of T2 high signal intensity and T1 low signal intensity, anteroposterior diameter of the spinal cord, and compression ratio of the spinal cord<sup>16,24</sup> (defined by dividing the anteroposterior diameter of the spinal cord by its transverse diameter).

### Statistical Analysis

Spearman's correlation was calculated to analyze the relationship between the NODDI metrics and mJOA score at each pre- and postoperative stage. Kendall's tau- $b$  correlation was used to compare the categorical variables and continuous variables. Then the changes in the NODDI and mJOA scores between the preoperative and 6-month follow-up stages were examined by a Wilcoxon signed rank test.

To evaluate the predictive capability of NODDI, Spearman's correlation between preoperative NODDI metrics and the mJOA recovery rate was calculated. Additionally, ROC analysis was used to further characterize this predictive capability. A positive recovery was considered if the mJOA recovery rate of one patient was larger than 50%; otherwise, they were considered to have a negative recovery. The state variable used in the ROC analysis was set to 1 for positive recovery, and to 0 for negative recovery. The cut-off value was set to be the value corresponding to the maximum Youden index (sensitivity + specificity - 1). For comparison, we also used the Spearman's correlation and ROC analysis to evaluate how the conventional MRI metrics can predict the mJOA recovery rate.

We implemented all the analysis procedures in SPSS software (version 20.0; IBM Corp). The level of significance was set at  $p < 0.05$ .

## Results

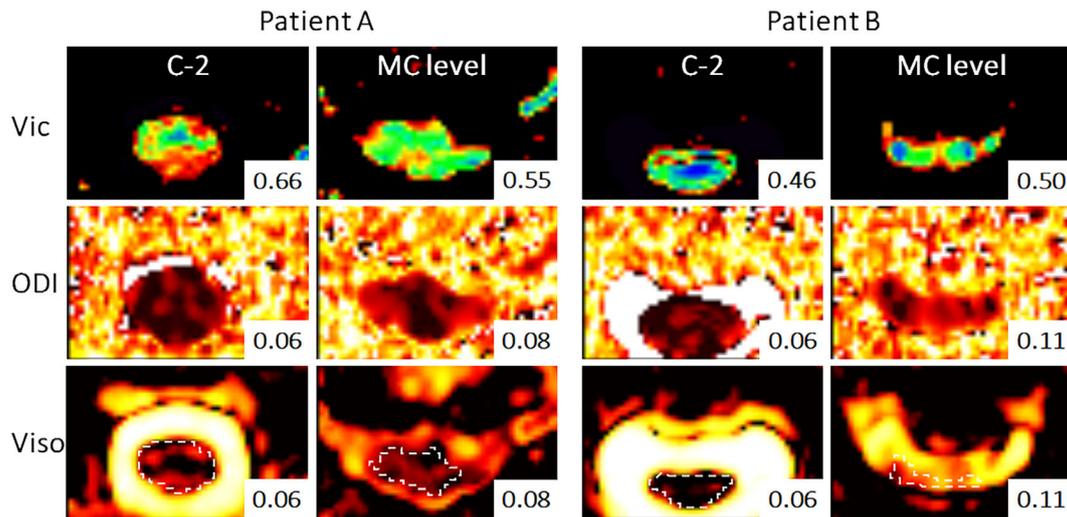
### Preoperative Evaluation of DCM

The NODDI maps of two representative patients are shown in Figure 1. Note that Vic at the C2 level of patient B with a negative mJOA recovery rate is smaller than that of patient A with a positive recovery rate (0.46 vs 0.66), while the Vic values at the MC level of the two patients are similar (0.50 vs 0.55).

The results of correlation between NODDI metrics and mJOA scores before surgery are shown in Table 1. While the NODDI metrics at the MC levels were not correlated with the preoperative mJOA score, Viso at the average of the OC levels and Vic at the C2 level were significantly correlated with the preoperative mJOA score ( $r = -0.322, 0.278$ ;  $p = 0.016, 0.048$ , respectively). Among the conventional MRI metrics, the signal changes of the MC level in the T1-weighted and T2-weighted images were correlated with the preoperative mJOA score ( $r = 0.215, p = 0.049$ ).

### Postoperative Evaluation of DCM

At the 3-month follow-up stage, the NODDI metrics at the MC level were not correlated with the mJOA score (Table 2).



**Fig. 1** The NODDI metric maps of two representative patients, one with a positive mJOA recovery rate, 92.31% (A), and the other with a negative mJOA recovery rate, 33.3% (B). Shown are the Vic, ODI and Viso maps at the non-compressed C2 level and maximally compressed (MC) level. The ROI was manually drawn on Viso maps, shown by the dashed contours. The number at the bottom right corner of each map is the mean value across the ROI. NODDI, neurite orientation dispersion and density imaging; mJOA, modified Japanese Orthopaedic Association; ODI, orientation dispersion index; ROC, receiver-operating characteristic; Vic, intracellular volume fraction; Viso, isotropic volume fraction.

**Table 1** Spearman's correlations between preoperative NODDI metrics at different levels and preoperative mJOA score

Levels (n)	NODDI metrics	Correlation coefficient	p-value
MC* level (n = 55)	Vic	0.026	0.853
	Viso	-0.077	0.578
	ODI	0.101	0.462
Average of OC† levels (n = 55)	Vic	-0.040	0.774
	Viso	-0.322	0.016‡
	ODI	-0.190	0.164
C2 level (n = 51)	Vic	0.278	0.048‡
	Viso	0.158	0.269
	ODI	-0.216	0.127

\* MC, maximal compressed.; † OC, other compressed.; ‡ Significant correlation.; Abbreviations: mJOA, modified Japanese Orthopaedic Association; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index.

**Table 2** Spearman's correlations between the postoperative NODDI metrics at the maximal compressed level and mJOA score at different follow-up stages

Follow-up stage (n)	NODDI metrics	Correlation coefficient	p-value
3-month (n = 49)	Vic	0.108	0.461
	Viso	-0.175	0.230
	ODI	-0.083	0.570
6-month (n = 45)	Vic	0.151	0.323
	Viso	-0.302	0.044*
	ODI	-0.160	0.294

\* Significant correlation.; Abbreviations: mJOA, modified Japanese Orthopaedic Association; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index.

**Table 3** Difference of NODDI metrics at the maximal compressed (MC) level and mJOA scores between the preoperative and 6-month follow-up stages calculated from Wilcoxon signed rank test

Stage (n)/statistics	Vic	Viso	ODI	mJOA score
Pre operation (n = 50)	0.55 (0.48,0.64)*	0.28 (0.16,0.47)	0.06 (0.04,0.10)	13.50 (12.00, 15.00)
6-month follow-up (n = 50)	0.54 (0.44,0.58)	0.19 (0.13,0.27)	0.06 (0.04,0.09)	15.25 (14.00, 16.50)
Z-value	Z = -1.990	Z = -4.171	Z = -1.132	Z = -5.741
p-value	0.047 <sup>†</sup>	<0.001 <sup>†</sup>	0.258	<0.001 <sup>†</sup>

\* Values are expressed as median (25th percentile; 75th percentile).; <sup>†</sup> Significant difference.; Abbreviations: mJOA, modified Japanese Orthopaedic Association; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index.

**Table 4** Spearman's correlations between preoperative neurite orientation dispersion and density imaging (NODDI) metrics at different levels and mJOA recovery rate

Levels (n)	NODDI metrics	Correlation coefficient	p-value
MC level (n = 52)	Vic	-0.020	0.882
	Viso	-0.092	0.505
	ODI	-0.181	0.185
Average value of OC levels (n = 52)	Vic	0.136	0.323
	Viso	-0.292	0.030*
	ODI	-0.248	0.067
C2 level (n = 49)	Vic	0.412	0.003*
	Viso	0.327	0.019*
	ODI	-0.480	<0.001*

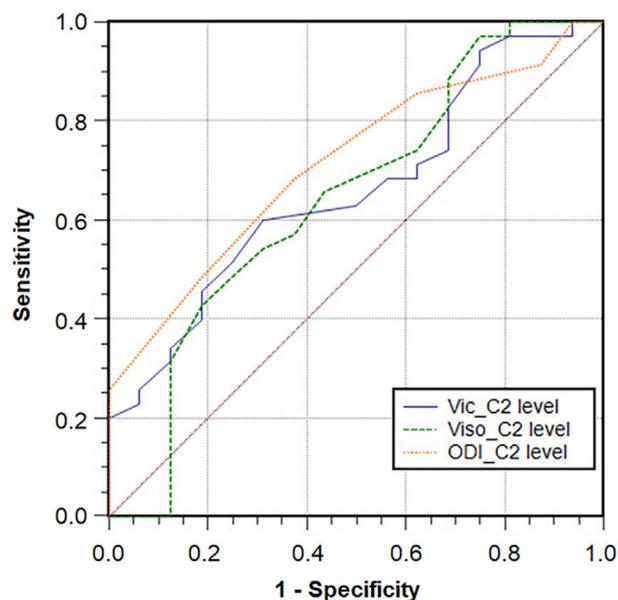
\* Significant correlation.; Abbreviations: MC, maximal compressed; mJOA, modified Japanese Orthopaedic Association; OC, other compressed; ODI, orientation dispersion index.

At the 6-month follow-up stage, Viso at the MC level was correlated with the score ( $r = -0.302$ ,  $p = 0.044$ ; Table 2).

Among the three NODDI metrics at the MC level, Vic and Viso were significantly different between the preoperative and 6-month follow-up stages ( $p = 0.047$ ,  $p < 0.001$  respectively; Table 3). Specifically, both Vic and Viso were decreased at the 6-month follow-up.

### Prediction of mJOA Recovery Rate

The preoperative Viso at the average of OC levels and Vic, Viso, and ODI at the C2 level were significantly correlated with the mJOA recovery rate ( $r = -0.292$ ,  $0.412$ ,  $0.327$ , and  $-0.408$ ;  $p = 0.030$ ,  $0.003$ ,  $0.019$  and  $<0.001$ , respectively; Table 4), while the NODDI metrics at the MC level were not. Among the conventional MRI parameters, the anteroposterior diameter of the spinal cord and T1 and T2 signal changes at the MC level were correlated with the mJOA recovery rate ( $r = 0.337$ ,  $-0.238$ ;  $p = 0.012$ ,  $0.030$ , respectively). The ROC analysis suggested that Vic and ODI at the C2 level had a predictive capability for the mJOA recovery rate with areas under the curve (AUC) of 0.66 and 0.72 ( $p = 0.042$  and  $0.014$ , respectively; Figure 2), but the



**Fig. 2** ROC analysis of the predictive value of NODDI metrics at the C2 level for the mJOA recovery rate. The ROC analysis revealed that Vic and ODI at the C2 level can predict the mJOA recovery rate, with AUCs of 0.66 and 0.72 ( $p = 0.042$  and  $0.014$ ), respectively. AUC, area under the curve. mJOA, modified Japanese Orthopaedic Association; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index; ROC, receiver operating characteristic; Vic, intracellular volume fraction; Viso, isotropic volume fraction.

conventional metrics did not show any predictive capability (data not shown). Though the preoperative Viso at the OC levels showed significantly correlation with the mJOA recovery rate, it did not show a predictive capability in the ROC analysis ( $p = 0.101$ ).

### Discussion

In this study, we explored the ability of NODDI metrics to evaluate spinal cord dysfunction and for predicting the surgical outcome for DCM patients. The results showed that before surgery, Vic at the C2 level was significantly

correlated with the mJOA score, while the NODDI metrics at the MC level or average of OC levels were not. After surgery, Viso at the MC level was significantly correlated with the mJOA score at 6-month follow-up. The preoperative Vic and ODI at the C2 level were significantly correlated with postoperative mJOA recovery, and they were shown to be capable of predicting mJOA recovery based on ROC analysis.

#### **Value of NODDI in Evaluating Spinal Cord Function for DCM Patients**

There have been numerous studies investigating the capability of DTI in evaluating spinal cord function for DCM patients. However, DTI is limited due to its inherent low sensitivity to microstructures. Recently, the advanced diffusion model, NODDI, was proven effective in characterizing the microstructural changes caused by the spinal cord compression. In our study, we further evaluated the correlation between NODDI metrics and clinical assessment for DCM patients. Our results suggested that Vic (i.e. the neurite density) at the C2 level is associated with the clinical assessment score, at both preoperative and postoperative stages, and both Vic and ODI (i.e. the neurite orientation dispersion) at the C2 level has predictive capacity of the recovery rate. It should be noted that the white matter and gray matter were not separately analyzed in this study because of the limited spatial resolution. Efforts should be put in improving the resolution so as to reveal microstructural changes of the white matter only.

#### **Discrepancy between Current and Previous Studies**

While several studies have claimed a significant relationship between the changes of NODDI metrics and spinal cord function, so far there have been few studies examining their predictive capacity for surgical outcome for DCM patients. A similar study was carried out by Iwama *et al.*<sup>16</sup> who included 28 DCM patients and followed them up for 2 years. They found that the preoperative Vic at the most compressed level was significantly correlated with the mJOA recovery rate. Compared with Iwama's study, our paper included more patients (55), and compared NODDI with conventional MRI metrics as well. Our study showed that there was no significant correlation between the preoperative NODDI metrics at the MC level and the preoperative mJOA score, which is consistent with Iwama's study. For the predictive capability, our results showed that the NODDI metrics at the C2 level, not the most compressed level, were able to predict the mJOA recovery rate. The reason might be that the degree of spinal cord compression in this study was severe (average compression ratio =  $0.25 \pm 0.08$ ), which could lead to aggravated partial volume and image artifacts thus biased measurements of NODDI metrics at the MC level. Another reason might be the difference in the follow-up time. In Iwama's study, the follow-up time calculating the mJOA recovery rate was 2 years after surgery, while in this study it was 1–2 years after surgery.

#### **Predictive Capability of NODDI Metrics at C2 Level**

We found that the preoperative Vic at the C2 level was significantly correlated with the preoperative mJOA score ( $r = 0.278$ ,  $p = 0.048$ ), indicating that the neurite density of white matter at the C2 non-compressed level is lower in patients with poorer spinal cord function. The changes of NODDI metrics at the non-compressed C2 level may be related to the occurrence of Wallerian degeneration in the cranial tracts of the compressed spinal cord, including axon demyelination, necrosis, and the disintegration of white matter.<sup>10</sup> Previous studies<sup>6,12</sup> found that the preoperative FA value at the C2/3 non-compressed level has a higher correlation with the preoperative mJOA score than that of the MC level, which is consistent with this study.

#### **Microstructural Dysfunction in DCM Patients**

Based on our results, the preoperative Vic and Viso at the MC level were significantly higher than those at 6-month follow-up. The decrease in Viso at the MC level after surgery may indicate the ability of spinal cord tissue to self-repair postoperatively or the gradual ebbing of inflammation. Vic at the MC level was also lower than during the preoperative period, which indicated a decrease in neurite density after the operation. The study of Ma *et al.*<sup>18</sup> showed that the Vic at the MC level in postoperative patients was lower than that in healthy controls. In this study, the decrease in Vic after surgery may be due to the expansion of the spinal cord cross-sectional area after decompression, which caused a reduction in the relative density of neurites.

A previous study suggested that a plateau in the improvement of symptoms and physical signs in patients with DCM starts from 6 months after surgery.<sup>25</sup> In this study, the correlation between the Viso at the MC level at 6-month follow-up and the mJOA score at 6-month follow-up was significant, but no significant correlation was found at the 3-month follow-up ( $r = -0.302$ ,  $p = 0.044$ ; Table 2). This finding indicates that the recovery of neural function is not synchronized with the repair of the spinal cord, which is consistent with the results of Iwama's study.<sup>16</sup>

#### **Limitations**

The novelty of this study is that we analyzed the NODDI metrics at the non-compressed C2 level as well as at all compressed levels other than the MC level. Our results revealed that NODDI at the C2 level is capable of evaluating and predicting the surgical outcome of DCM patients, which has not been reported in previous studies to our best knowledge.

Future studies may consider the following aspects as improvement. First, patients with DCM with mild spinal cord compression and mild symptoms could be included. Second, the longest follow-up period was 2 years in this study. With even longer-term follow-ups, robustness of the analysis could be strengthened. Third, the NODDI metrics of the gray and white matter could be separately

analyzed with high spatial resolution imaging methods that are able to distinguish them.

### Conclusion

In conclusion, the preoperative NODDI metrics at the C2 level are useful in evaluating the severity of spinal cord dysfunction and predicting the surgical outcome. NODDI metrics can indicate structural repair of the spinal cord after surgery and are associated with spinal cord function after surgery. The longitudinal comparison of preoperative and follow-up NODDI metrics could help evaluate the improvement in spinal cord function after surgical decompression. Currently we used mJOA score as the clinical assessment, whose accuracy relies on the measurement of the surgeons. Part of our future studies is to include more objective quantitative assessments such as electrophysiological measurement.

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### Author Contribution

Conception and design of study: W. Tian, X. Cheng, H. Guo, and X. Han; Acquisition of data: X. Ma, W. Jiang, J. Wang, D. Li, and G. Li; Analysis and interpretation of data: X. Ma, D. Li, and J. Wang.

### Conflicts of Interest

There were no conflicts of interest in this study.

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