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Utility and validity of neurite orientation dispersion and density imaging with diffusion tensor imaging to quantify the severity of cervical spondylotic myelopathy and assess postoperative neurological recovery

（頚椎症性脊髄症の重症度評価と術後神経回復の評価におけるDTIとNODDIの有用性）

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Clinical Study

Utility and validity of neurite orientation dispersion and density imaging with diffusion tensor imaging to quantify the severity of cervical spondylotic myelopathy and assess postoperative neurological recovery

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Abstract

BACKGROUND CONTEXT: Predicting postoperative prognosis with preoperative diagnostic imaging has clinical importance. Recent studies have indicated the utility of diffusion tensor imaging (DTI) to quantify the severity of cervical spondylotic myelopathy (CSM) and assess the prognosis of surgical outcomes. However, how to apply DTI to evaluate CSM in a clinical setting is not fully elucidated. Neurite orientation dispersion and density imaging (NODDI) is a model-based practical diffusion-weighted magnetic resonance imaging analysis for estimating specific microstructural features related directly to neuronal morphology. In a prior study, we indicated preoperative NODDI parameters are a promising tool with which to predict neuronal recovery after decompression surgery in patients with CSM with 2 years follow-up. However, the correlation between NODDI parameters and postoperative long-term outcomes and change of parameters over time postoperatively has remained largely unknown.

STUDY DESIGN: Retrospective cohort study.

PURPOSE: To determine the change of parameters of NODDI and conventional DTI over time, and the relationship between parameters and neurological recovery 2 years after surgery.

PATIENT SAMPLE: We included 28 consecutive patients with nontraumatic cervical lesions from CSM who underwent laminoplasty and were followed up for >2 years. Patients underwent magnetic resonance imaging before and approximately 2 weeks, 6 months, and 1 year after surgery.

OUTCOME MEASURES: In addition to conventional DTI metrics, we evaluated intracellular volume fraction (ICVF) and orientation dispersion index, which are metrics derived from NODDI. The Japanese Orthopedic Association (JOA) scoring system was used before and 2 years after surgery to assess neurological outcome (JOA recovery rate).

METHODS: NODDI and conventional DTI values were measured at the C2–C3 intervertebral level (control value) and the most compressed levels (C3–C7 intervertebral levels) were measured by 3 observers. The changes of these values from preoperatively, 2 weeks after surgery, 6 months after surgery, and 1 year after surgery, were determined. The correlations between preoperative neurological severity, postoperative neuronal recovery, and preoperative DTI or NODDI metrics

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RESULTS: The preoperative ICVF and fractional anisotropy at the most compressed level were significantly less than the preoperative values at the control C2–C3 intervertebral level and fractional anisotropy at the most compressed level was increased in the immediate postoperative period. By contrast, ICVF at the most compressed level was not increased in the immediate postoperative period and a significant increase was observed at 6 months after surgery. Preoperative ICVF was significantly correlated with JOA recovery rate at 2 years after surgery.

CONCLUSIONS: NODDI is a reproducible and reliable method for evaluation of CSM. ICVF improved after surgery and recovery of physical findings accompanied this change. ICVF may be applied clinically to predict postoperative recovery.

Keywords: Neurite orientation dispersion and density imaging; Cervical spondylotic myelopathy; Diffusion tensor imaging; Fractional anisotropy; Intracellular volume fraction; Neurological recovery

Introduction

The indication of surgery for degenerative cervical spondylotic myelopathy (CSM) is mainly determined by clinicians individually using the patient's neurological findings, clinical symptoms, and diagnostic imaging. Surgical outcomes are known to be unpredictable and vary among individuals, and may depend on the degree of spinal cord dysfunction, age, and other factors. Additionally, severe spinal cord damage is known to impair surgical outcome and patients receive less benefit from surgery [1]. Therefore, knowing the prognosis of surgical outcomes and the proper timing of surgery is clinically relevant for decisions about whether and when to perform surgical treatment. To achieve that, diagnostic imaging to estimate the actual neuronal damage and potential for recovery in each column of white matter should have great value.

Conventional magnetic resonance imaging (MRI) is currently used in clinical settings to evaluate CSM. However, the low sensitivity and limitations of conventional anatomical MRI using T1- and T2-weighted sequences to quantify the pathological impairment have become well known, and the establishment of a new diagnostic imaging method is expected [2,3]. Recent studies indicated the potential use of diffusion tensor imaging (DTI) as a biomarker for predicting functional impairment, providing reliable information about the relationship between symptoms and spinal cord structure, and assessing the prognosis of surgical outcomes in CSM [4–6]. However, application of DTI to evaluate CSM in a clinical setting is complicated by remaining issues [7]. For example, the value of DTI parameters might not be specific because they are influenced by various factors, such as reduced neurite density, increased dispersion of neurite orientation, or other related microstructural changes [8].

Neurite orientation dispersion and density imaging (NODDI) is an emerging advanced diffusion MRI method that enables investigation of the underlying tissue microstructure. [9]. NODDI provides a simplified, but sophisticated, three-compartment model of diffusion MRI, which separates the signal arising from three different tissue compartments – intraneurite or intracellular compartment water, extraneurite or extracellular compartment water and cerebrospinal fluid. Moreover, the orientation dispersion index (ODI) derived from NODDI data represents the angular variation of neurites. NODDI seems to have an advanced capacity to characterize tissue microstructure, compared with DTI [10,11]. Intraneurite or intracellular compartment water measured by NODDI is indexed as intracellular volume fraction (ICVF).

Preliminary analysis shows potential application of NODDI to spinal cord evaluations and shows ICVF as a potential parameter to predict postoperative neuronal recovery [9]. However, this analysis has been limited to a clinical outcome of only 1 year after surgery and for NODDI parameters 2 weeks after surgery. Therefore, the usefulness of NODDI to predict the postoperative long-term outcomes, and change of NODDI parameters over time postoperatively had remained largely unknown. Therefore, we sought to conduct a more long-term and accurate study to clarify the precise mechanisms of how NODDI parameters predict postoperative neuronal recovery.

The goal of the present study was (1) to clarify the reproducibility of NODDI parameters using interobserver error by three readers, (2) to determine the change of parameters of NODDI and conventional DTI over time throughout 1 year, and (3) to evaluate the relationship between parameters and neurological recovery 2 years after surgery in patients with CSM who underwent decompression surgery.

Materials and methods

Patients and surgical techniques

The study was approved by our institutional review board (No 1742). Patients who underwent conservative treatment without improvement were scheduled for surgery. All subjects provided their written informed consent. A previously published study had included 27 consecutive patients with CSM who were diagnosed with CSM based on clinical signs, symptoms, and imaging findings at a

single institution between April 2012 and April 2015 [9]. This is retrospective cohort study continued previous study. In the present study, 1 patient was added and all patients were followed-up 2 years after surgery. Therefore, data were obtained from the same patients that participated in the previous published study and one more patient was included; a longer follow-up and images analyzed by another two readers were used in the present study.

All patients were treated using a bilateral open-door laminoplasty with midsagittal splitting, but without lamina spacers by three board certified spinal surgeons. The inclusion criteria were – (1) patients with cervical spondylotic myelopathy and ossification of a longitudinal ligament with observation of cord compression in cervical spine MRI and clinical features of myelopathy or myeloradiculopathy, and (2) patients who had been followed up for >2 years. Patients were excluded from the present study for the presence of trauma, infection, neoplasm, or other etiologies.

Neurological assessment

The Japanese Orthopedic Association (JOA) scoring system and postoperative recovery rate (JOA recovery rate) at 6 months, and 1 and 2 years after surgery were used to assess preoperative neurological status and the postoperative neurological recovery of the patients, as described previously [10].

Image acquisition

Patients were supine while maintaining a neutral spine position with a pillow placed under their knees during imaging. MRI was obtained before and approximately 2 weeks after surgery, 6 months after surgery, and 1 year after surgery. These serial examinations assessed for the changes in the spinal cord signal intensity and the levels of cervical cord compression. All patient participants were scanned using a 3.0 T dual gradient superconducting MRI system (Discovery 750; GE Medical Systems, Milwaukee, WI, USA) with an 8-channel NV-full neck coil. Sagittal and axial T1-weighted and T2-weighted MRI were performed routinely. Moreover, after conventional MRI, including sagittal and axial T2- and T1-weighted imaging, multishell diffusion-weighted imaging using spin-echo echo-planar imaging for NODDI was performed with 6 MPG axes and 5 b-values (0, 500, 1000, 2000, 3000 s/mm^2), covering the entire cervical spinal cord. The imaging parameters were as follows: repetition time, 5000 ms; echo time, 103 ms; FOV, 200 mm × 200 mm; matrix size, 256 × 256; slice thickness, 3 mm; number of excitations, 4; and total scanning time, approximately 10 minutes.

Postprocessing

The diffusion-weighted images were first corrected for eddy-current distortions and for movement [12] and denoising techniques were applied using position-orientation adaptive smoothing [13], before NODDI and DTI procedure. All multishell data were analyzed using the software distributed by the developers of NODDI (http://www.nitrc.org/projects/noddi_toolbox), implemented in Matlab (MathWorks, Natick, MA, USA), which yielded maps of ICVF and ODI for each participant. Moreover, an in-house MATLAB routine was employed to fit DTI data to generate apparent diffusion coefficient (ADC) and fractional anisotropy (FA) maps based on a conventional monoexponential model [14] using only data with b=0 and 1,000 s/mm^2 for comparison with past reports of spinal cord DTI [15].

Regions of interest selection and measurement

NODDI and conventional DTI parameters were measured at both the C2–C3 intervertebral level (control value) and the most compressed levels (C3–C7 intervertebral levels). If there were two or more compressed levels, the most compressed level was decided based on both imaging diagnostics with T2-weighted imaging and neurological findings by three board certified spinal surgeons who were blinded to image analysis for this study. Regions of interest (ROI) for the entire spinal cord were traced manually at eight points by four places to the right and left including regions inside of the spinal cord, the edge of the cord, on the ICVF map images as previously described. The ROIs were selected to be as much as possible equally spaced intervals in the inner spinal cord to exclude partial volume effects because of cerebral spinal fluid. Each ROI comprised one pixel, approximately 0.78×0.78 mm^2 (Fig. 1). ICVF values and eigenvalues are presented automatically for each ROI in the software. FA, ADC, and ODI values were recorded as presented. Mean values of eight ROI points were used for analysis. NODDI and conventional DTI values were measured by three observers (TI; author 1, TO; author 2 and GO; author 4) to estimate inter-rater reliability. We applied the mean values of these measurements to the following analysis.

Statistical analyses

We reported means ± SD for continuous variables or number (percentage) for categorical variables. The data were analyzed using an unpaired *t*, Mann-Whitney *U*, and Fisher exact tests to compare means between two groups, assuming normal distributions for continuous variables. Correlations between ADC, FA, ICVF, and clinical outcome were determined by the Pearson correlation coefficient. All statistical calculations were performed using Prism (version 8.0; Graph Pad Software, La Jolla, CA, USA). Asterisks indicate statistical significance ($p<.05$).

Results

Interobserver error of FA and ICVF preoperatively

The intraclass coefficients were 0.754 (FA) and 0.69 (ICVF), indicating that the inter-rater reliability was almost ideal (Fig. 2A, B).

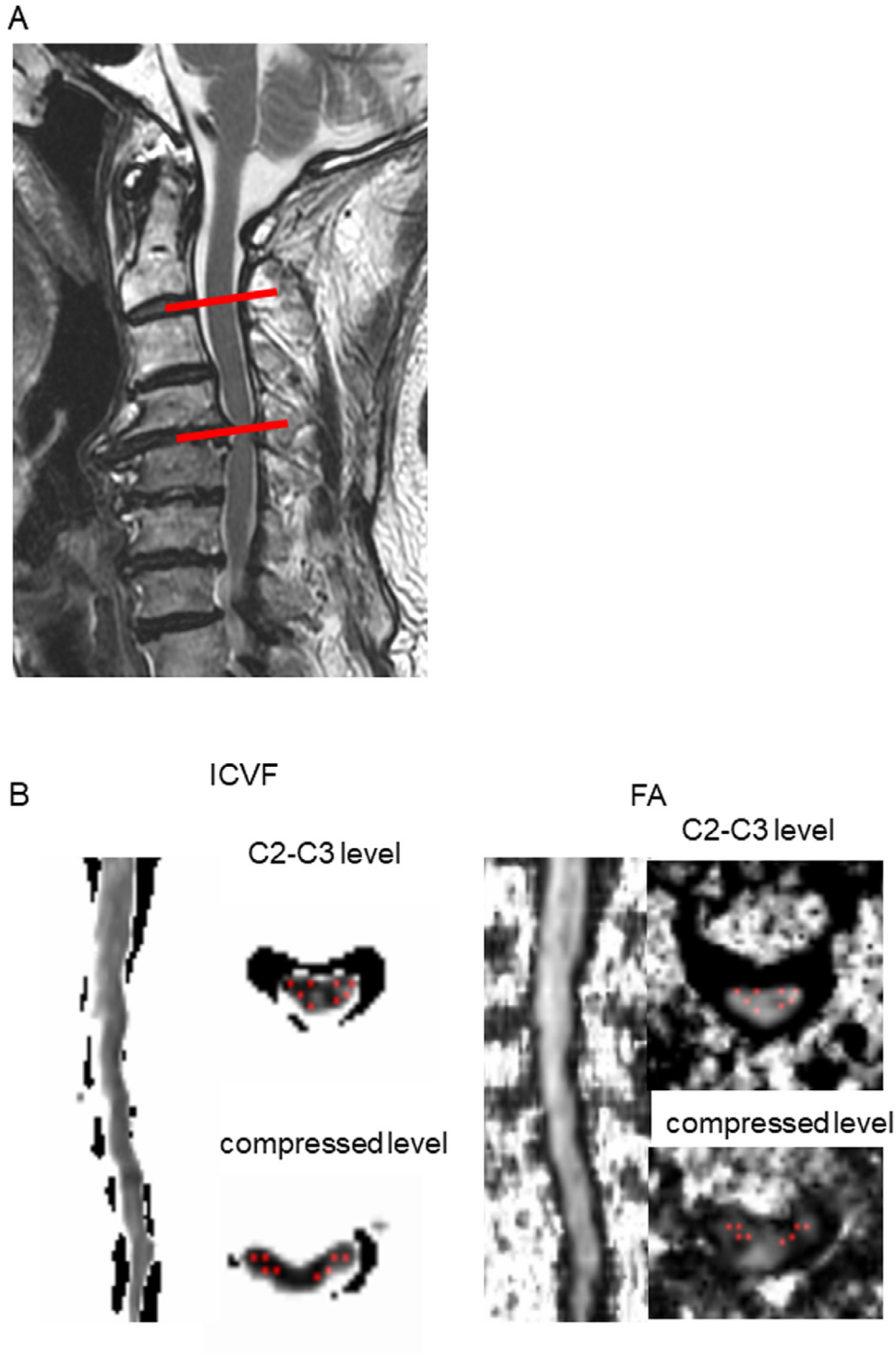

Fig. 1. (A) Referring to T2-weighted sagittal anatomical images, regions of interest (ROI) were traced manually at 8 points including regions inside of the spinal cord at the C2-C3 intervertebral level or the most compressed level on the ICVF axial map images. (B) Representative imaging for calculating DTI and NODDI metrics at the C2-C3 intervertebral level or the most compressed level on the ICVF axial map images of one patient.

Patient demographics and clinical outcomes

The 28 patients with CSM included 21 men and 7 women. Their mean age was 69.7 ± 10.3 (range 44−86) years. Mean course of the disease was 8.6 (range 6−21) months. The most compressed intervertebral level was C3−C4 in 3 patients, C4−C5 in 14, C5−C6 in 7, and C6−C7 in 4 (Table 1). The smoking rate was 7/28 (25%) and prevalence of diabetes was 6 of 28 (21.4%) (Table 1). Patients were followed up for a minimum of 2 years and their improvement

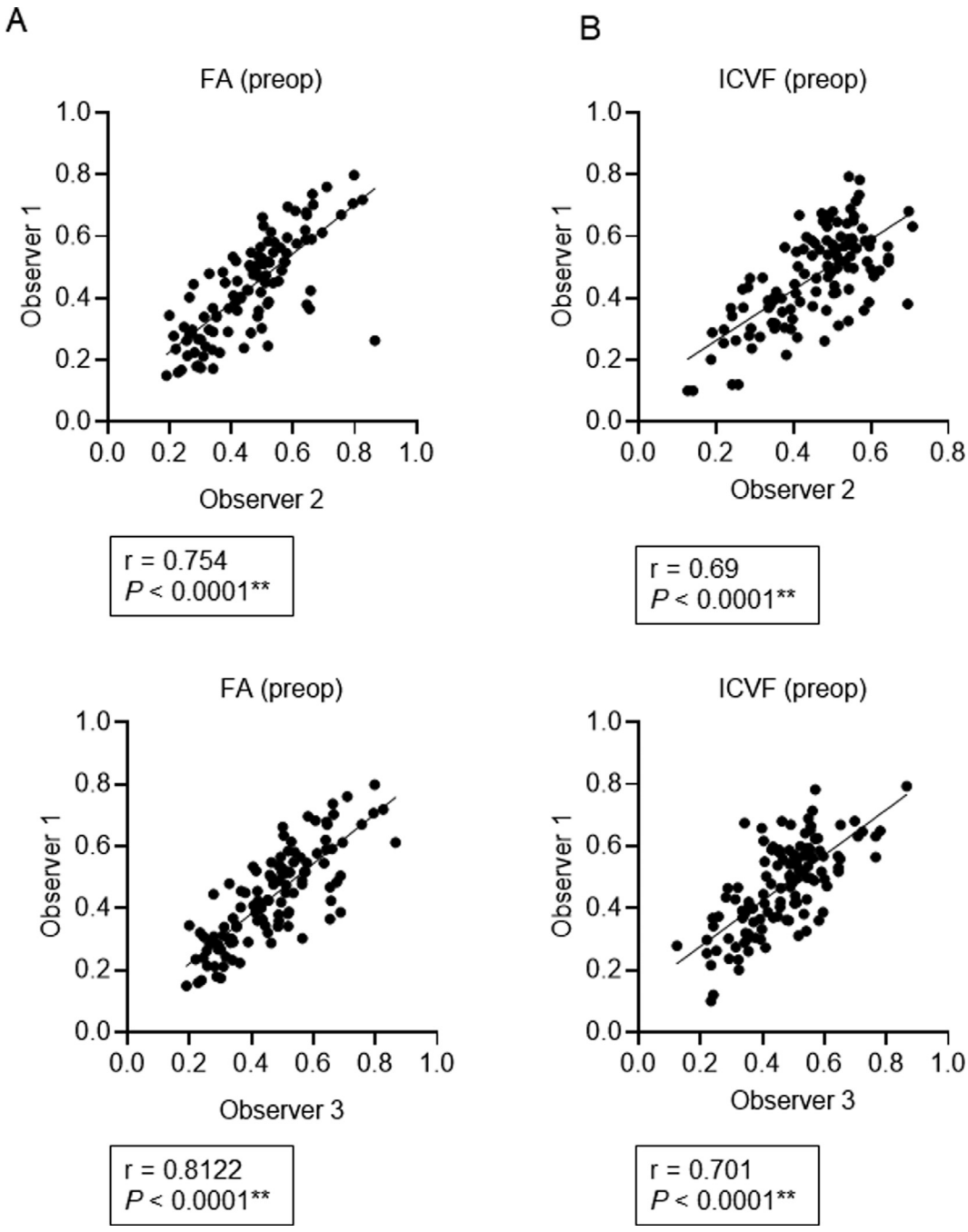

Fig. 2. Interobserver errors by three readers of FA and ICVF preoperatively (****p<.0001).

in neurological status was measured. Mean preoperative JOA score was 9.75 ± 2.5 points and the mean postoperative JOA score was 12.7 ± 1.9 points at 2 weeks after surgery, 13.4 ± 2.1 at 6 months after surgery, 13.6 ± 1.84 at 1 year after surgery and 14.0 ± 2.0 at 2 years after surgery. There was a significant improvement of JOA score until 6 months after surgery, but no difference after that (Fig. 3A). Mean recovery of the JOA score at 2 years after surgery was 54.5% ± 20.5%.

Comparison of NODDI and DTI metrics between the most compressed level and the control C2–C3 intervertebral level pre- and postoperatively

The preoperative ICVF and FA at the most compressed level was significantly less than the preoperative values at the control C2–C3 intervertebral level (Fig. 3B, C). By contrast, there were no significant differences between preoperative ODI and ADC at the most compressed level and the control C2–C3 intervertebral level (data not shown).

Table 1
Characteristics and variables of enrolled patients

Variables	N=28
Age (y)	69.7±10.3
Sex (female/male)	7/21
Smoking (CS/FS/NS)	7/5/16
Diabetes (+/−)	6/22
Most compressed level	
C3−C4	3
C4−C5	14
C5−C6	7
C6−C7	4

CS, current smoker; FS, former smoker; NS, never smoker.

There was no significant change between preoperative and postoperative ICVF, ODI, ADC, or FA at the C2−C3 intervertebral level (data not shown). Interestingly, FA at the most compressed level was increased in the immediate postoperative period (2 weeks after surgery) and the increase of FA values was observed until 6 months after surgery (Fig. 3B). By contrast, ICVF at the most compressed level was not increased in the immediate postoperative period (2 weeks after surgery) and a significant increase was observed at 6 months after surgery (Fig. 3B). Significant changes of FA and ICVF were not observed between 6 months and 1 year after surgery (Fig. 3B, C). The FA and ICVF increased to the same levels of values at

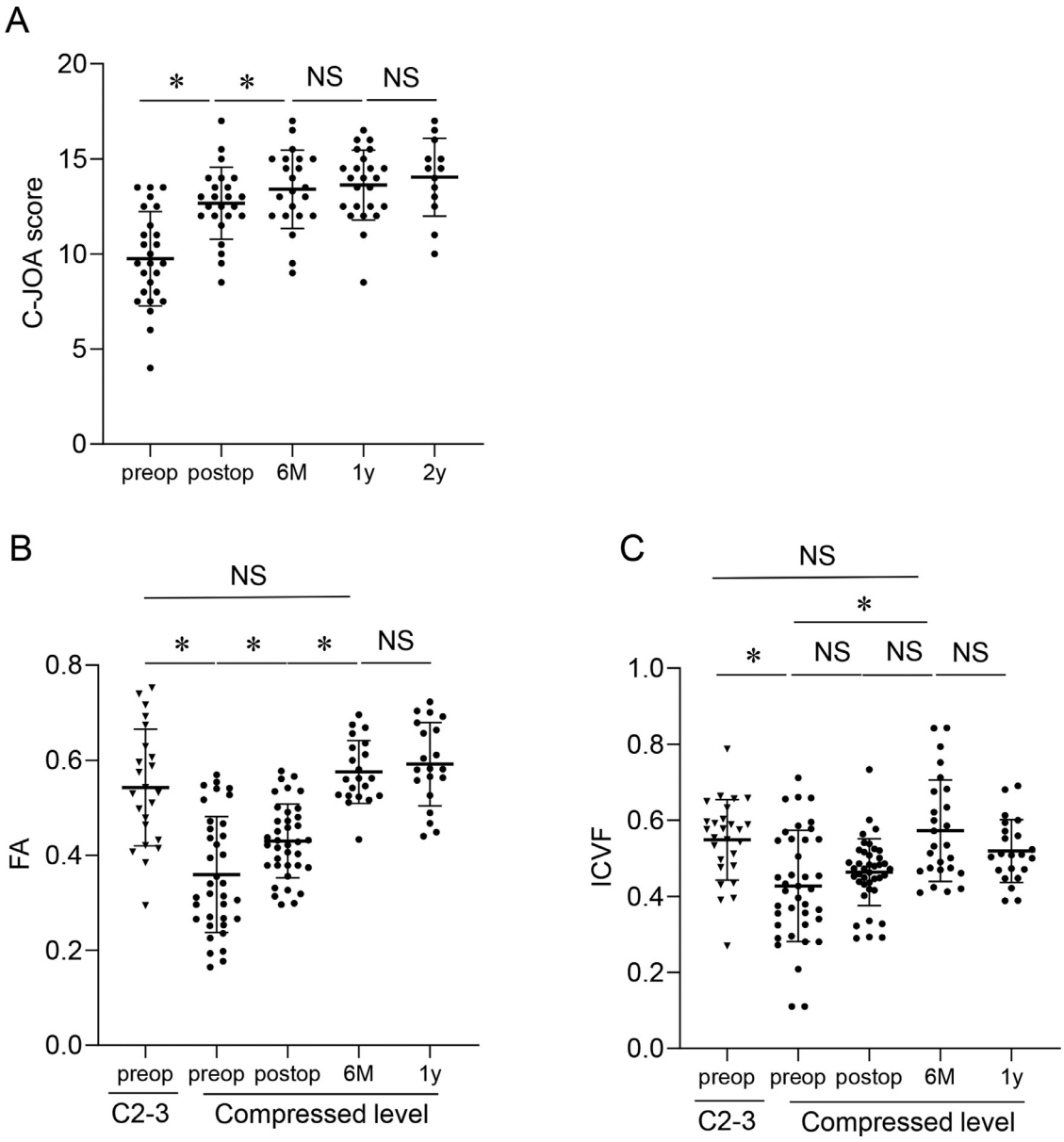

Fig. 3. (A) Comparison of C-JOA score among preoperative, 2 weeks postoperative, 6 months postoperative, 1 year and 2 years postoperative. (B) Comparison of FA among preoperative, 2 weeks postoperative, 6 months postoperative, 1 year and 2 years postoperative. (C) Comparison of ICVF among preoperative, 2 weeks postoperative, 6 months postoperative, 1 year and 2 years postoperative.

the C2–C3 intervertebral level 6 months postoperatively and significant changes of FA and ICVF were not observed between 6 months and 1 year after surgery (Fig. 3B, C). There was no significant change between preoperative and postoperative ADC or ODI at the most compressed level (data not shown).

Correlation between preoperative neurological severity, postoperative neuronal recovery, and preoperative DTI or NODDI metrics

The correlations between preoperative neurological severity (JOA score) and NODDI or DTI metrics are summarized in Table 2. Preoperative FA was significantly correlated with preoperative JOA scores (r=0.439, p<.05) (Table 2 and Fig. 4B). By contrast, there was no significant correlation between the preoperative ICVF, ODI, ADC, and preoperative neurological severity (Table 2 and Fig. 4A).

The correlations between postoperative neuronal recovery (JOA recovery rate) and preoperative NODDI or DTI metrics are summarized in Table 2. Preoperative ICVF was significantly correlated with JOA recovery rate at 2 years after surgery (r=0.38, p<.05). No significant correlation was found between the preoperative FA, ODI, or ADC and the postoperative neuronal recovery (Table 2).

Discussion

Our previous study shows potential application of NODDI to spinal cord evaluations and shows ICVF as a potential parameter to predict postoperative neuronal recovery [9]. However, this analysis has been limited to a clinical outcome of only 1 year after surgery and for NODDI parameters 2 weeks after surgery. Therefore, the usefulness of NODDI to predict the postoperative long-term outcomes, and change of NODDI parameters over time postoperatively had remained largely unknown.

In the present study, we first examined interobserver error of NODDI parameters and revealed reproducibility and reliability of NOODI for spinal cord evaluation. Second, the change over time of the NODDI and DTI parameters was examined up to 1 year. The value of FA was increased from immediately after surgery until 6 months after surgery. By contrast, ICVF was not increased immediately after surgery and a significant increase was observed at 6 months after surgery. Additionally, the present study clarified that both parameters were unchanged 1 year after surgery. Finally, we found among parameters, only preoperative FA was correlated significantly with preoperative neurological severity and only ICVF was correlated significantly with postoperative neuronal recovery.

Numerous studies have sought to determine the validity of DTI in spinal cord evaluation in degenerative cervical disorder. Unfortunately, the usefulness of DTI in the clinical setting remains controversial because of reproducibility and specificity issues [7,11 , 16, 12–14,17 ,18]. In recent years, attempts to apply NODDI to cervical cord evaluation have been reported [15, 19,20]. NODDI is a recently introduced tissue model-based analysis technique and can reveal more specific microstructural information for neural tissues as metrics, such as ICVF or ODI [8,17]. FA was found useful to access the severity of the disease of patients with CSM preoperatively, but had limited sensitivity to predict postoperative neuronal recovery. By contrast, we found that ICVF was more sensitive and useful for predicting postoperative recovery than FA. The present study confirmed this finding with longer-term follow up. However, the detailed reasons why only ICVF correlated with neuronal recovery among DTI and NODDI parameters remained largely unknown. Therefore, we set up a study to observe a change in parameters over time to answer the question. In the present study, FA at the most compressed level was increased in the immediate postoperative period. This finding indicated FA is affected by decompression immediately because the morphology of the cervical cord is supposed to be restored. By contrast, ICVF, which might evaluate neurite density specifically, was not increased immediately postoperatively. We consider these findings indicated that although spinal canal stenosis is relieved by surgery and edema is improved, neuronal necrosis, and neurite density reduction could not improve immediately. Surprisingly, the present study showed ICVF improved to that of preoperative control levels at 6 months after surgery and JOA recovery accompanied this change. This finding indicated neurite density reduction by CSM was not irreversible and improvement in neurite density might be expected for 6 months after surgery. Finally, the present study showed ODI did not change with surgery and was not correlated with clinical outcomes. This finding suggests that disorder in the spinal cord of CSM patients is mainly caused by decreased neurite density, not increased orientation dispersion.

A limitation of this study is the small sample size used. Therefore, longitudinal studies with larger sample sizes are needed to validate the correlation between NODDI indices, disease duration, and clinical severity to establish the

Table 2
Correlation between preoperative DTI and NODDI parameters and JOA score

		JOA score preoperative	JOA recovery rate 2 years
ICVF	r		**0.375**
	p	NS	**<.05***
ODI	r		
	p	NS	NS
ADC	r		
	p	NS	NS
FA	r	0.439	
	p	**<.05***	NS

ICVF = intracellular volume fraction; ODI = orientation dispersion index; ADC = apparent diffusion coefficient; FA = fractional anisotropy; GR test = 10 s grip and release test; JOA = Japanese Orthopaedic Association. (*p < .05, NS = not significant)

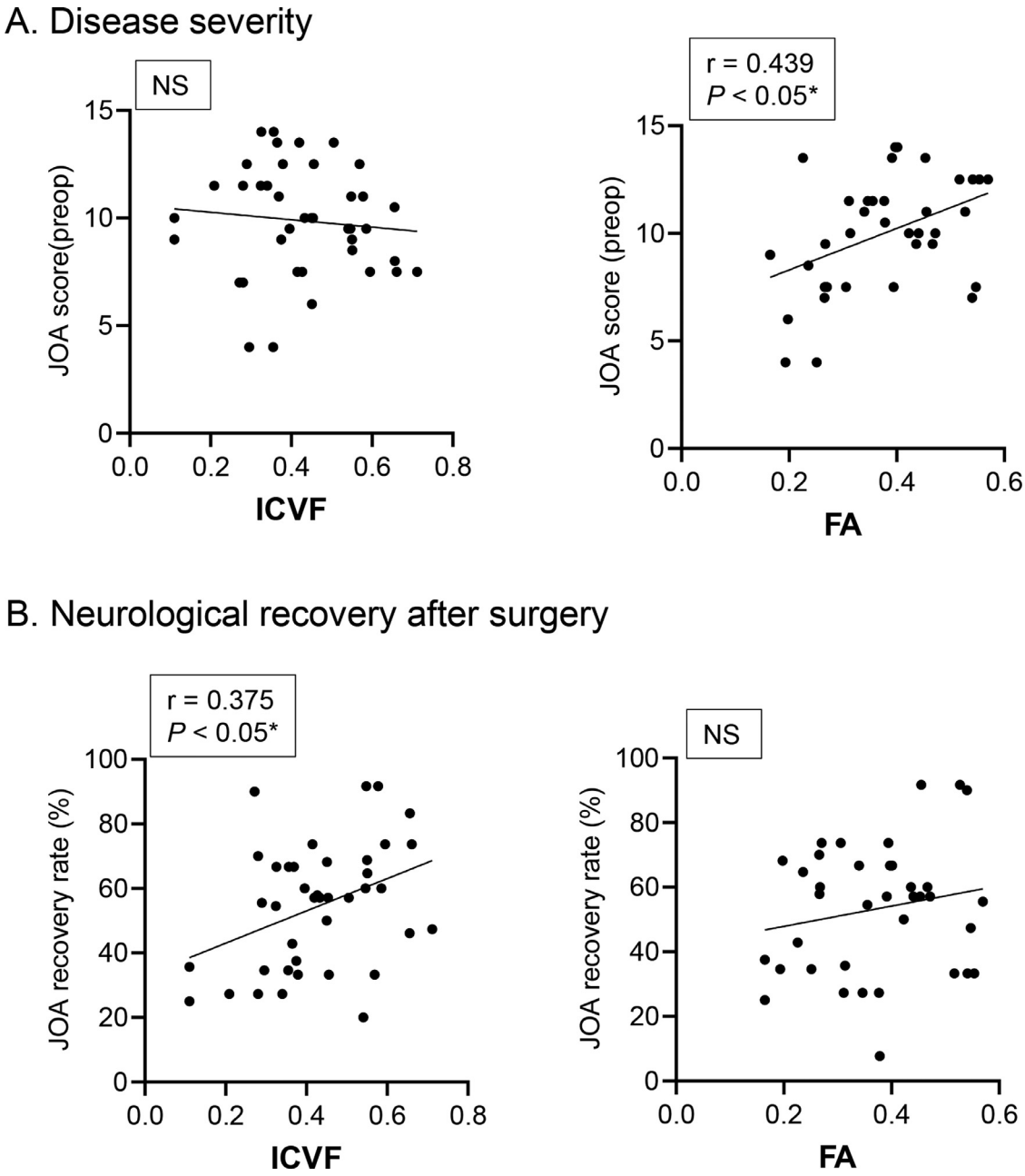

Fig. 4. (A) Correlation between preoperative ICVF at the most compressed level and preoperative C-JOA score. (B) Correlation between preoperative FA at the most compressed level and preoperative C-JOA score. (C) Correlation between preoperative ICVF at the most compressed level and JOA recovery rate (%) 2 years after surgery. (D) Correlation between preoperative FA at the most compressed level and JOA recovery rate (%) 2 years after surgery (*p<.05, NS=not significant).

NODDI indices as clinical biomarkers. To our knowledge, this is the first report (1) observing postoperative change in DTI and NODDI parameters over time; and (2) considering a detailed mechanism for why ICVF might be useful to predict postoperative neuronal recovery.

Conclusions

NODDI is a reproducible and reliable method for evaluation of CSM. ICVF improved after surgery and recovery of physical findings accompanied this change. Preoperative ICVF may be applied clinically to predict postoperative recovery.

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