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Diffusion tensor imaging and quantitative susceptibility mapping as diagnostic tools for motor neuron disorders[☆]

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ABSTRACT

Purpose: Diffusion tensor imaging (DTI) and quantitative susceptibility mapping (QSM) have been proposed as methods to aid in the diagnosis of amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS), both diseases affecting upper motor neurons. We test the performance of DTI and QSM alone and in combination to distinguish patients with diseases affecting upper motor neurons (ALS/PLS) from patients with other motor symptom-predominant neurologic disorders.
Methods: 3.0 Tesla MRI with DTI and QSM in patients referred to a subspecialty neurology clinic for evaluation of motor symptom-predominant neurologic disorders were retrospectively reviewed. Corticospinal tract fractional anisotropy and maximum motor cortex susceptibility were measured. Subjects were categorized by diagnosis and imaging metrics were compared between groups using Student's *t*-tests. Receiver operating characteristic curves were generated for imaging metrics alone and in combination.
Results: MRI scans for 43 patients with ALS or PLS and 15 patients with motor symptom predominant, non-upper motor neuron disease (mimics) were reviewed. Fractional anisotropy was lower (0.57 vs. 0.60, $p < 0.01$) and maximum motor cortex magnetic susceptibility higher (64.4 vs. 52.7, $p = 0.01$) in patients with ALS/PLS compared to mimics. There was no significant difference in area under the curve for these metrics alone (0.73, 0.63; $p > 0.05$) or in combination (0.75; $p > 0.05$).
Conclusion: We found significant differences in DTI and QSM metrics in patients with diseases affecting upper motor neurons (ALS/PLS) compared to mimics, but no significant difference in the performance of these metrics in diagnosing ALS/PLS compared to mimics.

1. Introduction

Amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS) are progressive neurodegenerative disorders affecting upper motor neurons. ALS is rapidly progressive and affects both upper and lower motor neurons, and PLS progresses more slowly and affects only upper motor neurons. The pathogenesis of these disorders is still under investigation, however autopsy studies have demonstrated corticospinal tract (CST) degeneration in both ALS and PLS [1,2]. The diagnosis of ALS and PLS is challenging: both diseases are currently diagnosed clinically on the basis of serial physical exam, electromyography, and exclusion of other neuropathology by imaging and laboratory tests [3,4]. No single test proves or excludes the diagnosis of ALS or PLS from other neurodegenerative disorders, resulting in delay and error in diagnosis, with false positive rate for diagnosis of ALS reported at 7–8%, and false negative rate reported at up to 27% [5–8]. The clinical differentiation of diseases affecting upper motor neurons (ALS and PLS) from other neurologic disorders is important for prognostication and treatment planning.

Diffusion tensor imaging (DTI) and quantitative susceptibility mapping (QSM) are promising tools to aid in diagnosing upper motor neuron (UMN) disease. Quantitative metrics of water diffusion

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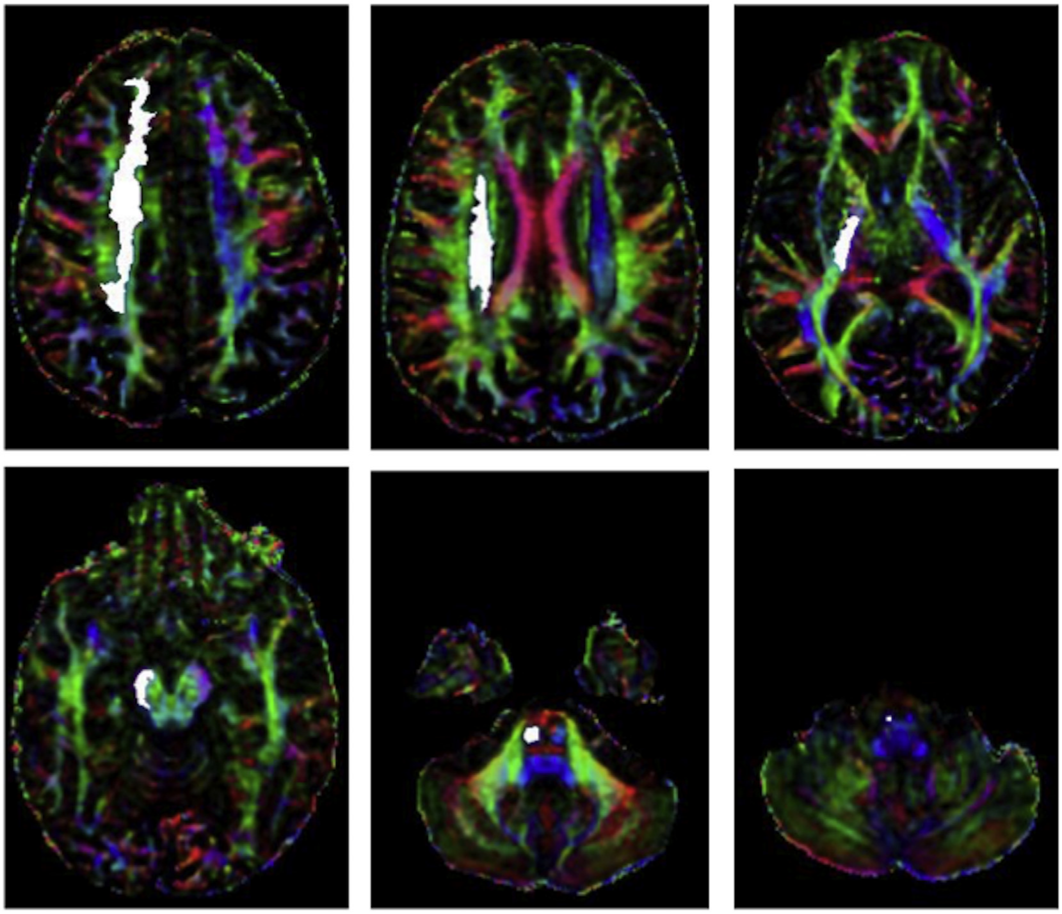

Fig. 1. ROI placement at 6 levels along the right CST. For each patient, ROIs were placed over the (top row, left to right) corona radiata, centrum semiovale, posterior limb of the internal capsule, (bottom row, left to right) cerebral peduncle, pons, and medullary pyramid.

calculated from DTI serve as estimations of white matter tract integrity. Fractional anisotropy (FA) is a measure of directionality of water molecule movement, and has been shown in numerous group-based analyses to be decreased in ALS patients at multiple levels of the CST [10–16]. QSM provides quantitative measurement of tissue magnetic susceptibility [17] and provides susceptibility values well correlated with iron concentration in gray matter [18–20]. Iron deposition in the motor cortex has been described in ALS and PLS patients on the QSM sequence [21,22], and a recent study found iron-related signal change in the motor cortex on 7 T MRI T2* sequences to correlate with disease severity measures and disease progression rate in patients with ALS [23].

While differences in DTI and QSM metrics have each been reported between patients with UMN disease (ALS and PLS) compared to healthy control subjects, no study has evaluated the combined use of DTI and QSM in diagnosing ALS and PLS. The combined use of these metrics would allow measurement of both white matter tract integrity (DTI) and motor cortex iron deposition (QSM), providing two distinct surrogate measures of neurologic degeneration. Additionally, differences in ALS and PLS imaging metrics have typically been reported in comparison with healthy control subjects. A recent report found differences in DTI measures between ALS patients and mimic syndromes [16], however differences in QSM metrics between these populations is not known. The purpose of our study is to test the performance of DTI and QSM alone and in combination in distinguishing ALS and PLS patients from patients with other motor symptom predominant neurologic disorders.

2. Methods

2.1. Data acquisition

An IRB-approved, retrospective study with waiver of informed consent was performed of consecutive patients seen at a subspecialty peripheral nerve and muscle disorders clinic and referred for MRI to exclude structural cause of symptoms between June 2012 and April 2015. ALS and/or PLS was a diagnostic consideration for all patients. Inclusion criteria included adult patients (18 years of age or older) with a final diagnosis of definite ALS determined by the El Escorial criteria, PLS, or non-UMN disease during our study follow-up period. Patients without a definite diagnosis, including patients with El Escorial possible or probable ALS or unknown diagnosis at the end of our study follow-up period, were excluded.

Chart review was performed to obtain demographic and clinical characteristics of the study population, including patient age, gender, date of symptom onset, and final clinical diagnosis. Patients were grouped by diagnosis into UMN (including definite ALS and PLS) or non-UMN groups. Clinical scores measured within two months of MRI, including ALS functional rating scale (ALS-FRS-R), percent-predicted forced vital capacity (FVC), and Medical Research Council (MRC) upper and lower extremity strength scores were collected, if available.

All patients underwent MRI on a 3-Tesla General Electric (Milwaukee, WI) Excite HD MRI system using an eight-channel head coil. MRI included 33-direction 2.5 mm DTI with b0 = 1000, 1 b = 0v volume, TR 10,000 ms, TE 96 ms, flip angle 90°, 60 2.5 mm interleaved axial slices with no skip, and NEX = 1. QSM sequences were obtained with TR 57 ms, TE 53 ms, flip angle 20°, thickness 3 mm/no gap, NEX

0.75, ETL 11. Images were acquired in oblique axial planes parallel to the anteroposterior commissure lines. Anatomic images including 3 mm axial T2, sagittal 3D T2 FLAIR, and sagittal 3D MPRAGE sequences were obtained and axial and coronal reformats were generated.

2.2. DTI post-processing

Eddy current correction and tensor fitting of DTI data were performed using FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) [24]. No co-registration of DTI and structural sequences was performed. Regions of interest (ROIs) were selected using Reproducible Objective Quantification Scheme (ROQS), a semi-automated technique operating in native space [25]. Six ROIs were selected along each corticospinal tract bilaterally at the level of the subcortical white matter, corona radiata, internal capsule, cerebral peduncle, pons, and medulla (Fig. 1) using a published white matter atlas for corticospinal tract location [26], for a total of 12 ROIs per patient. DTI metrics including FA, mean diffusivity (MD), and radial diffusivity (RD) were generated for each ROI. Mean corticospinal tract FA, MD, and RD values were calculated for each patient, generating one FA, MD, and RD value for each patient.

2.3. QSM post-processing

The central sulcus was identified on axial QSM images (Fig. 2) and the motor cortex of each subject was manually segmented in a standardized manner using OsiriX capturing ROIs of the hand, leg, and face motor cortex. A control ROI was placed in the ipsilateral centrum semiovale anterior to the CST and mean value for control ROI susceptibility was generated. The ipsilateral centrum semiovale anterior to the corticospinal tract was chosen as the control ROI for the following reasons: (i) the corticospinal tract is involved in the pathology of ALS, (ii) the subcortical white matter is susceptible to volume averaging with adjacent cortex, and (iii) the splenium of the corpus callosum is susceptible to artifacts related to proximity to the internal cerebral veins and vein of Galen [27]. Maximum motor cortex susceptibility (MMCS) was computed for each subject by subtracting mean control susceptibility from the maximum voxel value of motor cortex susceptibility in parts per billion (ppb).

2.4. Statistical analysis

Statistical analyses were performed by a biostatistician using Excel (Microsoft) and R Version 3.3.1 (R Core Team, Vienna, Austria). Demographic and clinical characteristics including age, ALSFRS-R and FVC were compared between UMN and non-UMN disease groups using two-tailed Student's *t*-tests, gender was compared using a Fisher's exact test, and median symptom duration was compared using a Mann-Whitney *U* test; $p < 0.05$ was considered statistically significant. Mean CST FA, MD, and RD of the CST were generated for each patient. A two-tailed Student t-test was used to compare mean CST FA, MD, and RD and MMCS between groups; $p < 0.05$ was considered statistically significant. Receiver operator characteristic (ROC) analysis was performed

Table 1
Clinical and demographic characteristics of study population.

	All patients (n = 58)	ALS or PLS (n = 43)	Not ALS/PLS (n = 15)	p
Age, years (mean, SD)	60.1 (13.5)	60.6 (14.9)	58.5 (8.4)	0.505
Median	61.0	62.2	58.8	
Range	19.9–91.4	19.9–91.4	44.0–73.4	
Male	58.6% (34/58)	58.1% (25/43)	60.0% (9/15)	0.999
Female	41.4% (24/58)	41.9% (18/43)	40.0% (6/15)	
Symptom duration (median)	18.3	15.9	41.9	0.019

	All patients (n = 39)	ALS or PLS (n = 26)	Not ALS/PLS (n = 13)	p
Sum MRC score	177.0 (20.0)	170.7 (20.2)	190.0 (12.9)	0.004
MRC UE score	88.6 ± 14.0	84.2 ± 15.2	97.0 ± 4.1	0.004
MRC LE score	88.4 ± 14.2	86.5 ± 15.8	92.0 ± 9.9	0.247

Symptom duration in months. Medical research council (MRC) score shown as mean ± SD.

Table 2
Quantitative DTI and QSM values.

	UMN	Non-UMN	p
DTI	(n = 42)	(n = 15)	
FA	0.57 ± 0.04	0.60 ± 0.04	0.006
MD (mm^2/s)	7.71×10^{-4} ± 6.48×10^{-5}	7.32×10^{-4} ± 5.28×10^{-5}	0.030
RD (mm^2/s)	4.96×10^{-4} ± 7.13×10^{-5}	4.48×10^{-4} ± 4.97×10^{-5}	0.008
QSM	(n = 43)	(n = 15)	
MMCS (ppb)	64.4 ± 24.51	52.7 ± 9.58	0.012

Data are shown as mean (standard deviation).

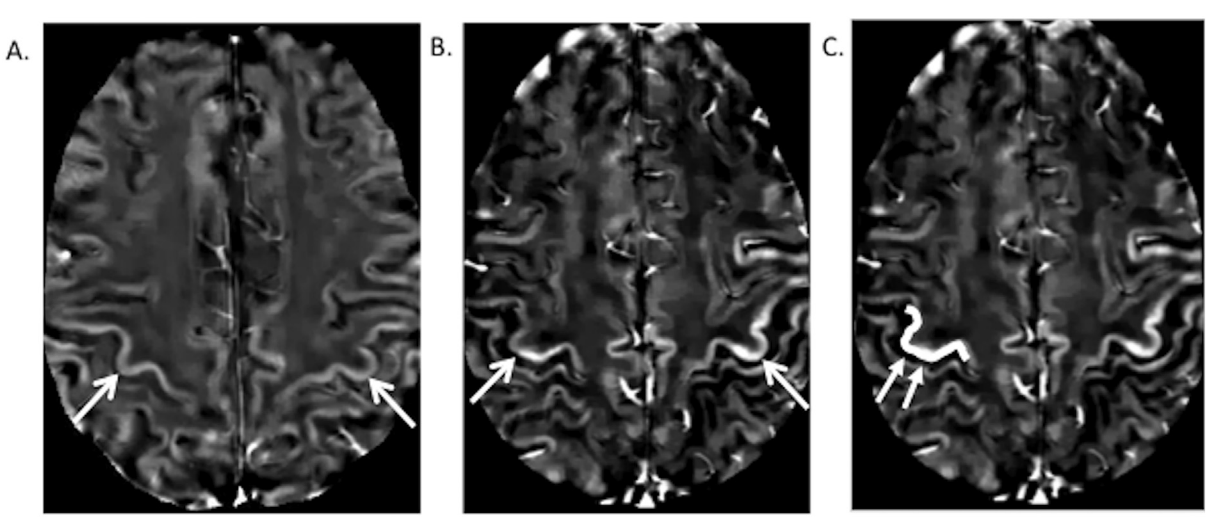

Fig. 2. Representative axial QSM image in a non-UMN patient (A) and an UMN patient (B), white arrows denote the motor cortex. (C) Axial QSM image in UMN patient with right motor cortex highlighted for segmentation, denoted by white arrows.

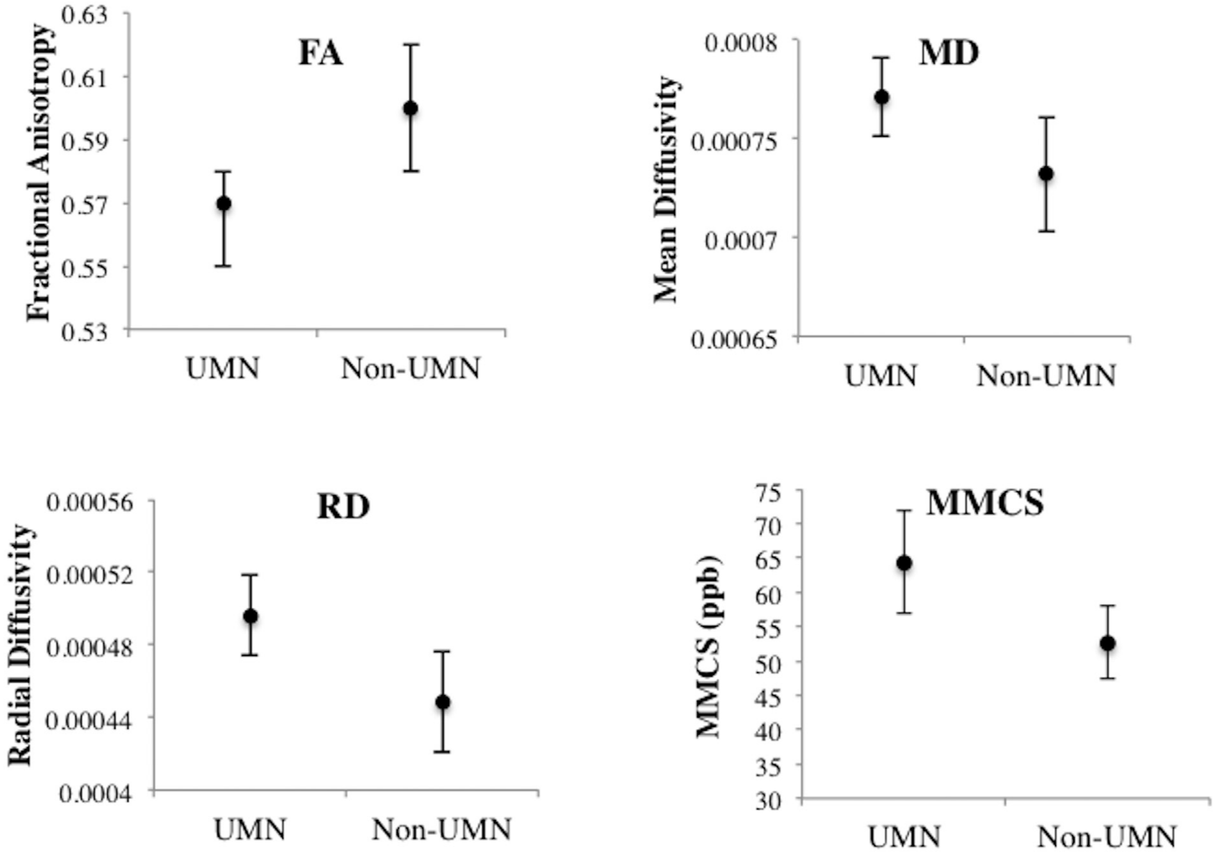

Fig. 3. Clockwise from top: DTI FA, DTI MD (mm^2/s), QSM MMCS, and DTI RD (mm^2/s). Mean value and 95% confidence interval for UMN and non-UMN patients.

for FA, MD, RD, and MMCS individually and FA and MMCS combined. The Delong test was used to compare AUCs. A Spearman's correlation was used to correlate DTI FA and QSM MMCS due to the right-skewed distribution of QSM. Youden's J statistic was calculated to identify optimal cut-off values for QSM MMCS and DTI FA in classifying UMN status. Confusion matrices were generated and sensitivity and specificity of optimal cut-off values were calculated.

3. Results

Seventy-six patients referred from a peripheral nerve and muscle disease clinic were screened for inclusion in this study. No patient had a structural cause of symptoms on MRI, and no patient was excluded based on MRI findings. Eighteen patients were excluded because definite diagnosis had not been established and the end of the study follow-up period. Thirty-eight patients with El Escorial definite ALS, 5 patients with definite PLS, and 15 patients with non-UMN disease (including multifocal motor neuropathy, Parkinson's disease, inclusion body myositis, stiff person syndrome, peripheral neuropathy, and chronic inflammatory demyelinating polyneuropathy) were included in this study as mimics. One patient's MRI included QSM but not a DTI sequence. Clinical and demographic characteristics of the study population are summarized in Table 1. ALSFRS-R was recorded for 36 patients in the UMN group (mean 36.1 ± 7.6), and for 2 patients in the non-UMN group (mean 46.0 ± 1.4). Percent predicted FVC was recorded for 33 patients in the UMN group (mean 29.2 ± 26.6) and 4 patients in the non-UMN group (mean 96.2 ± 27.6).

Comparing DTI metrics between UMN and non-UMN patients, CST FA value was significantly lower in UMN patients (Table 2). Mean CST MD and RD were significantly higher in the UMN group compared to the non-UMN group. Comparing QSM metrics between UMN and non-UMN groups, MMCS was significantly higher in the UMN group (Table 2). 95% confidence intervals around the mean are shown in Fig. 3.

Comparing the performance of QSM and DTI in distinguishing UMN from non-UMN patients, ROC analysis of QSM MMCS yielded an area under the curve (AUC) of 0.632 (Fig. 4) for distinguishing UMN from non-UMN patients. Evaluating DTI data, the AUC for mean CST FA was 0.733. QSM MMCS and DTI FA in combination yielded an AUC of 0.748 for distinguishing UMN from non-UMN patients. Comparing AUCs, there was no statistically significant difference between DTI FA vs. QSM MMCS, DTI FA vs. combined DTI FA and QSM MMCS, or QSM MMCS alone vs. combined DTI FA and QSM MMCS (p = 0.353, 0.198, 0.654, respectively). There was a weak, negative correlation (rho = −0.25, p = 0.059) between DTI FA and QSM MMCS.

A value of 65.6 on QSM MMCS was identified as the optimal cut-off (maximizing both sensitivity and specificity) using Youden's J statistic, yielding a sensitivity of 30% and a specificity of 100% (Table 3). A cut-off of value of 0.57 on DTI FA was identified, yielding a sensitivity of 62% and a specificity of 80% (Table 3).

4. Discussion

Despite recent advances in the understanding of genetic and pathogenic factors contributing to upper motor neuron diseases (ALS and PLS), the diagnosis of these diseases remains challenging. The lack of a quantitative test to confirm or exclude these diseases leads to delay and error in diagnosis. There is a 14 month median time from symptom onset to diagnosis of ALS and 3–4 year symptom duration required for the diagnosis of PLS [1,5]. Many patients undergo invasive diagnostic procedures to exclude these disorders, and studies have reported that 13% of patients ultimately diagnosed with ALS undergo unnecessary surgery as a result of delayed diagnosis [28]. Delayed diagnosis also results in delay in initiating treatment and supportive measures, which

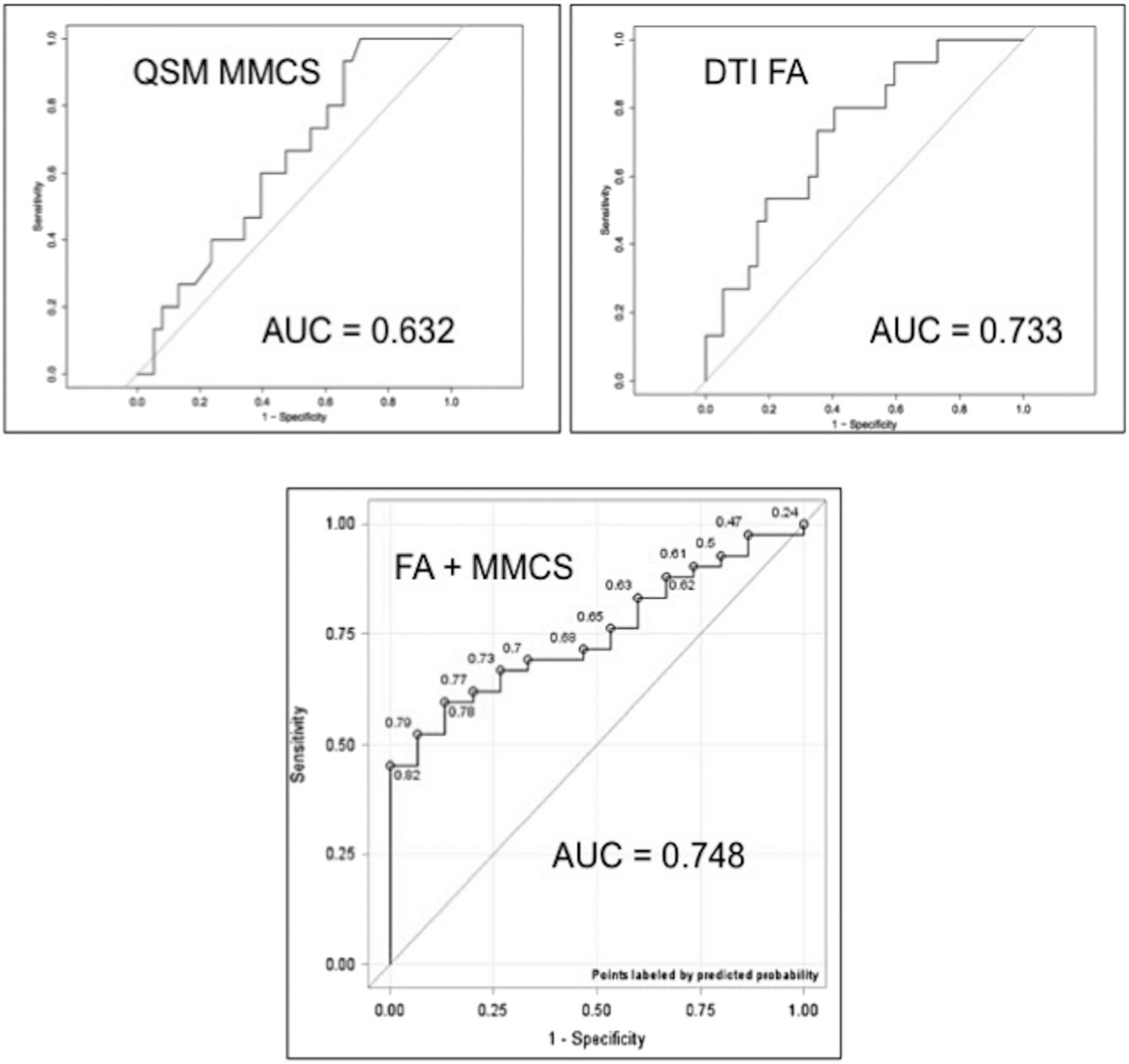

Fig. 4. ROC curves for QSM MMCS, DTI FA, and combined FA + MMCS in classifying ALS/PLS status.

Table 3
Confusion matrix for DTI, QSM, and combined DTI + QSM.

		Actual		SE	SP	PPV	NPV
		ALS	No ALS				
DTI	DTI+	TP = 26	FP = 3	61.9%	80.0%	89.7%	42.9%
	DTI−	FN = 16	TN = 12				
QSM	QSM+	TP = 13	FP = 0	30.2%	100.0%	100.0%	33.3%
	QSM−	FN = 30	TN = 15				
QSM & DTI	QSM & DTI+	TP = 25	FP = 2	59.2%	86.7%	92.6%	25.5%
	QSM & DTI−	FN = 17	TN = 13				

Confusion matrices for DTI FA and QSM MMCS alone and in combination. DTI FA threshold = 0.57; QSM MMCS threshold = 65.6 true positive (TP), true negative (TN), false positive (FP), and false negative (FN) are reported. Sensitivity (SE), sensitivity (SP), positive predictive value (PPV), negative predictive values (NPV). DTI $n = 57$. QSM $n = 58$.

may prove increasingly important with the development of combination therapies that may slow disease progression [29]. Also, an objective and quantifiable imaging biomarker for tracking disease progression and therapeutic effect is currently lacking for use in current and future clinical trials.

Applications of MRI including DTI and QSM have been proposed as non-invasive tools to aid in diagnosis and monitoring of ALS and PLS. Ample studies have compared DTI findings in patients with UMN disease compared to healthy control subjects. Decreased FA has been reported at varying levels along the CST [11,13,14,30–33] and averaged over sampled regions of the CST [10,12]. Increased MD [10,12,32] and increased RD [30] have been reported in some of these patients. Increased relative motor cortex susceptibility on QSM has been reported in patients with ALS and PLS compared with healthy controls [22,27]. Signal intensity changes on SWI have been reported in the motor cortex of patients with ALS compared to controls [34,35], and one recent study found a marginal increase in AUC when adding DTI to filtered SWI metrics for distinguishing ALS patients from healthy subjects [34].

In our study, we evaluated QSM, a validated marker for brain iron deposition [18–20], alone and in combination with DTI to evaluate for ALS and PLS in a cohort of patients with suspected UMN disease. Since FA is the most frequently reported abnormal DTI metric in the literature in patients with ALS, it was chosen for combination and correlation with QSM MMCS. In our study, FA had a slightly higher AUC compared to MMCS in distinguishing UMN from non-UMN patients, however this did not reach statistical significance. Likewise, combined FA + MMCS had a higher AUC compared to either FA or MMCS alone, but this difference did not reach statistical significance. It is possible that these differences may have reached statistical significance with a larger study population, or with comparison to a normative population. However, the pathogenesis of UMN disease remains under investigation and the role of iron deposition in UMN disease is not well understood. It is possible that QSM changes and white matter tract changes measured on DTI are equally effective as surrogate measures of UMN disease.

A non-statistically significant weak negative correlation was found between DTI FA and QSM MMCS. A negative relationship between these measures is expected as lower CST FA (indicating alterations in white matter tract integrity) and higher MMCS (indicating elevated iron deposition) were found in ALS patients versus mimics. However, given the negligible relationship between MMCS and FA at a single time point in our study, it is not clear that alterations in CST integrity and motor cortex iron deposition reflect synchronous sequelae of a single pathophysiologic process. Larger studies including longitudinal analysis of DTI and QSM metrics in UMN patients and including of healthy control subjects may be of benefit for further investigation into the relationship between white matter tract integrity and cortical iron deposition, and may provide further insight into the pathophysiology of UMN disease and of brain iron deposition.

Prior studies of QSM metrics in UMN patients have compared patients with ALS and/or PLS to healthy control subjects. In the clinical setting, this comparison may be less relevant, as clinicians are rarely tasked with differentiating patients with ALS from healthy patients. Rather, it is clinically pertinent to be able to discriminate patients with ALS or PLS from patients with other neurologic disorders with similar presenting symptoms, noted in a recent call for research comparing imaging patients with ALS and PLS from mimic syndromes [36]. One recent study reported lower mean CST FA in upper motor symptom predominant ALS patients compared to patients with disease mimics [16]. Similarly, we have found differences in FA, MD, and RD measurements between our study groups.

Our findings should be interpreted in light of several limitations. First, our sample size was limited with 42 patients in the UMN and 15 patients in the non-UMN group. With this limited sample size, we were able to demonstrate statistically significant differences in DTI and QSM between UMN and non-UMN patients. It is possible that differences might have been greater with a larger study group. Our study compared patients with a final diagnosis of either ALS or PLS to mimic syndromes, but our sample size did not allow comparison of ALS and PLS patients to each other. Both ALS and PLS affect upper motor neurons, however the disease course is highly variable between the two diagnoses and future studies evaluating differences in DTI and QSM metrics between ALS and PLS patients are warranted. Next, our study design was retrospective, limiting our ability to correlate imaging metrics with clinical scores of symptom severity/functional impairment, as these were not obtained for all patients at prescribed intervals. Finally, quantification of absolute iron deposition using QSM is not possible with current technology. There is no current standardized method of normalizing QSM values; the mean value of the ipsilateral centrum semiovale was chosen for normalization in our study for reasons detailed in our Methods section, however this might limit comparison with other studies utilizing different normalization techniques

In conclusion, we have demonstrated significant differences in DTI and QSM metrics in patients with ALS or PLS compared to other motor-predominant neurologic disorders, which may be of clinical utility in differentiating these diagnoses. We found no significant difference in the performance of DTI FA and QSM MMCS alone and in combination for distinguishing ALS and PLS from other motor symptom-predominant neurologic disorders.

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