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Noninvasive Assessment Follow-Up of Progress in MS Patients

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ABSTRACT

Introduction: Multiple sclerosis (MS) is the leading cause of disability in young adults. We aimed to monitor disease progression characteristics using cognitive and physical parameters with optical coherence tomography (OCT) and Magnetic Resonance Spectroscopy (MRS).

Methods: Fifteen relapsing remitting (RRMS), thirteen secondary progressive (SPMS) and twelve primary progressive (PPMS) patients were included. The Expanded Disability Status Scale (EDSS), Nine-Hole Peg Test (9 HPT), Timed 25-Foot Walk Test (T25FWT), Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Montreal Cognitive Assessment (MoCA), MRS and OCT examinations were performed at baseline and follow-up.

Results: EDSS, Beck Depression Scale scores, 9-HPT and T25FWT duration scores were higher in the PPMS group compared to the other groups, whereas MoCA, SDMT, CVLT2, and BVMT-R scores were the lowest in this group. Retinal nerve fiber layer (RNFL) measurements in the right (p=0.023) and left (p=0.028) nasal quadrants were found to be higher in the RRMS group compared to the progressive groups. Baseline MRS showed a lower Thalamus myoinositol/creatinine (mI/Cr) ratio in progressed patients compared to stable patients (p=0.003). A cut-off value of baseline Thalamus mI/Cr ratio <0.066 for predicting disease progression based on baseline Thalamus mI/Cr was determined to be <0.066, with an 81.82% sensitivity, and 79.17% specificity, 64.29% positive predictive value (PPV), and 90.48% negative predictive value (NPV) (p=0.003).

Conclusion: Early detection of disease progression has critical importance for MS. Besides prognostic serum or cerebrospinal fluid biomarker tests, noninvasive methods such as disability scales and/or imaging techniques may have a significant impact and are easily replicable. As an advanced imaging technique, MRS has the potential for ongoing tissue inflammation. In parallel with that, we have obtained a cut-off thalamic mI/Cr ratio value as a significant predictor of disease progression in MS patients.

Keywords: Cognitive impairment, MR spectroscopy, multiple sclerosis, ocrelizumab, optical coherence tomography (OCT), progression

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INTRODUCTION

Multiple sclerosis is a chronic inflammatory disease of the central nervous system (CNS), characterized by focal demyelinating plaque lesions that predominantly affect white matter, deep gray matter and cortex (1). Multiple sclerosis has become one of the leading causes of disability in young adults due to rising diagnosis rates (2).

Magnetic resonance imaging (MRI) is the most preferred imaging method for diagnosing MS and monitoring patients. Abnormalities in the T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) sequences were observed in 95% of patients (3). While conventional MRI measurements are strongly associated with focal MS pathology and are sufficient to evaluate macroscopic changes, they fail to detect microstructural alterations in the tissue surrounding plaques. Further imaging methods such as MRS are not routinely used for radiological follow up but they can provide a significant advantage in disclosing microstructural tissue alterations.

Magnetic resonance spectroscopy (MRS) is a water-suppressed technique that detects metabolite changes in MS plaques and normal brain tissue by recording frequencies from metabolites within the tissue. In long TE scans, four major metabolites were observed in the brain: choline (Cho) from the tetraamine family at 3.2 ppm, creatinine at 3.0 ppm, N-Acetyl-Aspartate (NAA) from the N-Acetyl group at 2.0 ppm, and lactate (Lac) at 1.3 ppm (4). Magnetic resonance spectroscopy findings in inflammatory demyelination diseases can be summarized as: Inflammation is indicated by choline increase, recent demyelination

Highlights

- **This study shows predicting prognosis by monitoring MRS metabolite changes.**
- **For the first time, cut-off value was used to determine prognosis.**
- **The Thalamus mI/Cr value was found to be a predictive marker.**

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is correlated with elevated lipids and choline, axonal dysfunction is characterized by a decrease in NAA, and gliosis is marked by an increase in myoinositol (5).

Optical coherence tomography (OCT) is a useful technique that can help to analyze neurodegeneration in MS by detecting thinning of the retinal nerve fiber layer (RNFL)(6).

In our study we aimed to show progression dynamics in multiple sclerosis patients by repeated OCTs and MRSs alongside clinical scales to obtain possible predictive and/or monitoring characteristics/data evaluating at baseline and follow up. In our study, we aimed to monitor both progressive and relapsing MS patients to predict and evaluate disease progression characteristics.

METHODS

Patients diagnosed according to the 2017 McDonald's criteria and treated at the Multiple Sclerosis Outpatient Clinic between June 2020 and June 2021 were included in the study.

Study Inclusion Criteria:

- Patients aged between 18 and 65 years.
- Not having taken steroids in the last three months of evaluation.
- Patients without advanced cognitive impairment or physical disability preventing daily activities.

Study Exclusion Criteria:

- Patients with a history of any neurological disorder other than MS (e.g., brain tumors, epilepsy, Parkinson's disease)
- Patients with any ocular disease (e.g., glaucoma, cataracts, retinopathy)
- Patients with severe psychiatric disorders (e.g., schizophrenia, bipolar disorder)
- Individuals who are pregnant or breastfeeding
- Patients with a high Expanded Disability Status Scale (EDSS) score (e.g., 7 or higher)
- Patients who smoke or engage in excessive alcohol consumption

Written consent was obtained from all patients included in the study. The study protocol was approved by the local ethics committee (2020.514.1171.3). Each patient's medical history was obtained, and neurological examinations were carried out at 6-month intervals.

Expanded Disability Status Scale (EDSS) is one of the most widely used tools for evaluating the severity and progression of MS EDSS score was calculated for all patients. 9-HPT is a standardized test which is commonly used in clinical settings to evaluate the upper limb function in individuals with neurological conditions (7).

25-TFWT is a commonly used clinical assessment tool designed to evaluate gait speed and mobility in patients. The primary purpose of the 25FWT is to measure a patient's walking speed over a short distance, which can provide insight into functional mobility, balance, and lower extremity function (8).

Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is a set of neuropsychological tests designed specifically to assess cognitive function. It is a short and standardized battery of tests that helps clinicians evaluate various cognitive domains commonly affected by MS, such as memory, attention, processing speed, and executive function (9).

The MRI scans were conducted at the Radiology Clinic using a 1.5 Tesla MRI machine. Axial, sagittal, and coronal T1-weighted (T1W) and T2-weighted (T2W) images were acquired. Additionally, 3D FLAIR and 3D T1A sequence imaging was performed. Lesions in the periventricular, cortical, juxtacortical, supratentorial white matter, infratentorial regions, black hole appearance, and cranial atrophy were assessed.

In MR Spectroscopy, metabolite analyses were performed in the NACM, thalamus, NAWM, and corpus callosum. Ratios of Choline/Creatinine, NAA/Creatinine, Myoinositol/Creatinine, and Choline/NAA were calculated.

Choline/Creatinine ratio provides information about cell membrane integrity and cellular turnover. The NAA/Creatinine ratio is used to evaluate neuronal damage or degeneration and is particularly useful for monitoring diseases that affect neuronal function. The mI/Cr ratio is used to assess neuroinflammation and glial cell activity. The Choline/NAA ratio is useful for assessing the balance between cellular turnover and neuronal integrity. All images were stored for further analysis. For radiological follow-up, MRS Multivoxel scans were conducted every 6 months on average (10).

Retinal nerve fiber layer and macular thickness measurements were applied in the superior, inferior, nasal, and temporal quadrants of both eyes by OCT. Scans were performed twice, with an average interval of 4.5 months.

Progression was considered in patients with a 1-point increase in EDSS ≤5.5 or a 0.5-point increase in EDSS ≥5.5.

Statistical analysis:

Statistical analyses were conducted using IBM Statistical Package for Social Sciences (SPSS) program version 17.0. The normality of the distribution of variables was assessed using histogram plots and the Kolmogorov-Smirnov test. Descriptive analyses were presented using mean, standard deviation, and median values. The relationship between categorical variables was examined using the Chi-Square Test. For non-normally distributed (nonparametric) variables, comparisons between groups were performed using the Kruskal-Wallis Test. Changes in measured values were analyzed using Repeated Measures Analysis for comparisons between groups and the Wilcoxon Test for within-group comparisons. The relationship between quantitative variables was assessed using the Spearman Correlation Test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Forty MS patients were included in the study. Eighteen male and twenty-two female patients participated. Fifteen were in the RRMS group, thirteen in the SPMS group, and twelve in the PPMS group. Patients' demographic data are listed in Table 1. Three patients from the RRMS group and 1 patient from the PPMS group dropped out of follow-up due to relocation.

The mean age of the patients was 30 years in the RRMS group; 39.67 years in the SPMS group and 43.77 years in the PPMS group. The mean age of the PPMS group was significantly higher than the RRMS group (p=0.004). The mean disease duration was 4.8 years in the RRMS group, 12.2 years in the SPMS group, and 10.5 years in the PPMS group.

Mean EDSS scores at baseline, 6 months and 1 year were 1.27, 1.33, and 1.41 in the RRMS group respectively; 3.0, 3.6, and 3.54 in the SPMS group; 4.8; 5.0, and 4.5 in the PPMS group. The RRMS group had significantly lower baseline, 6-month, and 12-month values compared to the SPMS and PPMS groups (p <0.001). In addition, a baseline-1-year change in EDSS score was found to be significant in the SPMS (Table 2).

Clinical and cognitive test results at baseline, 6 months and 1 year were compared both between and within the groups. Montreal Cognitive Assessment scores in the 6th month and 1st year were lower in the PPMS group compared to the RRMS group. Symbol Digit Modalities Test baseline, 6th-month, and 1st-year scores were lower in the PPMS group compared to the other two groups. CVLT-2 and BWMTR baseline, 6th-month, and 1st-year scores were higher in the RRMS group compared to the other two groups. T25WT baseline, 6th-month, and 1st-year scores

Table 1. Demographic data and lesion load using conventional MRI of patients according to disease phenotype

	RRMS	SPMS	PPMS	p[1]
Periventricular****	4.13 (±3.91) 3.00	8.00 (±4.02) 7.00	5.62 (±2.29) 6.00	**0.021****
Cortical****	1.33 (±1.84) 1.00	3.00 (±1.71) 3.00	1.31 (±1.49) 1.00	**0.015****
Juxtacortical****	2.93 (±2.15) 3.00	3.00 (±1.65) 3.00	3.15 (±2.08) 2.00	0.955
Supratent. white matter. ****	2.20 (±1.86) 1.00	2.25 (±0.87) 2.00	2.77 (±1.54) 3.00	0.435
Infratentorial****	0.27 (±0.46) 0.00	1.08 (±1.08) 1.00	0.92 (±1.04) 1.00	0.057
T1 hypointensity****	3.53 (±4.19) 2.00	11.67 (±8.84) 8.50	7.62 (±4.48) 8.00	**0.003*****

Kruskal-Wallis test was used for analysis; p[1]: $p<0.05$ was accepted for statistical significance; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; EDSS: the expanded disability status scale; * there is a statistically significant difference between the PPMS and RRMS groups. ** There is a statistically significant difference between the SPMS group and the other two groups. *** There is a statistically significant difference between the SPMS and RRMS groups. **** Mean, standard deviation and median values were calculated.

Table 2. Comparison of clinical and cognitive tests of patients according to disease phenotype

		RRMS			SPMS			PPMS				
		mean	s. d	Median	mean	s. d	Median	mean	s. d	Median	p[1]	p[2]
EDSS	0th	1.27	±0.65	1.00	3.04	±1.21	3.50	4.81	±1.48	4.50	**<0.001***	0.145
	6th	1.33	±0.83	1.50	3.60	±1.31	3.75	5.00	±1.48	4.50	**<0.001***	
	12th	1.41	±1.00	1.00	3.54	±1.48	4.00	4.50	±1.22	4.50	**<0.001***	
p[3]		0.564	0.564	1.000	0.109	**0.026****	0.180	0.785	0.671	0.336		
MOCA	0th	27.60	±2.72	28.00	26.08	±2.97	27.00	24.69	±5.76	27.00	0.178	0.353
	6th	28.25	±2.77	29.00	25.90	±3.51	27.00	24.00	±6.40	27.00	**0.007**	
	12th	28.55	±2.16	29.00	26.67	±2.99	27.50	25.33	±4.92	27.00	**0.028**	
p[3]		0.080	**0.017**	0.102	0.675	0.319	0.257	0.811	0.523	0.020		
SDMT	0th	61.87	±22.51	59.00	46.08	±18.40	48.00	30.38	±11.99	30.00	**<0.001**	0.205
	6th	59.08	±24.32	53.50	44.00	±14.09	47.00	30.73	±13.86	30.00	**0.009**	
	12th	63.73	±22.61	63.00	49.17	±16.03	47.50	32.42	±15.00	33.00	**0.003**	
p[3]		0.476	0.138	**0.021**	0.213	0.332	0.406	0.359	0.688	0.671		
CVLT2	0th	49.73	±12.62	49.00	39.75	±12.48	35.00	33.31	±16.22	33.00	**0.030**	0.078
	6th	58.42	±12.96	62.50	38.00	±12.97	32.00	30.82	±13.84	33.00	**0.001**	
	12th	57.18	±12.75	55.00	40.67	±12.69	38.50	31.83	±13.35	29.00	**0.001**	
p[3]		**0.015**	**0.021**	0.688	0.442	0.666	0.540	0.878	0.387	0.594		
BVMT-R	0th	9.60	±2.92	11.00	7.08	±3.12	7.00	7.00	±3.74	7.00	**0.049**	0.268
	6th	9.83	±3.24	11.50	7.50	±2.59	7.50	7.09	±3.39	8.00	**0.033**	
	12th	10.68	±2.61	12.00	8.17	±2.82	7.50	6.83	±3.10	7.00	**0.007**	
p[3]		0.572	**0.046**	0.114	0.324	0.235	0.296	0.372	0.671	**0.046**		
T25WT	0th	12.99	±3.91	12.11	17.73	±5.25	16.49	19.66	±7.18	16.22	**0.004**	0.803
	6th	11.55	±1.50	11.42	15.68	±4.92	15.00	19.04	±5.59	16.78	**0.002**	
	12th	11.92	±2.71	11.20	17.59	±5.73	16.48	21.43	±7.76	19.11	**0.001**	
p[3]		0.875	0.594	0.505	0.285	0.790	0.093	1.000	0.953	0.398		
9-HPT R	0th	22.57	±4.32	22.95	24.42	±7.16	21.42	34.47	±25.78	26.53	0.228	0.442
	6th	20.51	±4.50	20.27	24.71	±5.39	24.62	61.29	±109.52	24.16	0.160	
	12th	19.82	±4.32	19.02	26.39	±6.50	24.14	26.96	±14.80	25.37	**0.039**	
p[3]		0.209	**0.021**	0.091	0.241	0.859	0.575	0.799	0.424	0.401		
9-HPT L	0th	24.58	±8.23	23.97	25.60	±21.31	20.72	39.61	±23.87	33.01	**0.005**	0.438
	6th	22.37	±5.14	22.04	29.91	±15.17	25.90	52.95	±62.44	28.99	**0.024**	
	12th	24.11	±8.66	22.90	29.06	±13.45	25.27	33.41	±14.56	28.78	**0.030**	
p[3]		0.158	0.374	0.424	0.241	0.424	0.333	0.424	0.695	0.678		

[1]Kruskal-Wallis test; [2]repetitive measurements analysis; [3]Wilcoxon test (0th-6th month/0th-12th month/6th-12th month); EDSS: the expanded disability status scale; MoCA: Montreal cognitive assessment test; CVLT2: California verbal learning test; BVMT-R: short visual-spatial memory test; SDMT: symbol digit modalities test; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; T25FWT: 25-foot walk test; 9-HPT: nine-hole peg test; *a statistically significant difference was observed in the RRMS group compared to the other two groups; ** there is a statistically significant difference between the baseline values and the 12 th-month values.

Table 3. MRS measurement changes of patients (0–12 months)

		Progression (baseline – 1. year)						
		Yes			No			
		Mean	s. d.	Median	Mean	s. d.	Median	p
Thalamus mI/Cr	0th	0.33	±0.39	0.22	0.07	±0.09	0.04	**0.003***
	6th	0.24	±0.25	0.12	0.18	±0.39	0.04	0.129
	12th	0.17	±0.15	0.16	0.24	±0.38	0.08	0.528
Corpus Callosum Cho/Cr	0th	1.63	±1.31	1.15	1.15	±0.95	1.06	0.303
	6th	1.54	±0.86	1.22	1.08	±0.77	0.80	0.083
	12th	1.92	±0.82	2.15	1.30	±1.07	0.84	**0.034****

Cho/Cre: choline/creatinine; mI/Cr: myoinositol/creatinine; Mann-Whitney U test was used; * the baseline values of patients exhibiting progression are statistically significantly lower compared to the other group; ** the 12 th-month values of patients exhibiting progression are statistically significantly lower compared to the other group.

were lower in the RRMS group compared to the other two groups. 9 HPT-L baseline, 6th-month, and 1st-year scores were higher in the PPMS group compared to the other two groups. Detailed data are given in Table 2.

Magnetic resonance imaging T1W/T2W lesion loads were analyzed in all patients. The number of periventricular lesions in the SPMS group was higher than in the RRMS group (p=0.021). Cortical lesions in the SPMS group were higher than in the other two groups (p=0.015). The T1W (black hole) lesion count of the SPMS group was higher than in the RRMS group (p=0.003). There was no statistically significant difference in the number of juxtacortical lesions, supratentorial deep white matter lesions, and infratentorial lesions between the groups (Table 1).

Magnetic resonance spectroscopic evaluations revealed that patients with increased EDSS scores were classified as having disability progression. Two patients from the RRMS group, six from the SPMS group, and two from the PPMS group were considered to have progression due to increased EDSS scores. In patients with disease progression, NACM Cho/Cr, NAA/Cr, mI/Cr, and Thalamus Cho/Cr, Cho/NAA, NAA/Cr values, as well as the NAWM and Corpus Callosum Cho/Cr, Cho/NAA, NAA/Cr, and mI/Cr values, were within normal ranges; however, patients with progression had a lower thalamus mI/Cr ratios than in the stable group at baseline spectroscopy (p=0.003). Also in the same group, corpus callosum Cho/Cr ratios were significantly lower in the first-year analyses (p: 0.034) (Table 3).

For thalamus mI/Cr, a significant cut-off value that could predict no change/stability in EDSS values was examined and a value of <0.40 was found with 72.73% Sensitivity, 0% Specificity, 64% PPD, and 0% NPD.

A cut-off value of <0.066 of thalamus mI/Cr ratio at baseline analyses could predict progression with 81.82% sensitivity, 79.17% specificity, 64.29% PPD and 90.48% NPV (p=0.003) (Table 4) (Figure 1).

Follow-up MRS measurements in the normally appearing NACM, thalamus, NAWM and corpus callosum were compared in patients with worsening EDSS, and stable thalamus mI/Cr values at 6 months were significantly higher in those patients with stable EDSS values (p=0.039).

Optical Coherence Tomography Findings

Baseline and follow up OCT-RNFL values were compared between the groups. Detailed data are given in Table 5. While left nasal and temporal quadrant RNFL in the follow-up evaluation of the RRMS group were significantly higher than the PPMS group (p=0.028) (p=0.022), there was no significant difference between the SPMS group and the other two groups.

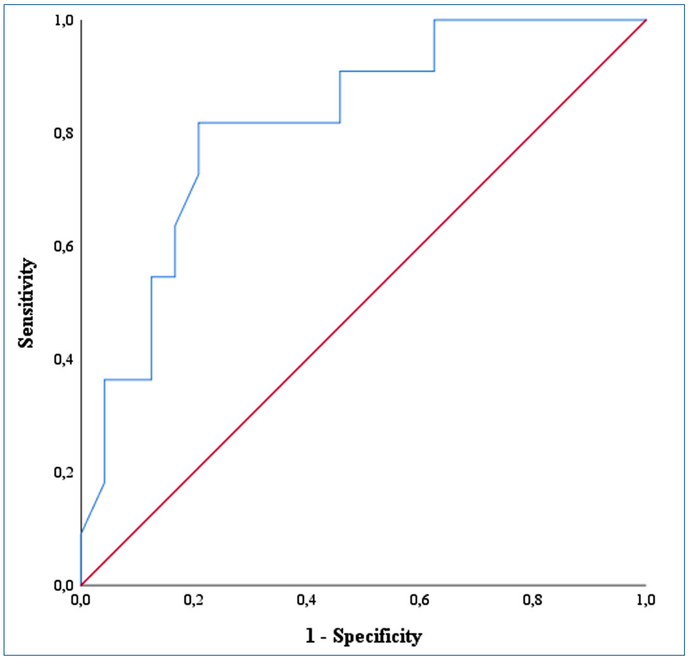

Figure 1. The specificity-sensitivity plot of the thalamus mI/Cr value (mI/Cr: myoinositol/creatinine).

Table 4. Cut-off evaluation of patients with progression and stability (0–12 months)

	Domain	s. d.	p	95% Confidence range		Cut-off	Sensitivity	Specificity	PPD	NPD
				Lower limit	Upper limit					
Thalamus mI/Cr (baseline)	0.818	±0.075	**0.003**	0.671	0.965	<0.066	%81.82	%79.17	%64.29	%90.48
Thalamus mI/Cr (<0.40)	0.740	±0.098	**0.039**	0.548	0.931	<0.4	%72.73	%0	%64	%0

mI/Cr: myoinositol/creatinine; ROC: receiver operating characteristic analyses.

Table 5. RNFL measurements by MS subgroups

		RRMS			SPMS			PPMS				
		Mean	**s. d.**	**Median**	**Mean**	**s. d.**	**Median**	**Mean**	**s. d.**	**Median**	**p^1**	**p^2**
R. Nasal	0th	77.80	±20.03	78.00	48.00	±22.69	50.00	64.15	±29.92	60.00	**0.023***	0.581
	4th	74.45	±15.46	72.00	59.55	±10.64	58.00	67.00	±22.24	61.00	0.099	
p^3			0.778			0.160			0.293			
R. Temporal	0th	66.70	±13.27	68.50	64.44	±22.89	55.00	61.69	±18.64	63.00	0.728	0.381
	4th	62.64	±11.62	62.00	57.73	±19.86	50.00	67.00	±28.86	61.00	0.482	
p^3			0.324			**0.012*****			0.813			
L. Nasal	0th	71.50	±28.41	65.50	64.22	±13.35	57.00	69.62	±36.87	62.00	0.697	0.653
	4th	71.91	±29.86	74.00	51.00	±21.94	56.00	48.50	±15.94	52.50	**0.028****	
p^3			0.123			0.160			0.123			
L. Temporal	0th	60.40	±14.55	59.00	79.22	±69.07	49.00	50.46	±13.34	49.00	0.313	0.267
	4th	69.00	±26.21	64.00	56.18	±14.91	53.00	46.60	±10.28	45.50	**0.022****	
p^3			0.944			0.735			0.084			

p^1: Kruskal-Wallis test; p^2: repetitive measurements analysis; p^3: Wilcoxon test; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; * There is a statistically significant difference in baseline evaluation between the RRMS group and the SPMS group; ** there is a statistically significant difference between the RRMS group and the PPMS group at 4 months; *** there is a statistically significant difference in the change over time in the SPMS group.

Retinal nerve fiber layer changes were examined between and within the groups. In the baseline and follow-up evaluations, there were no alterations in the RRMS group in the left eye nasal and temporal quadrant, while a statistically insignificant but decreased trend in mean values was observed in the PPMS patients. There was a significant decrease in RNFL right temporal quadrant value only in the SPMS group (p=0.012).

An inverse correlation was observed between the macular OCT right eye at baseline and the basal values of NACM Cho/Cr, NAWM mI/Cr, and corpus callosum NAA/Cr. An inverse correlation was also observed between the baseline left eye macular OCT and NAWM Cho/Cr and corpus callosum NAA/Cr values. An inverse correlation was also reported between the macular OCT right eye 4 th-month values and the NACM Cho/Cr and NACM Cho/NAA 6th-month values. An inverse correlation was observed between the macular thickness OCT right eye 4 th-month values and the thalamus mI/Cr 6th-month values.

DISCUSSION

In this study, we investigated whether MS progression could be predicted using noninvasive tests. To achieve this, we conducted radiological follow-up with MRS and OCT, alongside cognitive and clinical assessments, and compared the results.

Our findings indicate that PPMS group had the lowest scores on the MoCA test, consistent with previous studies emphasizing its role in detecting cognitive dysfunction in MS (11). While MoCA is typically used in dementia evaluations, we uniquely applied it to MS subtypes for direct comparisons. Among the three components of the BICAMS, the Symbol Digit Modalities Test (SDMT) has emerged as a highly specific tool for distinguishing MS patients from healthy individuals within a short assessment time (2,3). Our study found that SDMT scores were consistently lower in the PPMS group over 0, 6, and 12 months (RRMS > SPMS > PPMS), reinforcing previous findings linking disease progression to slower information processing (12).

Similarly, results from the California Verbal Learning Test (CVLT2) and Brief Visuospatial Memory Test-Revised (BVMT-R) revealed that RRMS patients had higher scores at baseline and during follow-ups compared to the other subgroups. Although data on MS subtypes using BICAMS are limited, a large-scale multicenter study of 1.606 individuals showed that RRMS patients had significantly higher scores on SDMT, CVLT2, and BVMT compared to progressive MS patients, while no significant difference was observed between PPMS and SPMS (13). This highlights cognitive speed and verbal learning performance as key distinguishing features between RRMS and progressive forms of MS (14). Notably, while RRMS patients demonstrated improvements in SDMT and CVLT2 scores over time, PPMS patients exhibited a decline in BVMT-R scores, suggesting a better treatment response in RRMS and disease progression in PPMS.

During the follow-up, six patients exhibited progression over one-year MRS scans conducted at six-month intervals revealed that patients who progressed had lower baseline thalamus mI/Cr values (p=0.003). Previous studies have established a correlation between EDSS scores and NAA/Cr ratios (15,16). Han et al. conducted one of the longest studies on disability progression, demonstrating similar findings and attributing them to neuronal/axonal dysfunction or loss (17). Myoinositol is recognized as a glial marker, and its elevation suggests increased glial activity or cell proliferation. Several studies have reported myoinositol increases in NAWM of RRMS and clinically isolated syndrome (CIS) patients (18). Ingle et al. similarly found elevated myoinositol in early PPMS, linking it to gliosis and glial proliferation, with a significant correlation between myoinositol levels in NAWM and disability (19). Some studies have even suggested that myoinositol may serve as a more sensitive marker than NAA (20). In the study conducted by Niess et al. (21) demonstrated that myo-inositol levels increased in a group of 25 MS patients who exhibited disease progression. Most prior research has focused on NAWM, with limited studies assessing myoinositol in the thalamus. However, recent investigations have increasingly emphasized gray matter involvement in MS progression (22,23), supported by histopathological evidence of neurodegeneration. The thalamus, a deep gray matter structure with multiple functional nuclei, plays a crucial role in MS-related disability (24). MRI-based thalamic atrophy assessments have been used to predict conversion from CIS to MS (25) and to estimate disability progression (26). These atrophic changes are believed to result from a combination of neurodegeneration and inflammation. Geurts et al. compared MS patients with healthy controls and found increased thalamic myoinositol levels, particularly in SPMS patients (27). In our study, most progressing patients were in the SPMS group, further supporting the hypothesis that reactive gliosis diminishes with disease progression, leading to glial cell loss. Given the limited number of thalamic MRS studies, our study is the first to establish a cut-off value for predicting MS progression. In our study, while we acknowledge the significance of changes in metabolite values, we consider the cut-off value we identified to serve merely as a reference for future research due to the limited sample size and short follow-up period. The ability to predict patients at risk of deterioration is crucial for optimizing the selection of more potent immunomodulatory treatments and reducing disease morbidity. Although we believe that the cut-off value is a guide, we are aware that validation tests are necessary.

Regarding OCT findings, baseline measurements revealed that RNFL thickness was higher in the RRMS group than in the SPMS group in the nasal quadrant, whereas no significant difference was observed in PPMS. At follow up, RNFL thickness in the nasal and temporal quadrants remained greater in RRMS compared to PPMS, though no significant difference was detected between RRMS and SPMS. These findings align with the hypothesis that retinal axonal loss begins early in MS and is more pronounced in progressive stages, potentially influenced by treatment response. Oberwahrenbrock et al. compared 414 MS patients (308 RRMS, 65 SPMS, 41 PPMS) and reported significantly reduced RNFL thickness and total macular volume in progressive MS compared to RRMS (28). Notably, SPMS patients without optic neuritis exhibited greater RNFL thinning than PPMS patients, though previous studies did not differentiate between progressive subtypes (29,30). Our study identified significant RNFL changes in the SPMS group over time, yet these changes did not correlate with clinical progression.

We also examined the relationship between OCT and MRS. An inverse relationship was observed between baseline macular OCT values and baseline MRS findings, particularly between NACM Cho/Cr, NAWM mI/Cr, NAWM Cho/Cr, and corpus callosum NAA/Cr. Optical coherence tomography and MRS were reversed between NACM Cho/Cr and NACM Cho/NAA; there is a direct relationship between thalamus mI/Cr.

The inverse correlation between macular OCT and NACM/NAWM Cho/Cr suggests inflammatory changes, whereas the inverse relationship with NAWM mI/Cr may reflect reactive gliosis differences. The observed variations in corpus callosum NAA/Cr likely arise from its heterogeneous pathology. Additionally, the delayed response of OCT in reflecting central demyelination may contribute to these findings.

In follow-up OCT assessments, an inverse relationship was noted between NACM Cho/Cr and inflammation-related changes, while thalamus mI/Cr and NACM Cho/NAA served as cut-off values for progression. As disease progression was observed in some patients, the correlation between these MRS and OCT findings may indicate a shared pathological mechanism. The use of OCT in monitoring subclinical progression has been established in previous studies (27,28) and is a frequently utilized assessment in MS follow-up. We believe that the correlation between the thalamus mI/Cr value, for which we calculated the cut-off, highlights its clinical significance. Further studies in larger cohorts will enhance its reliability as a predictive biomarker.

As a result, our study findings showed the importance of MRS utility in understanding the pathogenesis of MS and the follow-up of metabolite changes in predicting prognosis. Considering the heterogeneous process of MS disease, the expansion of radiological imaging in patient follow-up will provide us with an advantage in both determining prognosis and guiding the selection of the suitable treatment which may lead to significant impact on patients' quality of life.

Future studies should explore larger, multi-center cohorts to validate the proposed cut-off values for MRS in predicting MS progression. A longer-term follow-up study could be conducted. Additionally, investigating the interplay between inflammatory and neurodegenerative processes in different MS subtypes may enhance our understanding of disease mechanisms. Finally, integrating advanced imaging techniques, such as ultra-high-field MRI, with MRS and OCT could further refine MS monitoring and improve individualized treatment strategies.

Limitations of the Study

There are certain limitations to our study.

- **Limited Sample Size:** The sample size was relatively small, particularly for subgroup analyses, necessitating validation in larger cohorts.
- **Immunomodulator Use**: The majority of our patients were using immunomodulatory therapy and treatment effects may have influence the immunopathology of the disease.
- **Short Follow-Up Period**: Longitudinal studies with extended follow-up periods are required to further establish the prognostic value of these markers.
- **Preliminary Nature of the Study**: Due to the limited sample size and follow-up period, this analysis should be considered a preliminary study, requiring confirmation through longitudinal investigations with an extended course.
- **Need for Further Evidence for Clinical Implementation:** The cut-off value identified using MRS needs validation in larger patient groups with longer follow-up periods before it can be widely applied in clinical practice.

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital (2020.514.1171.3).

Informed Consent: Written consent was obtained from all patients included in the study.

Peer-review: Externally peer-reviewed.

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