

# An artificial intelligence model for Lhermitte's sign in patients with pediatric-onset multiple sclerosis: A follow-up study

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## Abstract

**Background.** Lhermitte's sign (LS) is an important clinical marker for patients with multiple sclerosis (MS). Research on pediatric-onset MS (POMS) and LS is limited. To date, there has been no research conducted on the clinical and artificial intelligence (AI)-based radiological correlation of LS.

**Objectives.** This follow-up study aims to investigate the relationship between LS and clinical findings according to AI-based radiological characteristics of patients with POMS.

**Materials and methods.** Basic descriptive statistics of patients with POMS according to sociodemographic, clinical and radiological findings were collected. Variables were evaluated at a 95% confidence level (95% CI), and a value of  $p < 0.05$  was accepted as statistically significant. The LS in patients with MS was classified according to its presence in the past and at the time of the study screening: group A: absent; group B: positive in the past but absent at screening; group C: present both in the past and at the screening; group D: absent in the past but present at the screening. In addition, patients were grouped according to the duration of their MS, with the following classifications: <10 years and at least 10 years.

**Results.** A total of 1,298 records were identified in the database search. Ninety-two patients who met the inclusion criteria were included in the study. The frequency of upper cervical lesions (C1–4 vertebral segmental levels) was higher in group B and C than in group A ( $p = 0.017$ ). Among patients with an MS duration of 10-years, C1–4 lesions were least frequent in group A.

**Conclusions.** Spinal imaging with AI-based programs can be used at least as much as brain magnetic resonance imaging (MRI) for early diagnosis, prognosis and treatment response. We have for the first time investigated LS in a large sample of patients with POMS. It is, however, recommended to conduct further multicenter studies to more specifically identify LS in patients with POMS.

**Key words:** artificial intelligence, multiple sclerosis, Lhermitte's sign, pediatric onset multiple sclerosis, spinal lesions

## Cite as

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## Background

Pediatric-onset multiple sclerosis (POMS), formerly referred to as juvenile multiple sclerosis (MS), has been increasingly diagnosed.<sup>1</sup> Despite heightened awareness, POMS remains a rare condition. The estimated annual incidence rates range from 1 to 5.4 cases per 100,000 people. This rate was determined to be 5.4 per 100,000 in a German cohort that included children under the age of 18.<sup>2</sup> It has been reported that at least 5% of patients with MS experience the clinical symptoms onset of disease prior to the age of 18 years.<sup>3,4</sup> The vast majority of children presenting with a 1<sup>st</sup> clinical demyelinating attack have a monophasic course, and fewer than 20% of children presenting with a 1<sup>st</sup> demyelinating attack are diagnosed with POMS, which has worse long-term physical and cognitive disabilities.<sup>5</sup> In the 2010 and 2017 McDonald criteria, the requirements for confirming the diagnosis of MS in the 1<sup>st</sup> demyelinating attack with pediatric onset were determined. Accordingly, children presenting with acute disseminated encephalomyelitis (ADEM), defined by polyfocal deficits and encephalopathy,<sup>6</sup> must have experienced a non-ADEM attack plus evidence for dissemination in time and space prior to MS diagnosis.<sup>7,8</sup> High relapse rates and rapid accumulation of lesion burden are typical features that distinguish patients from adult-onset multiple sclerosis (AOMS).<sup>9</sup> The positivity of oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) increased diagnostic performance.<sup>10</sup> Although spinal cord lesions are common, their diagnostic performance is poor due to the high frequency of juxtacortical and periventricular lesions.<sup>11</sup> Therefore, detailed brain magnetic resonance imaging (MRI) seems to be sufficient in patients without spinal cord complaints. Developing diagnostic criteria for patients with spinal cord complaints has become important, especially in those whose brain imaging is insufficient for diagnosis.

High levels of proinflammatory cytokines have been reported in the CSF and serum of POMS patients. Cytokine density has diagnostic value for both 1<sup>st</sup> attack and relapsed patients.<sup>12</sup> Biomarkers found in the serum or CSF of POMS patients that indicate diagnosis, disease activity/active neuroinflammation, or response to treatment include matrix metalloproteinase-9 (MMP-9),<sup>13</sup> some miRNAs (such as *miR-125a-5p* and *miR185-5p*)<sup>14</sup> and serum neurofilament light chain (sNfL).<sup>15</sup> In particular, the increase in serum neurofilament light chain levels is an important indicator of disease activity and response to treatment, in addition to its early diagnostic value. Additionally, glial fibrillary acidic protein (GFAP) levels were found to be high in the serum of patients with neuromyelitis optica spectrum disorder (NMOSD). A high sGFAP/sNfL ratio may help distinguish NMOSD from MS.<sup>16</sup>

The clinical features of POMS are comparable to those of AOMS, with recurrent episodes of optic neuritis, diplopia or transverse myelitis. However, isolated brainstem

syndrome, optic neuritis or encephalopathy symptoms are more likely to occur in children.<sup>17</sup>

The Lhermitte's sign (LS) was first described in 1917 by Pierre Marie and Chatelin in a soldier who had suffered a head injury during World War I.<sup>18</sup> The following year, it was described in spinal concussions by Babinski and Du-bois,<sup>19</sup> and then the observations of J. Ribeton in 12 cases with head or neck trauma captured the first attention for this phenomenon. Jean J. Lhermitte reported this symptom in 1920. In 1924, Lhermitte, Bollak and Nicholas published the seminal paper on the subject entitled "Les douleurs à type de décharge électrique consécutives à la flexion céphalique dans la sclérose en plaques: Un cas de forme sensitive de la sclérose multiple."<sup>20</sup> Thus, in addition to the observations of J. Ribeton, they provided the first description in the medical literature of an electrical discharge following neck flexion in a patient with MS.

It is believed that the LS is caused by ectopic firing and hyperexcitability of demyelinated sensory neurons located in the cervical spinal cord. It is also thought that increased spinothalamic nociceptive signal transmission and impaired function of inhibitory GABAergic interneurons affect this process.<sup>21</sup> Molecular mechanisms include downstream activated microglia that enhance pro-inflammatory cytokine signaling, activation of proteins such as bradykinin by B1 and B2 receptors, upregulation of Wnt signaling, cAMP-response element binding protein (CREB) phosphorylation, and other transcription factors that increase hyperexcitability and pain in the central nervous system (CNS).<sup>22</sup>

The LS is accepted both as a symptom and a sign of physical examination, and results from irritation of the spinal cord, especially the posterior and lateral columns.<sup>23</sup> The LS is not specific to MS. It may occur in autoimmune diseases such as Behçet's disease<sup>24</sup> and systemic lupus erythematosus,<sup>25</sup> as well as in various conditions in which the cervical spinal cord is affected, e.g., atlantoaxial subluxation, cervical myelitis, cisplatin toxicity, ionizing radiation affecting the cervical cord, pernicious anemia affecting the dorsal columns, prolapsed cervical disc, spinal cord tumor, syringomyelia, cervical spine trauma, tuberculous arachnoiditis, alcoholic myelopathy, intramedullary spinal cord hemorrhage (hematomyelia), and paroxetine withdrawal.<sup>26–29</sup> Hence, the overall prevalence of LS seems difficult to estimate or investigate. The LS may be observed in pediatric- or adult-onset MS.<sup>26</sup>

Studies on early diagnosis and prognosis of MS using multi-dimensional data with computer-aided diagnosis and deep learning (DL)/machine learning (ML) methods have focused mostly on brain imaging. Artificial intelligence (AI)-based automatic analyses of lesion classification provide a time advantage over manual measurements.<sup>30,31</sup> Machine learning refers to the concept of computers acquiring knowledge without being programmed directly, while DL involves software training via algorithmic exposure to extensive data sets through multi-layered neural

networks. In short, DL is a subset of ML. Recent studies have demonstrated the efficacy of AI techniques, including DL and ML, in the segmentation of white matter lesions and the evaluation of novel imaging markers, such as paramagnetic rim lesions and central vein sign.<sup>32,33</sup>

For AI-based spinal lesion definition in the radiological differentiation of conditions such as myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), NMOSD, ADEM and clinically isolated syndrome (CIS) with POMS, the characteristics of these lesions must be correctly recognized. Research into the clinical course of LS, or the association of LS with clinical or radiological features in MS, has been limited.

It is important to note that LS is indicative of neuronal damage, particularly in the posterior and lateral columns of the cervical spine. Therefore, it could be a useful early indicator of neuroinflammation in patients with POMS.

## Objectives

This retrospective study aimed to investigate the relationship between LS and clinical findings according to AI-based radiological characteristics of POMS patients.

## Materials and methods

### Study design

Patients diagnosed with MS and admitted to the neurology clinics of Izmir University of Economics Faculty Hospital (Turkey) between 2012 and 2023 were included in this retrospective study.

### Participants

Patients who were diagnosed with MS in childhood (age at diagnosis <16) were included in the study. The diagnosis and typing of MS was based on the criteria defined in the previous guidelines.<sup>6,34</sup> Participants for whom data were missing, those whose signs and symptoms were attributed to a diagnosis other than MS, or for whom a diagnosis of MS was confirmed after 16 years of age were excluded from the study. Patients with possible factors associated with LS other than MS, such as cervical disc herniation, vitamin B12 deficiency, systemic lupus erythematosus, spinal cord compression, spondylitis, or radiculopathy were excluded.

### Test methods and radiological work-up

Demographic (age at the diagnosis of MS, age at screening and sex), and clinical parameters (type of MS, past and present history of the presence of LS, confirmation of LS

by self-detection (symptom) or on physical examination (sign), the presence of vibration, position and tactile sensation, or Romberg's test on physical examination) and radiological findings were recorded using electronic and written patient files.

Types of MS were defined as CIS, RR (remitting–relapsing), SP (secondary progressive), and PP (primary progressive). We grouped the patients according to the presence of LS as follows: group A: absent; group B: positive in the past but absent at screening; group C: present both in the past and at the screening; group D: absent in the past but present at the screening. We also grouped the patients according to MS duration: <10 years vs >10 years.

Cervical and cranial MRI of all patients were performed upon the diagnosis of MS and at the screening. Gadolinium-based contrast agents were used during the imaging. The data presented in the result section represent comprehensive analysis of the aggregated data obtained from both sets of MRI scans. On the cervical MRI, localization of spinal cord lesions both at the level of the vertebra and localization in the spinal cord, identification of spinal cord lesions on T1 or T2-weighted images, gadolinium enhancement, and atrophy or expansion of the spinal cord lesions were assessed. The presence of intracranial lesions was evaluated on cranial MRI.

### Statistical analyses

The data obtained in the study were statistically analyzed using SPSS v. 25.0 software (IBM Corp., Armonk, USA). The conformity of the univariable data to normal distribution was evaluated using the Shapiro–Wilk–Francia test. Homogeneity of variance was evaluated with the Levene's test. When comparing more than 2 independent groups according to qualitative variables, the Kruskal–Wallis test with Monte Carlo simulation was used. The Monte Carlo simulation is regarded as a crucial tool in modeling uncertainty and supporting decision-making processes, as it allows for the evaluation of all possible outcomes and the estimation of their probabilities. The Monte Carlo simulation method was incorporated into IBM SPSS v. 25.0 through the installation of supplementary tools. Once added, it appears as an option in the relevant menus. When comparing 2 independent groups according to qualitative variables, the Mann–Whitney U test with Monte Carlo simulation was used with the Benjamin–Hochberg correction for the post hoc analysis. When comparing categorical variables to each other, the Fisher exact test and the Fisher–Freeman–Halton test were used. Nonparametric methods were used for the analysis of variables with a sample size smaller than 10. Quantitative variables were stated as n/median (min–max) (Q1–Q3) values and categorical variables as number (n) and percentage (%) in the tables. Variables were evaluated at a 95% confidence level (95% CI), and a p-value of <0.05 was accepted as statistically significant.

## Ethics

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the İzmir Bakırçay University Non-Interventional Transactions Ethics Committee (approval No. 926/906 issued on March 15, 2023). Written informed consent was obtained from all of the participants.

## Results

A total of 92 patients were included in this study. The flow chart of the study is shown in Fig. 1. The female-to-male ratio was 2.17 (63/29). The mean age at diagnosis was 14.67 ( $\pm 2.27$ ) years, and the mean age at screening

was 25.99 ( $\pm 8.08$ ) years. The LS was absent in 63 patients (68.5%) (group A), while 15 patients (16.3%) had a positive history of LS without current manifestation (group B). The LS was present in both the past and at the screening in 9 patients (9.8%) (group C), while 5 patients (5.4%) developed LS during the screening despite no prior history (group D).

The mean duration of MS was 123.65 ( $\pm 107.69$ ) months, with 33.7% of patients having an MS duration longer than 10 years. The majority (87%) of patients had relapsing–remitting (RR) MS. Detailed demographic, clinical and radiological features are presented in Table 1.

Table 2 provides a comprehensive breakdown of spinal cord lesions categorized according to the levels of cervical or thoracic vertebrae. The data are presented for the total cases and are further stratified based on the duration of MS (<10 years and >10 years). Percentages were

**Table 1.** Demographic, clinical and radiological features of the patients

Characteristics	n (%)
Lhermitte's sign	group A
	group B
	group C
	group D
MS duration	≤10-year
	>10-year
Sex	female
	male
Lhermitte's sign in the past	absent
	present
Lhermitte's sign at the screening (symptom and physical sign)	absent
	present
Lhermitte's symptom	absent
	present
Lhermitte's sign	absent
	present
MS type	CIS
	RR
	SP
	PP
C1–4 spinal lesion	absent
	present
C5–8 spinal lesion	absent
	present
Thoracal spinal lesion	absent
	present
Localization of cervical spinal lesion	lateral
	posterior
	posterolateral
	absent
Cervical lesion on T2-weighted MRI	absent
	present

Characteristics	n (%)
Cervical lesion on T1-weighted MRI	absent
	present
Gadolinium enhancement on cervical MRI	absent
	present
Atrophy on cervical MRI	absent
	present
Expansion on cervical MRI	absent
	present
Intracranial lesion	absent
	present
Right superficial sensation	absent
	present
Left superficial sensation	absent
	present
Vibration sensation abnormality on upper extremity	absent
	present
Vibration sensation abnormality on lower extremity	absent
	present
Position sensation abnormality on upper extremity	absent
	present
Position sensation abnormality on lower extremity	absent
	present
Romberg test	negative
	positive
Age at diagnosis [years], mean (SD)	14.67 (2.27)
Age at screening [years], mean (SD)	25.99 (8.08)
MS follow-up duration [months], mean (SD)	123.65 (107.69)

MRI – magnetic resonance imaging; MS – multiple sclerosis; CIS – clinically isolated syndrome; RR – relapsing–remitting; SP – secondary progressive; PP – primary progressive; SD – standard deviation; min – minimum; Q1 – percentile 25; Q3 – percentile 75; max – maximum.

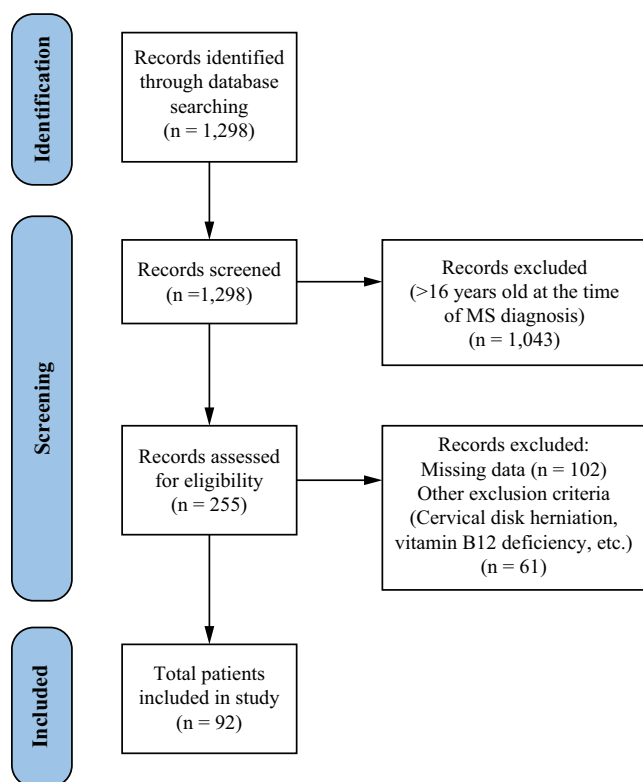


Fig. 1. The flowchart of the study

MS – multiple sclerosis.

calculated in relation to the total number of cases in each respective category.

Table 3 presents a thorough comparison of demographic, clinical and radiological characteristics among the different patient groups (group A, B, C, and D). The total number of patients included in the analysis was 92. Group A comprised 63 (68.5%) patients; group B 15 (16.3%); group C 9 (9.8%); and group D 5 (5.4%). There was a statistically significant difference in the distribution of C1–4 lesions among groups A, B, C, and D ( $p = 0.017$ ). The frequency of C1–4 lesions in group B and C was higher compared to group A ( $p < 0.05$ ). The frequency of the presence of cervical cord lesions on T2-weighted MRI was higher in group B when compared to that in group A ( $p = 0.038$ ). The frequency of the presence of cervical cord lesions on T1-weighted MRI was higher in group C when compared to that in group A ( $p = 0.021$ ) (Fig. 2).

In this segment, we present a thorough comparison of demographic, clinical and radiological features among distinct patient groups (group A, B, C, and D) within the subgroup of MS patients with a disease duration shorter than 10 years. A total of 61 patients are included in this analysis. Among those with an MS duration of less than 10 years, our investigation reveals striking similarities in demographic, clinical and radiological parameters across the various groups, as detailed in Table 4.

Table 5 presents a detailed comparison of demographic, clinical and radiological features among subgroups of MS

Table 2. Localization of spinal cord lesions

Localization of spinal lesion	Total n = 249	MS duration (<10 years) n = 173	MS duration (>10 years) n = 76
	n (%)	n (%)	n (%)
C1	8 (3.2)	5 (2.9)	3 (3.9)
C2	27 (10.8)	19 (11)	8 (10.5)
C3	45 (18.1)	33 (19.1)	12 (15.8)
C4	38 (15.3)	26 (15)	12 (15.8)
C5	18 (7.2)	13 (7.5)	5 (6.6)
C6	18 (7.2)	12 (6.9)	6 (7.9)
C7	10 (4)	5 (2.9)	5 (6.6)
C8	1 (0.4)	1 (0.6)	–
T1	10 (4)	7 (4)	3 (3.9)
T11	2 (0.8)	2 (1.2)	–
T12	2 (0.8)	2 (1.2)	–
T2	7 (2.8)	4 (2.3)	3 (3.9)
T3	6 (2.4)	4 (2.3)	2 (2.6)
T4	3 (1.2)	2 (1.2)	1 (1.3)
T5	5 (2)	5 (2.9)	–
T6	8 (3.2)	7 (4)	1 (1.3)
T7	4 (1.6)	3 (1.7)	1 (1.3)
T8	2 (0.8)	2 (1.2)	–
T9	2 (0.8)	2 (1.2)	–
Absent	33 (13.3)	19 (11)	14 (18.4)

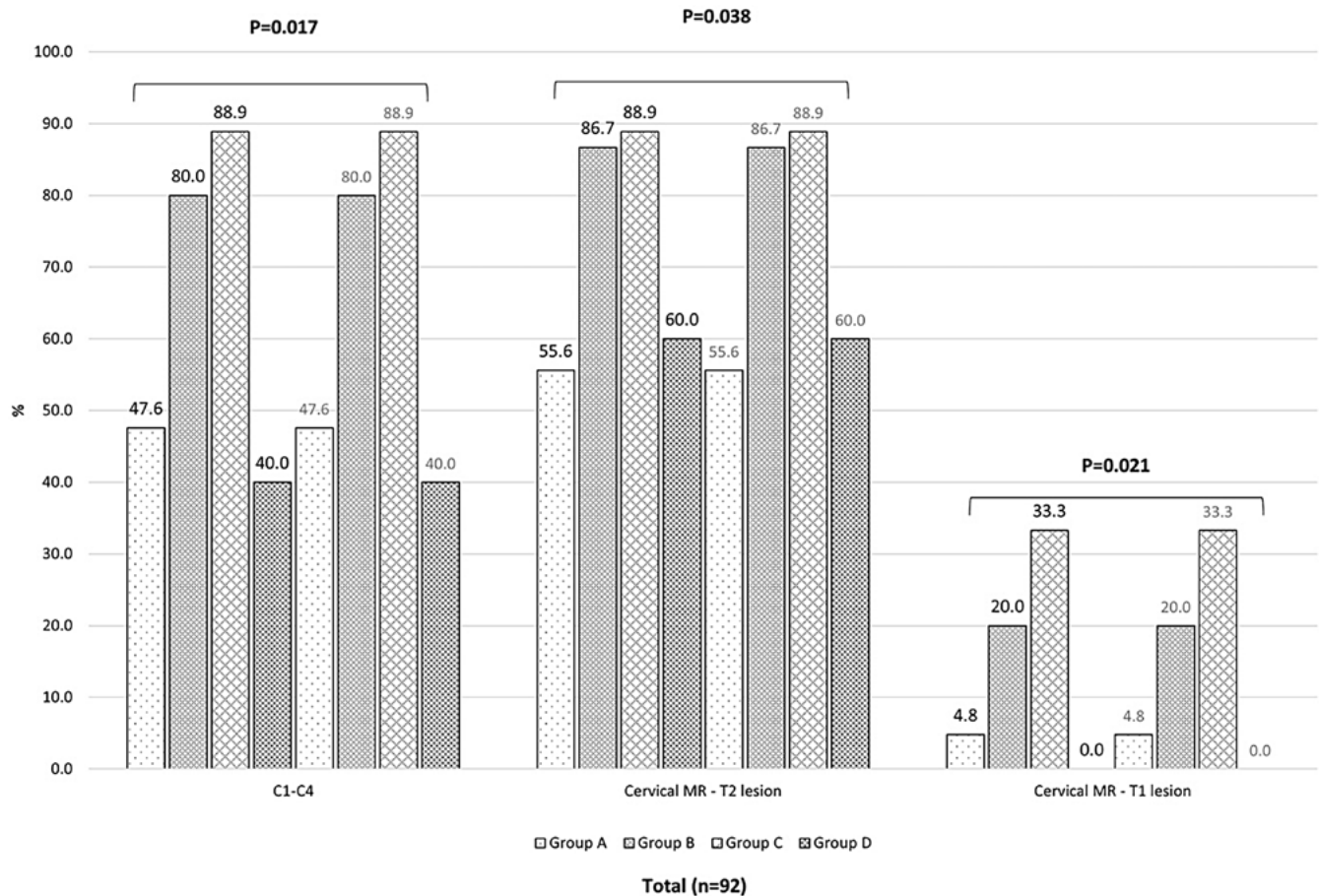
MS – multiple sclerosis.

patients with a disease duration exceeding 10 years, labeled as group A, B and C. The analysis encompasses a total of 31 patients. The localization of cervical spinal lesions was higher in group B than in group A ( $p = 0.010$ ) (Fig. 3). The C1–4 lesions were more frequent in group B than in group A ( $p = 0.030$ ). The frequency of the presence of cervical cord lesions on T2-weighted MRI, and atrophy and expansion on cervical MRI were higher in group B when compared to those in group A ( $p = 0.042$ ,  $p = 0.042$  and  $p = 0.042$ , respectively). Vibration abnormality in the upper extremity was found to be significantly more pronounced in group B compared to group A ( $p = 0.003$ ). A significant disparity was noted in the Romberg test, with 100% of group B exhibiting abnormalities compared to 24% in group A ( $p = 0.009$ ) (Fig. 4). The findings presented in the tables are derived from the results of current MRIs. The MRIs taken during the study for screening purposes were conducted for patient monitoring and were used for patient and lesion follow-up.

## Discussion

We have studied a considerable number of patients with POMS. About 1/3 of the patients had LS during the course of MS. We showed that the presence of LS was associated with cervical spinal lesions.





**Fig. 2.** Comparison of the Lhermitte's sign (LS) and radiological features. Group A: LS is absent. Group B: LS is positive. Group C: LS is present in both the past and at the screening. Group D: Developed LS during the screening despite no prior history. The frequency of C1–4 lesions was higher in groups B and C when compared to that in group A ( $p = 0.017$ ). Group B exhibited a higher frequency of cervical cord lesions on T2-weighted magnetic resonance imaging (MRI) compared to group A ( $p = 0.038$ ). The frequency of the presence of cervical cord lesions on T1-weighted MRI was higher in group C than in group A ( $p = 0.021$ )

Our research has demonstrated a complex relationship between LS and spinal cord lesion activity or contrast enhancement. Studies have shown that LS is not consistently associated with contrast enhancement on MRI, indicating its variable presentation in MS and other spinal pathologies.<sup>35,36</sup> This suggests that while LS is a significant clinical symptom, it does not reliably correlate with visible contrast-enhanced lesions in the spinal cord, underscoring the need for comprehensive diagnostic approaches beyond imaging alone.<sup>35</sup> Despite being an early indicator of neuroinflammation, it should be noted that clinical symptoms like LS may not always align with active MRI lesions.

We found that the RR type comprised the majority of patients. In 1 study from Turkey that investigated early-onset MS (<10 years of age), the RR type was found in 96.7% ( $n = 29$ ) of 30 children.<sup>37</sup> Similar findings were also reported in previous studies.<sup>22,38</sup> In a Serbian POMS cohort, all the patients had the RR course of the disease.<sup>39</sup>

Longitudinal follow-up studies regarding POMS are scant. Mean follow-up duration was more than 10 years in our study, and we followed-up 31 patients for >10 years.

Mean follow-up duration was relatively shorter in the previous studies, at about 2–4 years.<sup>37,39,40</sup>

We showed that cervical and thoracic spinal cord lesions were found in approx. 2/3 and 1/4 of the patients, and intracranial lesions in the vast majority of those. Similar findings were also reported.<sup>37,40</sup> The frequency of spinal cord lesions was lower in a previous report from Taiwan.<sup>41</sup> Cervical and thoracic spinal lesions were shown at a respective frequency of 33% and 43% in another study.<sup>42</sup> Differences in the frequency of spinal cord lesions in POMS may result from discrepancies in the manner in which systematic spinal cord imaging was obtained. We performed spinal cord MRI on all the participants. Given the high frequency of spinal cord lesions in our study, it is important to obtain a spinal cord MRI both for earlier diagnosis and follow-up. A study of the patient population revealed that more than 30% of patients had had MS for more than 10 years. This finding suggests the presence of numerous confounding factors that may contribute to the patients' current conditions and the burden of lesions as indicated by MRI. The most common symptoms associated with MS include visual disturbances, weakness

**Table 3.** Comparison of demographic, clinical and radiological features among the groups

Characteristics		Total (n = 92)				p-value
		Group A (n = 63)	Group B (n = 15)	Group C (n = 9)	Group D (n = 5)	
Age at onset [years], median (min/max)		14 (10/16)	14 (5/14)	14 (12/14)	14 (13/14)	0.936 <sup>k</sup>
Age at screening [years], median (min/max)		24 (15/50)	22 (18/54)	21 (18/37)	24 (20/26)	0.780 <sup>k</sup>
Sex (female), n (%)		43 (68.3)	10 (66.7)	7 (77.8)	3 (60)	0.889 <sup>f</sup>
MS, n (%)	CIS	3 (4.8)	0 (0)	0 (0)	0 (0)	0.301 <sup>f</sup>
	RR	53 (84.1)	14 (93.3)	8 (88.9)	5 (100)	
	SP	7 (11.1)	0 (0)	0 (0)	0 (0)	
	PP	0 (0)	1 (6.7)	1 (11.1)	0 (0)	
C1–4, n (%)		30 (47.6) <sup>B,C</sup>	12 (80)	8 (88.9)	2 (40)	0.017 <sup>f</sup>
C5–8, n (%)		15 (23.8)	6 (40)	3 (33.3)	2 (40)	0.479 <sup>f</sup>
Thoracal, n (%)		16 (25.4)	4 (26.7)	3 (33.3)	0 (0)	0.635 <sup>f</sup>
Localization, n (%)	lateral	6 (9.5)	0 (0)	0 (0)	0 (0)	0.106 <sup>f</sup>
	posterior	10 (15.9)	3 (20)	3 (33.3)	1 (20)	
	posterolateral	19 (30.2)	10 (66.7)	5 (55.6)	2 (40)	
	absent	28 (44.4)	2 (13.3)	1 (11.1)	2 (40)	
Cervical MR – T2 lesion, n (%)		35 (55.6)	13 (86.7) <sup>A</sup>	8 (88.9)	3 (60)	0.038 <sup>f</sup>
Cervical MR – T1 lesion, n (%)		3 (4.8)	3 (20)	3 (33.3) <sup>A</sup>	0 (0)	0.021 <sup>f</sup>
Cervical MR – gadolinium, n (%)		12 (19.1)	4 (26.7)	2 (22.2)	2 (40)	0.561 <sup>f</sup>
Cervical MR – atrophy, n (%)		2 (3.2)	3 (20)	1 (11.1)	0 (0)	0.099 <sup>f</sup>
Cervical MR – expansion, n (%)		10 (15.9)	3 (20)	1 (11.1)	2 (40)	0.482 <sup>f</sup>
Intracranial lesion, n (%)		62 (98.4)	15 (100)	8 (88.9)	5 (100)	0.313 <sup>f</sup>
Right superficial sensation, n (%)		3 (4.8)	2 (13.3)	1 (11.1)	0 (0)	0.401 <sup>f</sup>
Left superficial sensation, n (%)		4 (6.4)	2 (13.3)	0 (0)	0 (0)	0.553 <sup>f</sup>
Upper extremity vibration abnormality, n (%)		11 (17.5)	6 (40)	4 (44.4)	0 (0)	0.061 <sup>f</sup>
Lower extremity vibration abnormality, n (%)		33 (52.4)	10 (66.7)	6 (66.7)	4 (80)	0.523 <sup>f</sup>
Upper extremity position abnormality, n (%)		0 (0)	0 (0)	1 (11.1)	0 (0)	0.152 <sup>f</sup>
Lower extremity position abnormality, n (%)		0 (0)	0 (0)	1 (11.1)	0 (0)	0.152 <sup>f</sup>
Romberg test, n (%)		16 (25.4)	6 (40)	4 (44.4)	1 (20)	0.469 <sup>f</sup>

<sup>k</sup> Kruskal–Wallis H test (Monte Carlo); <sup>f</sup> Fisher–Freeman–Halton test (Monte Carlo); post hoc test: Benjamin–Hochberg correction; <sup>A</sup> statistically significant compared with group A; <sup>B</sup> statistically significant compared with group B; <sup>C</sup> Statistically significant compared with group C; min – minimum; max – maximum; MS – multiple sclerosis; CIS – clinically isolated syndrome; RR – relapsing–remitting; SP – secondary progressive; PP – primary progressive; MR – magnetic resonance.

and gait disturbances, as well as sensory difficulties.<sup>43</sup> These symptoms are easily identified causes of disability. However, other common and disabling symptoms such as fatigue, cognitive decline, emotional distress, and pain are invisible.<sup>44</sup> Bladder and bowel dysfunction are also hidden consequences of MS, but they are among the most common and distressing symptoms.<sup>43</sup> This may cause delayed recognition of spinal sensory complaints, deterioration of quality of life and increased lesion burden over the years.

Histopathological studies on the relationship between the venous system and plaque have been relatively less studied for the spinal cord, unlike the brain. However, a few studies have shown that the topographic distribution of focal spinal cord lesions is related to the spinal venous system and that even the drainage areas of the spinal cord veins and the shape of the plaques are correlated.<sup>45,46</sup> However,

visualizing the central vein sign, which is the radiological equivalent of the perivenous organization, for the spinal cord is a significant challenge. This is because the diameter of the spinal cord sulcal and radial vessels is only about 0.1–0.2 mm. On the other hand, with the developing MRI susceptibility-weighted imaging (SWI) techniques, at least 1 central vein sign can be detected in 40% of upper cord MS lesions.<sup>47</sup> These topographic features may also explain why LS symptoms may occur in cases involving spinal cord circulation, including cervical spinal stenosis, due to the involvement of both the venous and glymphatic systems.<sup>48</sup>

In a Serbian cohort including POMS, spinal cord lesions were detected in 33.3% of the patients.<sup>39</sup> Highly active demyelination and inflammation were observed on T1- and T2-weighted MR images in previous studies.<sup>17,43</sup> We found that all cervical spinal lesions were observed

**Table 4.** Comparison of demographic, clinical and radiological features among the groups in the patient subgroup with MS duration <10 years

Characteristics		MS duration (<10 years) (n = 61)				p-value
		Group A (n = 38)	Group B (n = 11)	Group C (n = 7)	Group D (n = 5)	
Age at onset [years], n/median (min/max)		38/13 (9/16)	11/14 (12/15)	7/14 (11/15)	5/13 (12/16)	0.437 <sup>k</sup>
Age at screening [years], n/median (min/max)		38/21.5 (15/27)	11/21 (18/27)	7/21 (18/27)	5/24 (20/26)	0.356 <sup>k</sup>
Sex (female), n (%)		27 (71.1)	6 (54.6)	5 (71.4)	3 (60)	0.744 <sup>f</sup>
MS, n (%)	CIS	3 (7.9)	0 (0)	0 (0)	0 (0)	0.562 <sup>f</sup>
	RR	32 (84.2)	11 (100)	6 (85.7)	5 (100)	
	SP	3 (7.9)	0 (0)	0 (0)	0 (0)	
	PP	0 (0)	0 (0)	1 (14.3)	0 (0)	
C1–4, n (%)		21 (55.3)	8 (72.7)	6 (85.7)	2 (40)	0.313 <sup>f</sup>
C5–8, n (%)		9 (23.7)	3 (27.3)	2 (28.6)	2 (40)	0.899 <sup>f</sup>
Thoracic, n (%)		14 (36.8)	2 (18.2)	2 (28.6)	0 (0)	0.380 <sup>f</sup>
Localization, n (%)	lateral	3 (7.9)	0 (0)	0 (0)	0 (0)	0.863 <sup>f</sup>
	posterior	6 (15.8)	3 (27.3)	2 (28.6)	1 (20)	
	posterolateral	15 (39.5)	6 (54.6)	4 (57.1)	2 (40)	
	absent	14 (36.8)	2 (18.2)	1 (14.3)	2 (40)	
Cervical MR – T2 lesion, n (%)		25 (65.8)	9 (81.8)	6 (85.7)	3 (60)	0.614 <sup>f</sup>
Cervical MR – T1 lesion, n (%)		1 (2.6)	1 (9.1)	1 (14.3)	0 (0)	0.315 <sup>f</sup>
Cervical MR – gadolinium, n (%)		10 (26.3)	3 (27.3)	1 (14.3)	2 (40)	0.844 <sup>f</sup>
Cervical MR – atrophy, n (%)		1 (2.6)	1 (9.1)	0 (0)	0 (0)	0.616 <sup>f</sup>
Cervical MR – expansion, n (%)		9 (23.7)	1 (9.1)	1 (14.3)	2 (40)	0.536 <sup>f</sup>
Intracranial lesion, n (%)		37 (97.4)	11 (100)	6 (85.7)	5 (100)	0.390 <sup>f</sup>
Right superficial sensation, n (%)		2 (5.3)	1 (9.1)	0 (0)	0 (0)	0.769 <sup>f</sup>
Left superficial sensation, n (%)		2 (5.3)	1 (9.1)	0 (0)	0 (0)	0.769 <sup>f</sup>
Upper extremity vibration abnormality, n (%)		7 (18.4)	2 (18.2)	2 (28.6)	0 (0)	0.785 <sup>f</sup>
Lower extremity vibration abnormality, n (%)		22 (57.9)	6 (54.6)	4 (57.1)	4 (80)	0.895 <sup>f</sup>
Upper extremity position abnormality, n (%)		0 (0)	0 (0)	1 (14.3)	0 (0)	0.192 <sup>f</sup>
Lower extremity position abnormality, n (%)		0 (0)	0 (0)	1 (14.3)	0 (0)	0.192 <sup>f</sup>
Romberg test, n (%)		10 (26.3)	2 (18.2)	3 (42.9)	1 (20)	0.690 <sup>f</sup>

<sup>k</sup> Kruskal–Wallis H test (Monte Carlo); <sup>f</sup> Fisher–Freeman–Halton test (Monte Carlo); min – minimum; max – maximum. MS – multiple sclerosis; C – cervical; MR – magnetic resonance. CIS – clinically isolated syndrome; RR – relapsing remitting; SP – secondary progressive; PP – primary progressive.

on T2-weighted images, but the minority in T1-weighted images. These findings suggest that edema predominates atrophy or axonal death in our patients.

We evaluated sensory abnormalities and found that superficial tactile sensation or position sensation was abnormal in a minority of the patients. Vibration sensation was abnormal in about 1/5 of them in the upper extremities and in more than a half of them in lower extremities. Romberg test results were positive in about 1/3 of the participants. In 1 study analyzing Turkish POMS (<10 years), sensory findings were detected in 16.7% of the patients.<sup>37</sup> In 2 different pediatric-onset MS cohorts, sensory deficits were detected in less than half of the patients at diagnosis, and in more than a half of them during the later course of the disease.<sup>39,49</sup> We have identified sensory abnormalities, particularly with regard to vibration sensation. However, some previous studies did not specify sensory abnormalities or analyzed superficial sensory defects.<sup>39,49</sup>

The prevalence of LS could not be investigated in this study; hence, data are scant. In various studies analyzing MS patients, the prevalence of LS was shown to be about 9–41%.<sup>26,50</sup> One study comparing MS with neuromyelitis optica revealed a very low frequency of LS (4.5%) in MS patients.<sup>51</sup> To our knowledge, the present study is the first to investigate the frequency of LS and the association of it with both clinical and radiological parameters in POMS patients. We found that the frequency of LS was 31.5% in the present study and observed that LS was positive only in the past in half of the patients with LS, and it was positive in the past in the majority of those patients. This finding may suggest that paroxysmal findings may occur earlier in the course of MS. Another study suggests that LS may commonly start early in the disease course, and follow a paroxysmal pattern in some patients.<sup>52</sup>

We showed that the presence of LS in the past was associated with C1–4 spinal lesions in the overall patient



**Table 5.** Comparison of demographic, clinical and radiological features among the groups in the patient subgroup with multiple sclerosis (MS) duration >10 years

Characteristics		MS duration (>10 years) (n = 31)			p-value
		Group A (n = 25)	Group B (n = 4)	Group C – excluded (n = 2)	
Age at onset [years], n/median (min/max)		25/14 (10/16)	4/12 (5/15)	2/12 (10/14)	0.110 <sup>u</sup>
Age at screening [years], n/median (min/max)		25/33 (24/0)	4/38 (27/54)	2/34.5 (32/37)	0.618 <sup>u</sup>
Sex (female), n (%)		16 (64)	4 (100)	2 (100)	0.280 <sup>f</sup>
MS, n (%)	CIS	0 (0)	0 (0)	0 (0)	0.211 <sup>f</sup>
	RR	21 (84)	3 (75)	2 (100)	
	SP	4 (16)	0 (0)	0 (0)	
	PP	0 (0)	1 (25)	0 (0)	
C1–4, n (%)		9 (36)	4 (100)	2 (100)	<b>0.030<sup>f</sup></b>
C5–8, n (%)		6 (24)	3 (75)	1 (50)	0.076 <sup>f</sup>
Thoracal, n (%)		2 (8)	2 (50)	1 (50)	0.080 <sup>f</sup>
Localization, n (%)	lateral	3 (12)	0 (0)	0 (0)	<b>0.010<sup>f</sup></b>
	posterior	4 (16)	0 (0)	1 (50)	
	posterolateral	4 (16)	4 (100) <sup>A</sup>	1 (50)	
	absent	14 (56)	0 (0) <sup>A</sup>	0 (0)	
Cervical MR – T2 lesion, n (%)		10 (40)	4 (100)	2 (100)	<b>0.042<sup>f</sup></b>
Cervical MR – T1 lesion, n (%)		2 (8)	2 (50)	2 (100)	0.080 <sup>f</sup>
Cervical MR – gadolinium, n (%)		2 (8)	1 (25)	1 (50)	0.371 <sup>f</sup>
Cervical MR – atrophy, n (%)		1 (4)	2 (50)	1 (50)	<b>0.042<sup>f</sup></b>
Cervical MR – expansion, n (%)		1 (4)	2 (50)	0 (0)	<b>0.042<sup>f</sup></b>
Intracranial lesion, n (%)		25 (100)	4 (100)	2 (100)	–
Right superficial sensation, n (%)		1 (4)	1 (25)	1 (50)	0.261 <sup>f</sup>
Left superficial sensation, n (%)		2 (8)	1 (25)	0 (0)	0.371 <sup>f</sup>
Upper extremity vibration abnormality, n (%)		4 (16)	4 (100)	2 (100)	<b>0.003<sup>f</sup></b>
Lower extremity vibration abnormality, n (%)		11 (44)	4 (100)	2 (100)	0.100 <sup>f</sup>
Upper extremity position abnormality, n (%)		0 (0)	0 (0)	0 (0)	–
Lower extremity position abnormality, n (%)		0 (0)	0 (0)	0 (0)	–
Romberg test, n (%)		6 (24)	4 (100)	1 (50)	<b>0.009<sup>f</sup></b>

<sup>u</sup> Mann–Whitney U test (Monte Carlo); <sup>f</sup> Fisher–Freeman–Halton test (Monte Carlo); post hoc test: Benjamin–Hochberg correction; <sup>F</sup> Fisher’s exact test (Monte Carlo); <sup>A</sup> statistically significant compared with group A; min – minimum; max – maximum; group D (n = 0) was not demonstrated in the table. Bold numbers indicate statistical significance. MS – multiple sclerosis; C – cervical; MR – magnetic resonance.

population. The “LS in the past” refers to LS at the disease onset. We showed that the other clinical findings of the patients with LS did not differ based on whether LS was positive in the past or later. In a study analyzing adult patients with MS, the earlier onset of the disease was associated with more positive LS.<sup>52</sup> Similar to our findings, the presence of LS was not associated with sex or disease pattern. They showed that female sex was associated with the presence of LS later in the disease course rather than the presence of LS at clinical onset. However, similar to our findings, the disease pattern or age at diagnosis were not associated with the time of the onset of LS in the disease course.<sup>52</sup> They also showed that cervical spinal lesions were associated with the presence of LS.

Lhermitte’s sign is caused by a stretching of the hyperexcitable demyelinated dorsal column of the spinal cord, especially at the cervical level.<sup>52</sup> It is a symptom like “electric

shock sensation”, but may also be induced during physical examination, which makes it a sign. We analyzed both LS and symptoms, and showed a significant level of compatibility between symptom and sign. However, previous studies revealed Lhermitte’s finding to be either a symptom or sign.<sup>26,53</sup> In a previous study, LS was defined as a symptom and grouped as a probable, definite or possible LS.<sup>26</sup> They also showed that limb movements, laughing, sneezing, or coughing, other than neck flexion, may precipitate LS. Lhermitte’s sign is not a sensitive or specific sign, which may occur in a number of conditions such as MS, Behçet’s disease, systemic lupus erythematosus, herpes zoster, spinal cord compression, vitamin B12 deficiency, radiculopathy, or spondylitis.<sup>54</sup> In a previous study, LS was shown to be more common in MS or subacute combined degeneration.<sup>26</sup> It may suggest that demyelination with axonal preservation could be valuable for spontaneous

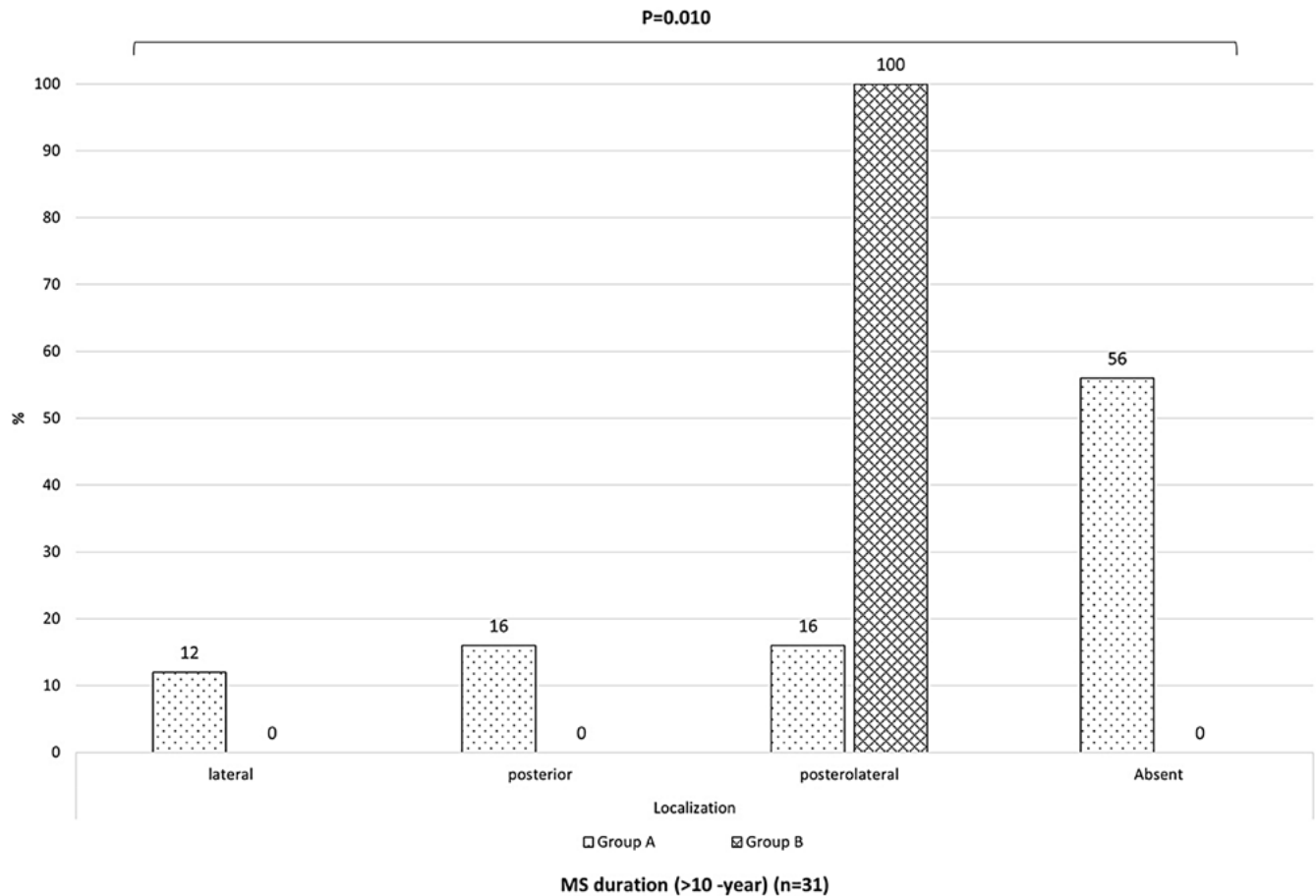


Fig. 3. Comparison of localization features among the groups in the patient subgroup with multiple sclerosis (MS) duration >10 years

activity to emerge. We excluded vitamin B12 deficiency, SLE, spinal cord compression, spondylitis, radiculopathy, and cervical disc herniation.

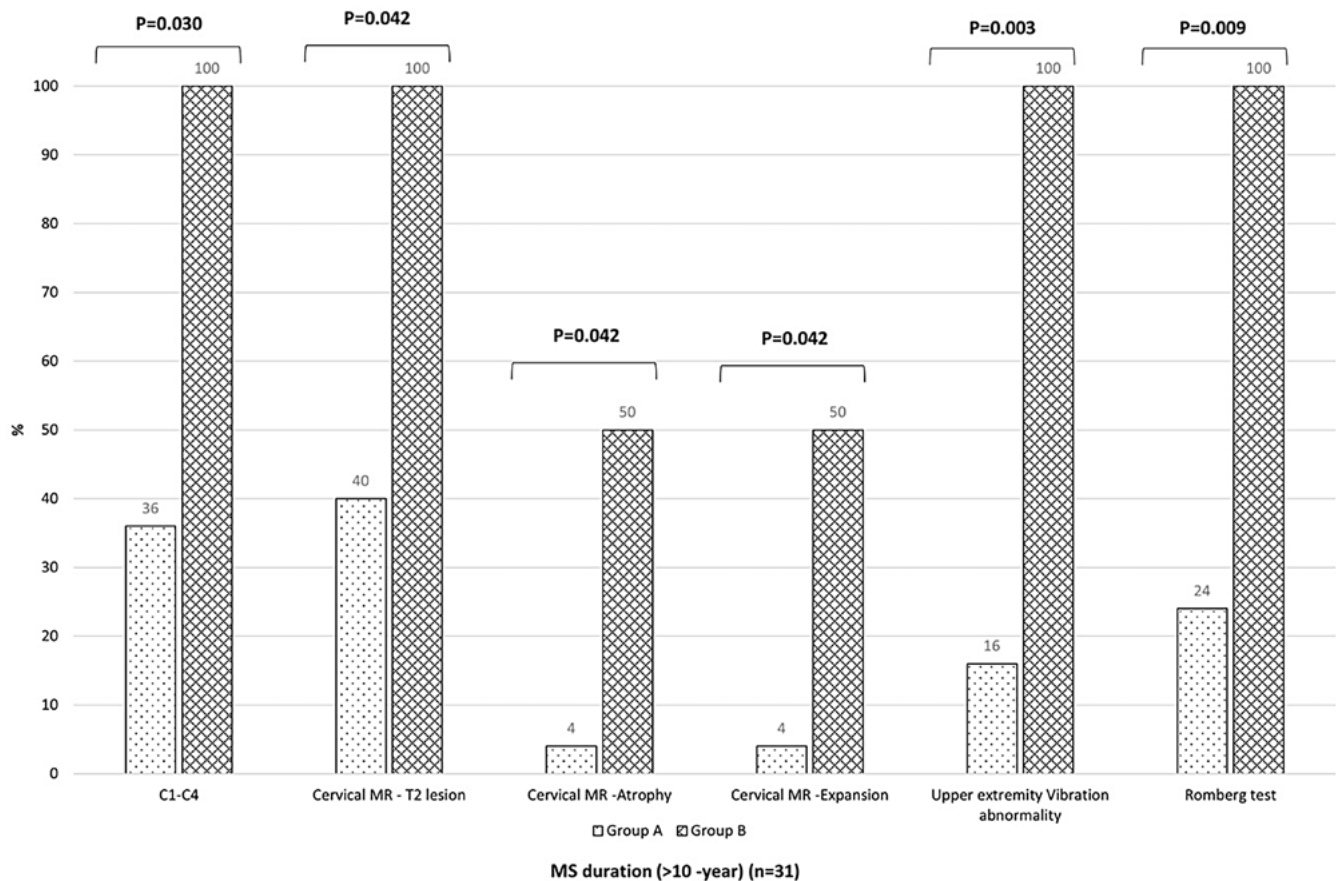
In our study, in the subgroup of patients with a follow-up duration >10 years, the presence of LS in the past was associated with C1–4 and posterolateral spinal lesions, spinal lesions on T2-weighted MRI, atrophy or expansion on MRI, and abnormality of vibration sensation on the upper extremities. An unexpected finding was that there was no correlation between contrast enhancement and the presence of LS. This can be explained by the relatively low number of patients included in the study. In addition, the intricate relationship between LS and spinal cord lesion activity or contrast enhancement reveals that LS does not consistently correlate with contrast enhancement on MRI, thus demonstrating its variable manifestation in MS and other spinal conditions. Romberg positivity was also associated with LS. Given the known mechanism of LS, such findings can be expected. The spine is known to be most mobile in the neck, which may suggest the association of cervical spinal MS lesions with LS. This association was also observed in a previous study.<sup>27</sup> One study did not show any correlation of clinical symptoms with MRI findings.<sup>55</sup> We showed that clinical features were not associated with the presence of LS in the subgroup of those patients

with a follow-up duration <10 years. Hence, localization of spinal lesions was associated with the presence of LS only later in the disease course.

Harmony in brain–body communication is the basis of wellbeing. The interaction between cognitive and behavioral wellbeing and brain and body functioning has become a central area of study for neurologists and neuroscientists in clinical and non-clinical contexts. Brain–body axis dysfunctions occur in many psychiatric and neurological diseases.<sup>56</sup>

Chronic immunological dysregulations in MS may reflect a long-term stress response to homeostatic dysregulation in the CNS, ultimately leading to neurodegeneration. Increasing evidence has shown that similar processes occur in conditions such as ischemic stroke and that inflammation is important in neurodegeneration beyond primary vascular changes.<sup>57</sup>

Glucocorticoid receptors are one of the most important components of the stress response. In neuroscience studies related to fear extinction, evaluation of functional brain regions and connections with functional MRI helps to find the organ underlying fear regulation and the potential therapeutic target by providing valuable information, especially about neuropharmacology, neurotransmitters and protection systems.<sup>58</sup> Integrating these mechanisms with



**Fig. 4.** Detailed comparison of clinical and radiological features among subgroups of multiple sclerosis (MS) patients with a disease duration exceeding 10 years, labeled as group A and B. The analysis encompasses a total of 31 patients. C1–4 lesions were more frequent in group B than in group A ( $p = 0.030$ ). The frequency of the presence of cervical cord lesions on T2-weighted magnetic resonance imaging (MRI), and atrophy and expansion on cervical MRI were higher in group B when compared to those in group A ( $p = 0.042$ ,  $p = 0.042$  and  $p = 0.042$ ; respectively). Vibration abnormality in the upper extremity was found to be significantly more pronounced in group B compared to group A ( $p = 0.003$ ). A significant disparity was noted in the Romberg test, with 100% of group B exhibiting abnormalities compared to 24% in group A ( $p = 0.009$ ).

abnormal oscillatory patterns in electroencephalography (EEG) may provide a better understanding of the disease-initiating processes in POMS.<sup>58</sup>

Both MRI and some electrophysiological and specific laboratory tests are used for early indicators of chronic inflammation.<sup>59,60</sup> Different markers from brain and body functioning can be integrated into these tests to improve diagnostic and prognostic accuracy. An integrative brain–body assessment approach can provide a more comprehensive understanding of neurobiological mechanisms and help guide treatment strategies, such as selecting appropriate medications or implementing targeted interventions for personalized medical approaches. Recent studies have shown that EEG biomarkers such as abnormal oscillatory patterns or decreased connectivity may indicate early signs of cognitive decline, while cardiac measurements may reflect autonomic dysfunction associated with neurodegenerative processes.<sup>61,62</sup> By integrating these measurements with AI-based MRI techniques, it is possible to increase diagnostic accuracy and follow the progression of the disease, facilitating the development of personalized treatment plans.

## Limitations

We investigated POMS and LS in a relatively large population, within a long follow-up period, and revealed the association of clinical and radiological findings with LS. For the first time, the frequency of LS in a POMS sample was investigated. We conducted routine spinal MRI examinations in the whole group, but could not analyze either somatosensorial-evoked potential or visual-evoked potential. In a study reporting a strong relationship between the presence of abnormalities seen on MRI of the cervical spinal cord and the LS in MS, it was stated that the posterior column was particularly affected.<sup>27</sup> In another study, delayed somatosensory evoked potentials (SSEP) conduction was detected in 92% of patients who were identified as having LS.<sup>63</sup> Therefore, we think that SSEP examination can be performed for patients who define LS but do not have a cervical cord lesion, and that the clinical benefit of SSEP can be evaluated with larger patient groups in patients who define LS and have cervical cord abnormalities. Additionally, the absence of data regarding other clinical characteristics, such as the Expanded Disability Status Scale (EDSS),

relapse rate, and time from recent relapse at screening, as well as the history of treatment with disease-modifying therapies, represents another limitation of the study.

## Conclusions

We included a relatively large sample of POMS patients with a long follow-up and found LS in 1/3 of the patients. The presence of LS seems to be associated with cervical spinal lesions, but not with sex or disease pattern. Our study is the first study to analyze the frequency and association of LS with other clinical and radiological findings in a POMS cohort. Studies on early diagnosis and prognosis of MS using multidimensional data with computer-aided diagnosis and DL/ML methods have focused mostly on brain imaging. In order to make AI-based spinal lesion definition in the radiological differentiation of conditions such as MOGAD, NMOSD, ADEM, and CIS with POMS, the characteristics of these lesions must be recognized correctly. We recommend routine spine imaging upon a diagnosis of MS. Further multicenter studies should be conducted to more specifically identify LS in POMS patients. Based on the results of our study, we recommend considering advances in AI and ML to analyze multimodal data for future research directions.

## Supplementary data

The Supplementary materials are available at <https://doi.org/10.5281/zenodo.14188165>. The package includes the following files:

Supplementary Table 1. Normality assumption table.

Supplementary Table 2. Analysis of test statistics of Table 3,4,5.

## Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Consent for publication


Not applicable.


## Use of AI and AI-assisted technologies


Not applicable.


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