

Predictors of Long-Term Disability in Multiple Sclerosis: Up to 10 Years of Follow-up in a Real-World Cohort Study

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ABSTRACT

Introduction: Multiple sclerosis (MS) shows substantial interindividual variability in clinical course, yet early predictors of long-term disability remain incompletely defined. This retrospective cohort study aimed to investigate the impact of demographic characteristics, family history, comorbidities, and initial clinical and radiological features on disability progression over time.

Methods: We retrospectively evaluated MS patients with respect to initial clinical presentation, relapse frequency, baseline magnetic resonance imaging (MRI) characteristics, early radiological progression, and acute relapse treatment. We also examined the association between recovery after the first relapse and long-term disability outcomes, assessed at years 1, 2, 5, and 10.

Results: Of the 346 patients, 69% were female, and the mean age was 43.4±11.0 years. Most patients had relapsing-onset disease (96%). Sensory symptoms and optic neuritis were the most common

presenting symptoms, while motor and cerebellar onset were significantly associated with higher EDSS scores at years 1, 2, and 5. Relapse activity within the first year after diagnosis correlated positively with fifth-year EDSS, whereas relapse frequency prior to diagnosis showed no association with long-term progression. Neither the presence nor the number of contrast-enhancing MRI lesions predicted disability progression.

Conclusions: Early clinical phenotype and early treatment response carry important prognostic information in MS. Motor or cerebellar onset, incomplete early recovery, and persistent relapse activity after diagnosis identify patients at higher risk for disability accumulation. Spinal cord involvement was the only MRI parameter associated with 10-year EDSS.

Keywords: disability, magnetic resonance imaging, multiple sclerosis, relapse, spinal cord

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INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated disease characterized by both inflammatory activity and neurodegenerative processes, ultimately leading to cumulative neurological disability. It remains the most common cause of non-traumatic neurological disability in young adults (1). Although advances in diagnostic criteria and disease-modifying therapies (DMTs) have substantially improved disease control, long-term outcomes remain highly heterogeneous. Some patients maintain minimal disability for decades, whereas others experience rapid progression despite treatment (2). Identifying individuals at higher risk for disability accumulation remains one of the central challenges in MS management (3).

Early clinical and radiological features are believed to carry important prognostic information. Previous studies have examined the impact of initial symptom topography, relapse dynamics, MRI lesion burden, and recovery after early attacks on long-term outcomes (4–6). However, results across cohorts have been inconsistent, and many studies focus on isolated predictors rather than integrating multiple early disease characteristics within a single clinical framework (7,8). Moreover, real-world longitudinal data reflecting contemporary diagnostic and therapeutic practice remain limited.

Highlights

- Motor and cerebellar onset were associated with higher EDSS scores.
- Incomplete recovery after the first relapse increased early disability risk.
- First-year relapse activity correlated with higher 5-year EDSS scores.
- Spinal lesion involvement was the only MRI parameter linked to 10-year EDSS.
- Contrast-enhancing lesions were not associated with disability progression.

In routine care, clinicians must make early therapeutic decisions under uncertainty, often without robust individualized risk-stratification tools. Understanding how readily available clinical and MRI markers relate to

future disability could support more personalized treatment strategies, particularly in identifying patients who may benefit from closer monitoring or earlier escalation to high-efficacy therapy.

The present study aimed to evaluate the relationship between early demographic, clinical, and radiological characteristics and disability progression over long-term follow-up in a large real-world cohort of patients with definite MS. By examining multiple early disease features simultaneously, we sought to identify clinically accessible predictors that may refine early prognostic assessment and inform treatment decision-making.

METHODS

This was a single-center retrospective cohort study. We reviewed medical records of 629 MS patients who presented to our Multiple Sclerosis outpatient clinic after November 2018 and fulfilled the 2017 McDonald diagnostic criteria for definite MS. Patients who discontinued follow-up within the first five years after presentation were excluded to ensure adequate longitudinal assessment. Since some patients had been diagnosed several years before referral, follow-up years were calculated from disease onset, even if they had been diagnosed at another center. The remaining 346 patients were included in the final analysis. Clinical, radiological, and treatment-related variables were extracted from patient files and evaluated in relation to disability progression at years 1, 2, 5, and, when available, year 10 after diagnosis (n=98). Multiple sclerosis diagnosis date was accepted as the baseline date for the 1-, 2-, 5-, and 10-year evaluations. Disability progression was assessed using the Expanded Disability Status Scale (EDSS). Progression was defined as an increase of ≥1.5 points for patients with a baseline EDSS of 0–1, ≥1 points for EDSS 2–5, and ≥0.5 point for EDSS ≥6. ‘Incomplete recovery’ was defined as the persistence of an EDSS score higher than the pre-relapse EDSS for ≥6 months after the relapse. As part of routine clinical care, all patients underwent standardized MS protocol brain and spinal magnetic resonance imaging (MRI) at diagnosis and during annual follow-up visits. The study was approved by the local institutional ethics committee and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program standard concurrent user version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as counts (n), percentages (%), and mean ± standard deviation. Normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed variables, comparisons between groups were performed using the independent-samples t-test; otherwise, the Mann-Whitney U test was applied. Associations between numerical variables were evaluated using Spearman’s correlation coefficient. Questions allowing multiple responses were analyzed using the multiple-response method. The impact of study variables on disability outcomes was examined using linear regression analysis. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 346 patients with definite MS were included in the study. Of these, 239 (69%) were female, and 107 (31%) were male. The mean age was 43.41±10.99 years. Among patients diagnosed prior to presentation at our center, the diagnosis had been established on average 62.73±88.69 months earlier (Table 1). At disease onset, 332 patients (96%) had a relapsing course consistent with relapsing-remitting MS (RRMS), while 14 patients (4%) exhibited a relapsing-progressive course (RPMS). A positive family history of MS was present in 20 patients (5.8%), including

8 patients (40%) with an affected first-degree relative and 12 (60%) with an affected second-degree relative (Table 1).

Comorbid conditions included hypertension in 4.6%, diabetes in 4.0%, coronary artery disease in 0.6%, rheumatologic disease in 1.4%, migraine in 1.4%, thyroid disorders in 3.8%, psoriasis in 0.3%, and familial Mediterranean fever in 0.9% of patients.

Initial presenting symptoms were sensory in 33.2% of patients, followed by optic neuritis (26.9%), brainstem involvement (19.9%), motor symptoms (17.9%), spinal symptoms (15.9%), and cerebellar symptoms (12.7%). Motor and cerebellar onset were significantly associated with higher EDSS scores at years 1, 2, and 5, indicating a negative impact on long-term disability progression (Table 2).

Within the year preceding diagnosis, 79 patients experienced no relapses, 255 had one relapse, 11 had two relapses, and one patient had three relapses. Over the two years preceding diagnosis, 48 patients had no relapses, 268 had one, 26 had two, three patients had three, and one patient had four relapses. During the first year after diagnosis, 261 patients remained relapse-free, while 72 experienced one relapse, 11 had two, and one patient each had three and four relapses. Within the first two years after diagnosis, 220 patients had no relapses, 79 had one, 38 had two, five had three, two had four, one had five, and one had six relapses. At the first attack, 43.1% of patients recovered spontaneously, 53.2% received intravenous methylprednisolone (IVMP), and 3.7% received IVMP combined with plasmapheresis. Following treatment, 74.3% achieved complete recovery, whereas 25.7% had incomplete recovery. The mean EDSS score before initiation of disease-modifying therapy was 1.20±1.52 (median 1, range 0–7). No statistically significant association was observed between relapse frequency in the two years preceding diagnosis or within the first two years after diagnosis and EDSS scores across follow-up. However, the number of relapses occurring during the first year after diagnosis showed a positive correlation with the fifth-year EDSS score. Total relapse number was positively associated with EDSS scores across follow-up years (Table 3). No relationship was found between IVMP treatment versus spontaneous recovery and EDSS progression over time. However, when patients with spontaneous recovery were compared to those treated with IVMP plus plasmapheresis, the risk of first-year EDSS progression was 17.8 times higher in the spontaneously recovered group (Table 4). Baseline MRI

Table 1. Demographic data of study cohort

	n	%
Age $\bar{x}$ mean ± SD M (min-max)	43.41±10.99 43 (17–78)	
Gender		
Female	239	69.0
Male	107	31.0
Disease duration/months $\bar{x}$ mean ± SD	62.73±88.69	
Disease course		
Relapsing	332	96
Progressive	14	4
Familial MS		
Not present	326	94.2
Present	20	5.8
Degree of relative		
1st degree	8	40
2nd degree	12	60

MS: multiple sclerosis.

Table 2. Multivariable linear regression analyses of the association between presenting symptom domains and EDSS scores at years 1, 2, 5, and 10

			95% Confidence interval			
Predictor	Regression coefficient (B)	SE	Lower	Upper	t	p
Model coefficients – 1st year EDSS (n=346)						
Intercept	0.8408	0.198	0.451	1.231	4.238	<0.001
Sensory	0.0132	0.190	-0.361	0.388	0.0692	0.945
Optic neuritis	0.1422	0.206	-0.263	0.548	0.6899	0.491
Motor	0.6289	0.211	0.215	1.043	2.986	0.003
Cerebellar	0.6459	0.236	0.182	1.110	2.737	0.007
Brainstem	0.0483	0.213	-0.371	0.468	0.2265	0.821
Spinal cord	0.1492	0.225	-0.293	0.591	0.6638	0.507
Model coefficients – 2nd year EDSS (n=346)						
Intercept	0.8277	0.200	0.435	1.220	4.146	<0.001
Sensory	-0.0251	0.191	-0.401	0.351	-0.131	0.896
Optic neuritis	0.2344	0.208	-0.174	0.643	1.129	0.260
Motor	0.6785	0.212	0.261	1.096	3.197	0.002
Cerebellar	0.7876	0.238	0.319	1.256	3.309	0.001
Brainstem	0.0860	0.213	-0.334	0.506	0.403	0.687
Spinal cord	0.0516	0.226	-0.394	0.497	0.228	0.820
Model coefficients – 5th year EDSS (n=346)						
Intercept	0.8123	0.227	0.366	1.259	3.578	<0.001
Sensory	-0.20336	0.217	-0.631	0.224	-0.9357	0.350
Optic neuritis	0.01603	0.236	-0.449	0.481	0.0679	0.946
Motor	0.90701	0.241	0.432	1.382	3.759	<0.001
Cerebellar	0.95132	0.271	0.420	1.483	3.510	<0.001
Brainstem	0.18734	0.243	-0.291	0.665	0.7711	0.441
Spinal cord	-0.00402	0.258	-0.511	0.503	-0.0156	0.988
Model coefficients – 10th year EDSS (n=98)						
Intercept	0.8345	0.255	1.499	3.267	3.272	<0.001
Sensory	-0.8076	0.427	-1.652	0.0367	-1.892	0.061
Optic neuritis	-0.6195	0.439	-1.488	0.2490	-1.411	0.161
Motor	0.5688	0.434	-0.291	1.428	1.309	0.193
Cerebellar	0.4242	0.578	-0.719	1.567	0.734	0.464
Brainstem	-0.0592	0.458	-0.965	0.8468	-0.129	0.897
Spinal cord	-0.2733	0.504	-1.270	0.7233	-0.543	0.588

Separate multivariable linear regression models were fitted for EDSS scores at years 1, 2, 5, and 10. All presenting symptom domains were entered simultaneously as dichotomous predictors, coded as present (1) or absent (0), with absence of the corresponding symptom serving as the reference category. B values represent unstandardized regression coefficients and indicate the adjusted mean difference in EDSS score associated with the presence versus absence of each symptom domain, while holding the other presenting symptom domains constant. The intercept represents the predicted EDSS score when all symptom indicators are coded as absent. CI: confidence interval; EDSS: expanded disability status scale; SE: standard error. Bold values indicate statistical significance at $p < 0.05$.

Table 3. The relationship between the number of relapses and EDSS scores by year

		Relapse number during the 1 year before the diagnosis	Relapse number during the 2 years before the diagnosis	Relapse number during the 1 year after the diagnosis	Relapse number during the 2 years after the diagnosis	Total Relapses
1st-year EDSS n=346	Spearman's ρ	0.053	0.076	0.049	0.033	0.205
	p	0.338	0.162	0.371	0.551	<0.001
2nd-year EDSS n=346	Spearman's ρ	0.014	0.045	0.054	0.053	0.213
	p	0.794	0.416	0.326	0.330	<0.001
5th-year EDSS n=346	Spearman's ρ	-0.004	0.039	0.119	0.068	0.235
	p	0.938	0.471	0.030	0.213	<0.001
10th-year EDSS n=98	Spearman's ρ	0.087	0.123	0.082	0.138	0.268
	p	0.313	0.155	0.343	0.112	0.002

Values are presented as Spearman rank correlation coefficients (ρ) with corresponding two-sided p values. Positive coefficients indicate that higher relapse counts are associated with higher EDSS scores. Relapse windows were defined relative to the diagnosis date, and the 1- and 2-year periods were calculated as intervals. Bold values indicate statistical significance at $p < 0.05$.

EDSS: expanded disability status scale.

Table 4. Multivariable multinomial logistic regression analysis of the association between EDSS scores at years 1, 2, 5, and 10 and relapse-management category

Relapse treatment	Predictor	Estimate	95% Confidence interval		SE	z	p	Odds ratio
			Lower	Upper				
IVMP versus spontaneous resolution	Intercept	0.6044	0.0365	1.172	0.290	2.0859	0.037	1.830
	1st year EDSS	-0.3031	-1.436	0.831	0.578	-0.5240	0.600	0.7385
	2nd year EDSS	-0.1629	-1.331	1.006	0.596	-0.2733	0.785	0.8497
	5th year EDSS	0.0342	-0.4887	0.557	0.267	0.1283	0.898	1.0348
	10th year EDSS	-0.0317	-0.3795	0.316	0.177	-0.1785	0.858	0.9688
IVMP plus PLEX - spontaneous resolution	Intercept	-2.768	-4.786	-0.750	1.030	-2.6885	0.007	0.0628
	1st year EDSS	-2.879	-5.610	-0.149	1.393	-2.0668	0.039	0.0561
	2nd year EDSS	1.343	-0.6156	3.302	1.000	1.3441	0.179	3.832
	5th year EDSS	0.3785	-1.272	2.029	0.842	0.4494	0.653	1.460
	10th year EDSS	0.0372	-1.137	1.211	0.599	0.0621	0.951	1.037

A multivariable multinomial logistic regression model was used to evaluate the association between EDSS scores measured at years 1, 2, 5, and 10 and relapse-management category. Spontaneous resolution was specified as the reference category. Model results are presented as regression coefficients (β), standard errors, Wald z statistics, p values, and odds ratios with 95% confidence intervals. (IVMP n: 184, Spontaneous resolution n: 149, IVMP Plus PLEX n: 13)

IVMP: intravenous methylprednisolone; PLEX: plasmapheresis; EDSS: expanded disability status scale.

Table 5. Multivariable linear regression analyses of the association between baseline lesion locations and EDSS scores at years 1, 2, 5, and 10

			95% Confidence interval			
Predictor	Estimate	SE	Lower	Upper	t	p
Model coefficients – 1st year EDSS (n=346)						
Intercept	0.12334	0.446	-0.7556	1.002	0.2762	0.783
Periventricular	-0.00654	0.434	-0.8604	0.847	-0.0151	0.988
Pericallosal	0.80632	0.282	0.2519	1.361	2.8631	0.005
Juxtacortical/Cortical	-0.06773	0.155	-0.3738	0.238	-0.4356	0.663
Brainstem	0.21140	0.170	-0.1241	0.547	1.240	0.216
Cerebellar	0.30771	0.178	-0.0425	0.658	1.729	0.085
Spinal cord	-0.00421	0.152	-0.3034	0.295	-0.0277	0.978
Optic nerve	-0.09707	0.564	-1.2081	1.014	-0.1720	0.864
Model coefficients – 2nd year EDSS (n=346)						
Intercept	0.20847	0.452	-0.6811	1.098	0.4614	0.645
Periventricular	0.06341	0.439	-0.8007	0.928	0.1445	0.885
Pericallosal	0.68096	0.285	0.1200	1.242	2.3900	0.018
Juxtacortical/Cortical	-0.10478	0.158	-0.4168	0.207	-0.6611	0.509
Brainstem	0.70012	0.272	0.1652	1.235	2.574	0.011
Cerebellar	0.27056	0.182	-0.0875	0.629	1.487	0.138
Spinal cord	-0.00536	0.154	-0.3095	0.299	-0.0347	0.972
Optic nerve	-0.23664	0.640	-1.4958	1.023	-0.3700	0.712
Model coefficients – 5th year EDSS (n=346)						
Intercept	0.2179	0.528	-0.8216	1.257	0.4128	0.680
Periventricular	-0.0594	0.513	-1.0693	0.950	-0.1159	0.908
Pericallosal	0.9633	0.333	0.3077	1.619	2.892	0.004
Juxtacortical/Cortical	-0.1043	0.184	-0.4663	0.258	-0.5675	0.571
Brainstem	0.71058	0.285	0.1505	1.271	2.4932	0.013
Cerebellar	0.4337	0.210	0.0196	0.848	2.0618	0.040
Spinal cord	0.4235	0.142	0.1452	0.702	2.9891	0.003
Optic nerve	0.0234	0.667	-1.2902	1.337	0.0351	0.972
Model coefficients – 10th year EDSS (n=98)						
Intercept	1.914	1.871	-1.753	5.581	1.023	0.309
Periventricular	0.726	2.165	-3.5795	5.031	0.335	0.738
Pericallosal	0.955	1.152	-1.3366	3.246	0.828	0.410
Juxtacortical/Cortical	0.231	0.412	-0.5886	1.052	0.561	0.576
Brainstem	0.823	0.433	-0.0378	1.684	1.901	0.061
Cerebellar	0.555	0.442	-0.3243	1.435	1.255	0.213
Spinal cord	0.541	0.183	0.177	0.905	2.954	0.004
Optic nerve	-1.024	1.010	-3.0311	0.984	-1.014	0.314

Separate multivariable linear regression models were performed for EDSS scores at years 1, 2, 5, and 10. Values are presented as unstandardized regression coefficients, standard errors (SE), 95% confidence intervals (CI), t statistics, and p values. Bold values indicate statistical significance at $p < 0.05$. Spinal cord lesions were significantly associated with higher EDSS scores at years 5 and 10. EDSS: expanded disability status scale.

showed periventricular involvement in 96.8% of patients, pericallosal in 91.6%, juxtacortical/cortical in 60.2%, brainstem in 32.6%, cerebellar in 28.1%, spinal in 59.8%, and optic nerve involvement in 1.8%. Contrast-enhancing lesions were present in 27% of patients; 13.1% had one lesion, 6.4% had two, 5.3% had three, and 1.1% each had four or five lesions. At one-year follow-up MRI, lesion progression was observed in 24.5% of patients, while 75.5% showed no new lesions. Among patients with new lesions, involvement was periventricular in 70.5%, pericallosal in 59%, juxtacortical/cortical in 49.1%, brainstem in 26.2%, cerebellar in 21.3%, and spinal in 32.7%; no optic nerve progression was observed. Baseline lesion localization was associated with disability progression as follows: pericallosal lesions were correlated with first-year EDSS; pericallosal and brainstem lesions with second-year EDSS; and pericallosal, brainstem, cerebellar, and spinal lesions with fifth-year EDSS. Spinal lesions were the only MRI parameter associated with tenth-year EDSS progression (Table 5). No significant relationship was found between the presence or number of contrast-enhancing lesions and EDSS progression.

DISCUSSION

In this retrospective cohort of 346 definite MS patients followed for at least five years after first presentation to our center, the demographic profile was broadly consistent with prior cross-sectional reports, including a mean age of 43.4 years and a female predominance (female/male ratio ~2.2), reflecting the established sex distribution of MS (9). The proportion of PPMS in our cohort (~4–5%) was at the lower end of published ranges (approximately 5–15%) (10). While this discrepancy is likely multifactorial, it may relate to changes in diagnostic pathways and phenotypic definitions over time, as well as potential shifts in early disease expression in the era of earlier recognition and DMT use.

Family history of MS was present in 5.8% of our patients, with 40% involving first-degree relatives and 60% involving second-degree relatives. This rate is lower than some prior reports from Türkiye and pooled international estimates (11,12), underscoring the well-recognized heterogeneity in familial MS frequencies across populations. Differences in study design, ascertainment methods, and regional genetic structure may contribute to this variability.

Comorbidities are increasingly recognized as relevant modifiers of MS outcomes, influencing both disease course and treatment choices. Large registry studies have reported substantial comorbidity burdens, often dominated by psychiatric and cardiovascular conditions (13). However, comorbidity patterns vary widely across countries and healthcare settings (14,15). In our cohort, recorded rates of hypertension, diabetes, thyroid disorders, migraine, rheumatologic disease, coronary artery disease, psoriasis, and familial Mediterranean fever were generally lower than those described in several international studies. This may reflect differences in population characteristics, underreporting in retrospective chart reviews, selection related to follow-up continuation, and the study's design. Importantly, some comorbidities may also be influenced by DMT exposure itself—for example, thyroid autoimmunity after alemtuzumab and, to a lesser degree, interferon- β —complicating causal interpretation (16,17). These considerations highlight the need for prospective comorbidity assessment using standardized definitions and appropriate comparator groups (18).

A central observation in our study was the prognostic relevance of initial clinical phenotype. Motor and cerebellar onset were significantly associated with higher EDSS scores at years 1, 2, and 5, indicating an adverse disability trajectory. This finding is consistent with earlier work showing that onset involving efferent systems, multifocal involvement, or sphincter impairment is linked to worse long-term prognosis (19). From a biological and functional perspective, early involvement of motor and

cerebellar pathways may reflect disease activity in eloquent networks with limited compensatory reserve, and EDSS is particularly sensitive to impairments in ambulation and coordination (20). Our results support the view that first-attack topography provides clinically accessible prognostic information and should be considered when planning the intensity of follow-up and the treatment strategy.

Relapse dynamics in the early disease period remain a key topic in prognostic research. Previous studies have suggested that frequent early relapses and shorter inter-attack intervals predict earlier disability and transition to SPMS (21–23). However, the strength of association between lifetime relapse burden and long-term disability has varied (24). In our cohort, relapse counts in the two years prior to diagnosis and within the first two years after diagnosis were not significantly associated with subsequent EDSS scores. In contrast, relapses occurring within the first year after diagnosis correlated positively with fifth-year EDSS, and total relapse number was positively associated with EDSS across follow-up. Taken together, these findings suggest that inflammatory activity persisting despite early treatment may be a more informative marker of future disability than pre-diagnostic relapse history, which may be vulnerable to recall bias and heterogeneity in healthcare access. Clinically, this supports the importance of early disease control and prompt treatment optimization when relapse activity continues after therapy begins.

Acute relapse management and recovery also emerged as clinically meaningful. In our cohort, approximately half of patients received IV methylprednisolone for the first attack, while a smaller subset received IVMP plus plasmapheresis. Overall, IVMP treatment versus spontaneous recovery showed no consistent relationship with EDSS progression across follow-up. However, when spontaneous recovery was compared with IVMP plus plasmapheresis, the risk of first-year EDSS progression was substantially higher in the spontaneous recovery group. Interpretation of this comparison requires caution, given the very small number of patients receiving combination therapy and the likelihood of confounding by indication and baseline severity. Nevertheless, the broader message is clinically intuitive: in severe attacks, escalation to rescue strategies may be justified to maximize recovery and preserve functional reserve.

Consistent with this concept, incomplete recovery after the first attack was associated with a markedly increased risk of subsequent disability progression in our cohort (including a higher risk at year 2). This aligns with prospective and long-term observational studies demonstrating that residual deficit after early attacks predicts poorer outcomes (25–27). Mechanistically, incomplete recovery may reflect greater acute axonal injury, limited remyelination capacity, or reduced central nervous system reserve, potentially accelerating the cascade toward later progression. These findings emphasize the importance of preventing relapses, treating them effectively, and closely monitoring patients who fail to recover fully.

Magnetic resonance imaging characteristics are frequently used to inform prognosis and guide initial DMT selection. Prior literature has consistently linked infratentorial and spinal cord lesions to worse long-term outcomes (28). In our cohort, baseline lesion distribution across periventricular, pericallosal, juxtacortical/cortical, brainstem, cerebellar, spinal, and optic nerve regions was described. Still, neither the presence nor the number of gadolinium-enhancing lesions at baseline predicted disability progression. This is in keeping with evidence suggesting that contrast enhancement primarily reflects transient inflammatory activity and correlates more strongly with recent relapse risk than with long-term disability (29). A plausible clinical explanation in contemporary cohorts is treatment confounding: patients with high inflammatory MRI activity are often escalated to more effective therapies early, potentially attenuating long-term disability differences.

In contrast to enhancement, baseline radiological involvement carried prognostic value. Although one-quarter of patients demonstrated new lesions on annual follow-up MRI, baseline lesion location revealed more pronounced associations with EDSS over time: pericallosal involvement related to early EDSS changes; brainstem, cerebellar, and spinal lesions related to fifth-year disability; and involvement of the spinal cord emerged as the only MRI parameter associated with tenth-year EDSS progression. This pattern is clinically coherent, as spinal cord pathology has a disproportionate impact on motor function and gait, and compensatory capacity is limited. These results reinforce the prognostic importance of lesion topography—particularly spinal and infratentorial involvement—over isolated measures of acute enhancement burden.

Several limitations should be acknowledged. The most important aspect is the retrospective design of the study. Data were derived from chart review, and incomplete or irregular documentation prevented inclusion of additional patients, which may introduce selection bias. Another limitation is the relatively small number of patients within certain treatment subgroups, which restricted our ability to adequately evaluate the differential impact of specific therapies on long-term disability progression. In particular, the effect of initiating second- or third-line high-efficacy therapies as first-line (“naïve”) treatment on 5- and 10-year EDSS outcomes could not be reliably assessed. Despite these limitations, the study has notable strengths. Compared with prior investigations of long-term MS progression, our cohort represents a relatively large and well-characterized patient population. Clinical records and MRI follow-up were performed systematically within a dedicated MS clinic, providing consistent longitudinal data. The observed relationships between initial clinical phenotype, MRI involvement patterns, and long-term disability were broadly concordant with existing literature, reinforcing the external validity of our findings. Importantly, our results offer clinically relevant information that may support early therapeutic decision-making.

As a result patient with multiple sclerosis should be evaluated comprehensively from the time of diagnosis, with particular attention to early clinical and radiological features that signal increased risk of long-term disability. Our findings indicate that motor and cerebellar onset, relapse activity persisting during the early treated phase, incomplete early recovery, and especially spinal radiological involvement are associated with less favorable disability trajectories. Early recognition of these high-risk characteristics may justify closer monitoring and timely escalation of therapy. Integrating such readily available clinical and MRI markers into routine assessment supports a more individualized treatment approach aimed at preventing disability accumulation and improving long-term outcomes in MS.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of İzmir Katip Çelebi University (2023/578).

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Data Availability Statement: The data supporting the findings of this study are not publicly available due to patient privacy, but are available from the corresponding author upon reasonable request.

REFERENCES

- Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. *N Engl J Med*. 2000;343:1430–1438. [\[Crossref\]](#)
- Mrabet S, Garcia EC, Giovannoni G. Prediction of long-term outcome in multiple sclerosis: a systematic review. *Mult Scler Relat Disord*. 2025;103:106667. [\[Crossref\]](#)
- Lublin FD, Häring DA, Ganjgahi H, Ocampo A, Hatami F, Čuklina J, et al. How patients with multiple sclerosis acquire disability. *Brain*. 2022;145:3147–3161. [\[Crossref\]](#)
- De Meo E, Bonacchi R, Moiola L, Colombo B, Sangalli F, Zanetta C, et al. Early predictors of 9-year disability in pediatric multiple sclerosis. *Ann Neurol*. 2021;89:1011–1022. [\[Crossref\]](#)
- Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain*. 2003;126:770–782. [\[Crossref\]](#)
- Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain*. 2010;133:1914–1929. [\[Crossref\]](#)
- Scott TF, Diehl D, Elmalik W, Gettings EJ, Hackett C, Schramke CJ. Multiple sclerosis relapses contribute to long-term disability. *Acta Neurol Scand*. 2019;140:336–341. [\[Crossref\]](#)
- Tiftikcioglu BI, Ilgezdi I, Zorlu Y, Sener U, Tokucoglu F. Long-term disability and progression in spinal onset multiple sclerosis. *Acta Neurol Belg*. 2018;118:217–225. [\[Crossref\]](#)
- Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vécsei L, et al. The epidemiology of multiple sclerosis in Europe. *Eur J Neurol*. 2006;13:700–722. [\[Crossref\]](#)
- Miller DH, Leary SM. Primary-progressive multiple sclerosis. *Lancet Neurol*. 2007;6:903–912. [\[Crossref\]](#)
- Bulut S, Kılıç H, Demir CF. Yukarı Fırat bölgesinde multipl skleroz tanısı ile izlenen hastaların klinik ve demografik özellikleri. *Fırat Tıp Derg*. 2011;16:84–90.
- Harirchian MH, Fatehi F, Sarraf P, Honarvar NM, Bitarafan S. Worldwide prevalence of familial multiple sclerosis: a systematic review and meta-analysis. *Mult Scler Relat Disord*. 2018;20:43–47. [\[Crossref\]](#)
- Magyar M, Sorensen PS. Comorbidity in multiple sclerosis. *Front Neurol*. 2020;11:851. [\[Crossref\]](#)
- Marrie RA, Fisk JD, Fitzgerald K, Kowalec K, Maxwell C, Rotstein D, et al. Etiology, effects and management of comorbidities in multiple sclerosis: recent advances. *Front Immunol*. 2023;14:1197195. [\[Crossref\]](#)
- Marrie RA, Yu BN, Leung S, Elliott L, Caetano P, Warren S, et al.; CIHR Team in Epidemiology and Impact of Comorbidity on Multiple Sclerosis. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. *Mult Scler*. 2012;18:1310–1319. [\[Crossref\]](#)
- Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, et al. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2017;11:CD010968. [\[Crossref\]](#)
- Syed YY. Alemtuzumab: a review in relapsing remitting multiple sclerosis. *Drugs*. 2021;81:157–168. [\[Crossref\]](#)
- Leal Rato M, Santos M, de Sá J, Ferreira J. Comorbid autoimmune disorders in people with multiple sclerosis: a retrospective cohort study. *J Neuroimmunol*. 2023;385:578226. [\[Crossref\]](#)
- Zhang Y, Xu Y, Xu T, Yin H, Zhu Y, Peng B, et al. Prediction of long-term disability in Chinese patients with multiple sclerosis: a prospective cohort study. *Mult Scler Relat Disord*. 2020;46:102461. [\[Crossref\]](#)
- Kalnina J, Trapina I, Sjakste N, Paramonova N. Clinical characteristics and dynamics of disability progression in a cohort of patients with multiple sclerosis in Latvians. *Neurol Sci*. 2024;45:3347–3358. [\[Crossref\]](#)
- Tur C, Carbonell-Mirabent P, Cobo-Calvo Á, Otero-Romero S, Arrambide G, Midaglia L, et al. Association of early progression independent of relapse activity with long-term disability after a first demyelinating event in multiple sclerosis. *JAMA Neurol*. 2023;80:151–160. [\[Crossref\]](#)
- Kuhlmann T, Moccia M, Coetzee T, Cohen JA, Correale J, Graves J, et al.; International Advisory Committee on Clinical Trials in Multiple Sclerosis. Multiple sclerosis progression: time for a new mechanism-driven framework. *Lancet Neurol*. 2023;22:78–88. [\[Crossref\]](#)
- Brieva L, Calles C, Landete L, Oreja-Guevara C. Current challenges in secondary progressive multiple sclerosis: diagnosis, activity detection and treatment. *Front Immunol*. 2025;16:1543649. [\[Crossref\]](#)
- Scalfari A, Neuhaus A, Daumer M, Deluca GC, Muraro PA, Ebers GC. Early relapses, onset of progression, and late outcome in multiple sclerosis. *JAMA Neurol*. 2013;70:214–222. [\[Crossref\]](#)

25. Scott TF, Schramke CJ. Poor recovery after the first two attacks of multiple sclerosis is associated with poor outcome five years later. *J Neurol Sci.* 2010;292:52–56. [\[Crossref\]](#)
26. Sotiropoulos MG, Lokhande H, Healy BC, Polgar-Turcsanyi M, Glanz BI, Bakshi R, et al. Relapse recovery in multiple sclerosis: effect of treatment and contribution to long-term disability. *Mult Scler J Exp Transl Clin.* 2021;7:20552173211015503. [\[Crossref\]](#)
27. Novotna M, Paz Soldán MM, Abou Zeid N, Kale N, Tutuncu M, Crusan DJ, et al. Poor early relapse recovery affects onset of progressive disease course in multiple sclerosis. *Neurology.* 2015;85:722–729. [\[Crossref\]](#)
28. Dekker I, Sombekke MH, Balk LJ, Moraal B, Geurts JJ, Barkhof F, et al. Infratentorial and spinal cord lesions: cumulative predictors of long-term disability? *Mult Scler.* 2020;26:1381–1391. [\[Crossref\]](#)
29. Kappos L, Moeri D, Radue EW, Schoetzau A, Schweikert K, Barkhof F, et al. Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. *Gadolinium MRI Meta-analysis Group. Lancet.* 1999;353:964–969. [\[Crossref\]](#)