

Modeling Disability Progression in Patients With SPMS Shows Non-linearity of EDSS Changes Over Time

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Introduction

- Disability progression is the main clinical outcome used to assess the disease course in SPMS¹
- A better understanding and prediction of disease progression is needed to select the best suited clinical practice for individual patients²
- The EDSS is the commonly used clinical outcome measure to quantify physical disability progression in MS patients¹

Objective

- To describe and model disability progression of patients with SPMS over time
 - We examined EDSS progression using multivariate statistical modeling to better understand the trajectory of disability progression and the contribution of different covariates

Methods

- We used data from the Swedish MS registry, including patients (aged ≥ 18 years) with clinically assigned SPMS at the beginning of the index period (January 01, 2001–November 30, 2019) and a known year of SPMS conversion
 - **Index:** The date of the nearest clinic visit around the year of SPMS conversion
- Disability assessment was based on the EDSS score
- A set of four mixed models for repeated measures of EDSS score change over time was build. In all the models, the random effect was the patient's ID, whereas the fixed effects were the index EDSS score, age and gender. The time since SPMS conversion was fitted both as a categorical (main analysis) and a continuous (sensitivity analysis) parameter to allow non-linear progression
- In two models, interactions between the time and the index EDSS score were included to test the different rates of progression

Results

- Overall, 5780 SPMS patients from the Swedish MS registry were considered for the longitudinal analysis
 - 1885 patients had a clinical visit around the year of conversion (**Table 1, Figure 1**)
- At index, over 40% of patients were not treated with DMTs, while over 30% were treated with subcutaneous or intramuscular DMTs
- Around 80% of patients did not have relapses in the 2 years prior to SPMS conversion
- Mean EDSS at index was 4.3. Mean (median) changes in the EDSS from index to 1, 2, 3, 4- and 5-years post-index were 0.4 (0), 0.6 (0.5), 0.9 (0.5), 1.1 (1.0), and 1.3 (1.0), respectively

Figure 1. Proportion of SPMS patients enrolled into the study over time

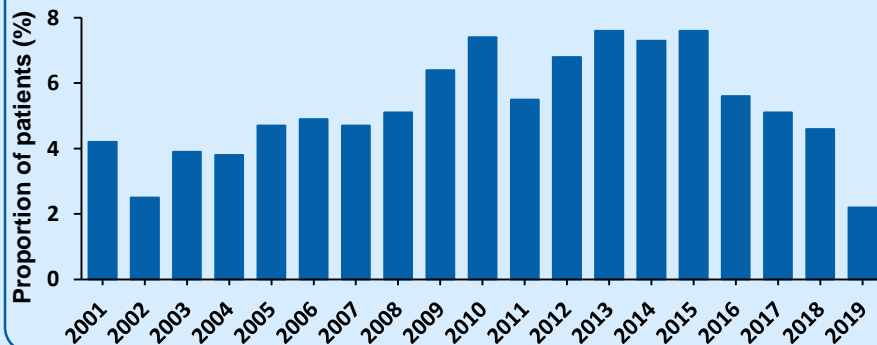


Table 1. Demographic and clinical characteristics

Parameter	N=1885 n (%)
Women	1344 (71.3)
Age at index, mean (SD), y	51.3 (10.1)
Time since MS onset, mean (SD), y	16.2 (9.9)
EDSS score at index, mean (SD)	4.3 (1.8)
Patients with number of relapses in 2 years prior to index	
No relapse	1510 (80.1)
1 relapse	270 (14.3)
2 relapses	65 (3.4)
3 relapses	31 (1.6)
≥4 relapses	9 (0.5)
Patients with DMTs at index	
Subcutaneous/intramuscular	633 (33.6)
Intravenous	342 (18.1)
Oral	82 (4.4)
Other	31 (1.6)
No treatment	797 (42.3)

Data are presented as n (%) unless otherwise specified

Results (Contd.)

- A set of subgroup analyses for EDSS change showed that the trajectory of progression is different when the cohort was split by quartiles of EDSS and age (**Figure 2**)
 - The EDSS change was analyzed in subgroups of patients by quartiles of EDSS (0–2.5; 3–3.5; 4–5.5; 6–9.5) and age (<45 y; 45–<51 y; 51–<58 y and ≥58 y)
- At least 25% of patients did not demonstrate an increase in the EDSS score during the follow-up
- During the analysis of relapses, there was an increase in the proportion of patients without relapses over time despite the continuing disease progression—84.6%, 90.0%, 93.0%, 94.3% and 95.6% at Year 1, 2, 3, 4 and 5 post-index, respectively (**Figure 3**)

Figure 2. Change in the observed EDSS score in subgroups of patients by quartiles of EDSS and age over time

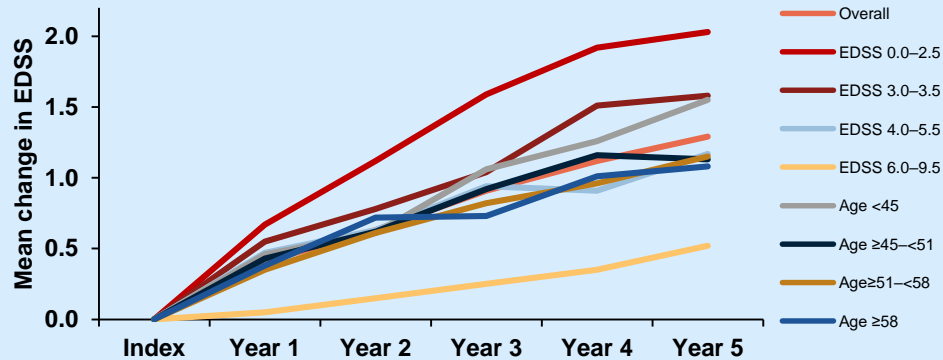
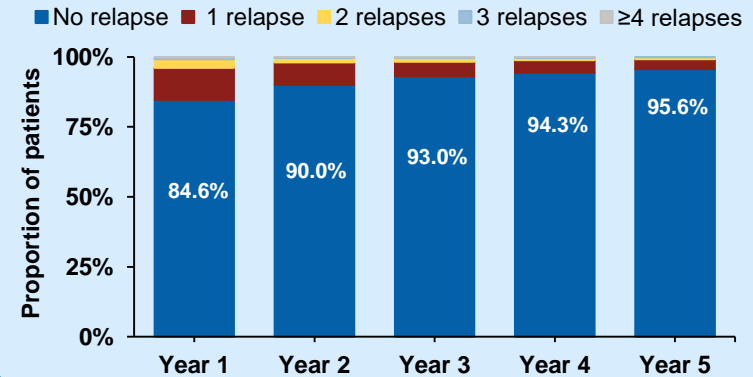


Figure 3. Proportion of patients by number of relapses and year after SPMS conversion



Results (Contd.)

- A lower EDSS score and younger age at the time of SPMS conversion resulted in greater changes in the EDSS score over time
 - Gender did not have a significant effect on the rate of progression
- A significant non-linearity of disability progression over time was observed while fitting the time since SPMS conversion as a categorical variable
- Moreover, adding an interaction term to the models, we found that the rate of progression is different over time and is dependent on the EDSS score at index (**Table 2**)
- Sensitivity analyses using the time since SPMS conversion as a continuous variable generated similar results

Limitations

- This type of model might not fit the nature of the EDSS, which is an ordinal scale with uneven distance between the scores. However, the analysis of residuals showed a sufficient goodness of fit for the models
- Some of the key patient characteristics that could be included in the model were not recorded in the registry. Therefore, they were not included in the models

Table 2. Contribution of various covariates—mixed model results for EDSS progression over time

Covariates	Model 1 with interactions		Model 2 without interactions	
	Estimate	P value	Estimate	P value
Age	-0.0042	0.0093	-0.0038	0.019
Male vs. female	0.018	0.60	0.022	0.54
Index EDSS	-0.00088	0.94	-0.12	<0.00001
Year 1 post-index	0.93	<0.00001	0.33	<0.00001
Year 2 post-index	1.41	<0.00001	0.56	<0.00001
Year 3 post-index	1.98	<0.00001	0.83	<0.00001
Year 4 post-index	2.48	<0.00001	1.01	<0.00001
Index EDSS* Year 1	-0.14	<0.00001	NA	
Index EDSS* Year 2	-0.20	<0.00001	NA	
Index EDSS* Year 3	-0.27	<0.00001	NA	
Index EDSS* Year 4	-0.34	<0.00001	NA	

Conclusion

- Understanding and prediction of disability progression is important for personalized treatment decisions in SPMS
- Our models help understand disability progression in MS and the contribution of different variables such as age and the EDSS scores at SPMS conversion
 - A lower EDSS score at SPMS conversion is associated with a faster progression
 - The progression rate is not linear over time, and the progression appears to be slower with higher EDSS scores and a longer time since SPMS conversion
- Despite the non-linearity of progression, a clear upward trend was observed over time in all subgroups
- The model confirmed clinical observations that as MS continues, disability worsens despite no or few relapses in the later stages
- Although the model performed well at the cohort level, complex approaches using pattern recognition and machine learning techniques may be required for a more precise prediction at the individual level

Disclosures

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