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Comparative-Effectiveness Research/HTA

Multiple Sclerosis Progressive Courses: A Clinical Cohort Long-Term Disability Progression Study

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ABSTRACT

Objectives: Improving the understanding of multiple sclerosis (MS) mechanism and disability progression over time is essential to assess the value of healthcare interventions. Poor or no data on disability progression are available for progressive courses. This study aims to fill this gap.

Methods: An observational cohort study of patients with primary MS (PPMS) and secondary progressive MS (SPMS) was conducted on 2 Italian MS centers disease registries over an observational time of 34 years. Annual transition probabilities among Expanded Disability Status Scale (EDSS) states were estimated using continuous Markov models. A sensitivity analysis was performed in relation to clinical characteristic associated to disability progression.

Results: The study cohort included 758 patients (274 PPMS and 434 SPMS) with a median follow-up of 8.2 years. Annual transition probability matrices of SPMS and PPMS reported different annual probabilities to move within EDSS levels. Excluding EDSS associated to relapse events or patient with relapses, the annual probability of staying stable in an EDSS level increased in both disease courses even not significantly.

Conclusions: This study provides estimates of annual disability progression as EDSS changes for PPMS and SPMS. These estimates could be a useful tool for healthcare decision makers and clinicians to properly assess impact of clinical interventions.

Keywords: annual transition matrix, cohort studies, disability evaluation, Markov models, multiple sclerosis, natural history studies, progressive course.

VALUE HEALTH. 2022; 25(9):1489–1498

Introduction

Multiple sclerosis (MS) is the most prevalent chronic inflammatory disease of central nervous system, affecting > 2.2 million people worldwide.[1-3] It remains the major cause of neurological disability in young adults.[4-6] MS often leads to significant accumulated disability, which is associated to worse clinical status and to higher economic burden.[3,7]

MS is classified into relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS).[8] In the past 2 decades, multiple therapeutic options for RRMS have become available, and consequently, main research activities have focused on this form.[4,9-11] Only in the last years, clinical trials on therapies aimed at affecting long-term progression of PPMS and SPMS became available,[12,13] opening a new era of proactive approach for the treatment of progressive courses.[11] This new therapeutic scenario highlights the need of improving the understanding of disease mechanism and disability progression over time for progressive courses.[11,14]

Researchers and health national agencies used the Expanded Disability Status Scale (EDSS) to evaluate disability progression over time, which is a basic point in the evaluations of the impact of healthcare interventions. There is still a debate on the selection of the best cohort and the best methods to produce reliable estimates to use as reference.[14-16] Poor or no data are available to define EDSS progression over time in progressive MS courses.

The main aim of this study was to fill this important gap, assessing disability progression in patients with SPMS and PPMS and providing reliable baseline transition probability among EDSS levels for assessing healthcare interventions impact in the progressive courses of the disease.

Methods

Data Source

In this study, we selected patients from the disease registries of 2 Italian MS centers: the center of Brescia in the north of Italy, which covers an area of approximately 1.2 million inhabitants, and the center of Catania in the south of Italy, which covers an area with approximately 1.1 million inhabitants. Both centers are active since the 1980 and they are the referral centers for adult and

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pediatric patients with MS. Both disease databases collect information about demographic and clinical data for patients at each visit.[17,18] Patients' informed consent for MS Registry and future research was obtained at first visit at MS centers.

Study Design and Selection Criteria

We conducted an observational cohort study of patients with a diagnosis of PPMS or SPMS. Diagnosis was based on the definition of MS clinical course reported in Lublin in 1996 and updated in 2014.[8,19] Patients with a progressive course and EDSS between 3.0 and 7.0 were included in the cohort.[12,13] Patients were followed from the first visit with EDSS 3.0 to 7.0 (study entry) to last visit registered in the databases or to February 2018. Patients with only one visit available were excluded. Year of study entry ranges from 1983 to 2017.

Data and Outcome Definition

Demographic and clinical data were extracted from the 2 MS centers databases. Demographic data included year of study entry, age at study entry, and sex. Date of progressive course diagnosis, disease course, visit dates, and EDSS collected at each visit were included too. For the analysis, EDSS fractional values were rounded down (ie, EDSS 3.5 was scored as 3.0) following the approach used in the Palace et al[15] study for RRMS course.

Other parameters included were relapses and use and type of disease-modifying treatment (DMT) during the observational period. Relapse was defined as neurologic deficit associated with acute inflammatory demyelinating event that lasts at least 24 hours in the absence of fever and infection. Moreover, we used magnetic resonance imaging data to identify patients with disease activity (DA). DA was identified as an increased number or volume of T1 gadolinium-enhancing or T2 lesions, as defined in previous studies.[8,12,13] Rates of relapse and DA were reported per 1 person-year.

The main outcome of the study was disability progression as annual disease transition among EDSS states. Disease progression was also analyzed as progression to the hard endpoints of requiring aids for walking (EDSS 6)[17,20] or development of inability to walk (EDSS 7) that is generally used as a stopping rule for DMTs.[5,6,10] A patient progressed to EDSS 6 when he reached an EDSS $\geq$ 6, and the progression was confirmed after 24 weeks. The same definition was used for progression to EDSS 7. Mortality was analyzed too.

Statistical Analysis

We first describe patients' characteristics and disability progression by disease course. Categorical variables were reported as percentages, and differences between groups were tested using chi-squared test. Continuous variables with normal distribution were reported as mean $\pm$ SD, whereas non-normal continuous variables as median and quartiles (Q_1-Q_3). Two-tailed t test was used to compare means for normal-distributed variables whereas 2-tailed Wilcoxon Mann-Whitney test was used otherwise. Mortality was analyzed using Kaplan-Meir curves, and log-rank test was used to test difference between MS courses. Cumulative incidence functions for progression to EDSS 6 and 7 were computed considering death as a competing risk for the whole cohort and separately by EDSS level at study entry. Gray's test was used to test differences between MS courses.

In the main part of the analysis, we evaluated annual disability progression, estimating EDSS annual transition probabilities for patients with PPMS and SPMS, separately. We define an EDSS transition as change of at least 1.0 point, to account for both increases and decreases of EDSS state. We used a multistate Markov model that is suitable for longitudinal data and assumes time homogeneity, which means that future evolution only depends on the current state.[21] We used a 7 state Markov model, from EDSS 3 to 9, without any constraints on acceptable transitions within states. Transition probabilities and relative 95% confidence intervals (CIs) are reported. CIs were computed by repeated sampling from the asymptotic normal distribution of the maximum likelihood estimates of the log of the transitions intensities.[21] We tested goodness of fit of the Markov models comparing observed and expected prevalence of EDSS states by time.

We also did a sensitivity analysis calculating transition probabilities matrix for cohort subgroups identified by factors significantly associated to disability progression (reaching EDSS 6 and 7). These factors were selected using Cox proportion hazard regression models, and the details of the analyses are presented in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.03.010.

The study significance level was .05. Statistical analyses were conducted in SAS 9.4 and R 3.6.2. We used the "msm package" of R software to implement multistate Markov models. Data are available upon approval from the respective register holders.

Results

Patients' Characteristics and Outcome Descriptions

From a cohort of 1013 patients with a progressive course diagnosis, we excluded 29 patients for missing data on the diagnosis date, 107 patients for EDSS status not in the selected range, and 119 patients because data for only 1 visit were available. The final study cohort included 758 patients of which 274 (36%) with PPMS and 484 (64%) with SPMS (Table 1). Males accounted for 45% of the cohort; mean age at study entry was 49 years for PPMS and 46 years for SPMS. Median EDSS level at study entry was 5 for both courses, but we observed significantly different EDSS level distributions between groups.

We observed patients for a median follow-up of approximately 8 years (Table 1). The median (Q_1-Q_3) number of visit with EDSS was 11 (5-21) with a median (Q_1-Q_3) lag time between visit of 7.1 (5.7-9.2) months. In PPMS group, 24% of patients had at least one relapse, 41% had DA and 52% had relapses or DA during the observation period. For SPMS group, the quote of patients with relapses (44%) or DA (50%) was higher than in the PPMS group, with 62% having relapses or DA. Relapse rate was 0.05 (95% CI 0.04-0.06) per person-year for patients with PPMS and 0.11 (0.10-0.12) for patients with SPMS, with statistically significant difference between groups. Rates of DA and magnetic resonance imaging frequency were similar between courses (Table 1). Moreover, 32% of patients with PPMS and 46% of patients with SPMS were treated at least once with DMTs during follow-up.

Almost all patients achieved EDSS 6 during follow-up (Fig. 1). Progression to EDSS 6 was faster in patients with SPMS (Gray's test, $P < .001$); at 10 years from study entry, the probability of reaching EDSS 6 was 82% for SPMS and 67% for PPMS (Fig. 1A). When stratifying the population by the EDSS at study entry (Fig. 1B-D), patients with SPMS still had a higher probability of achieving EDSS 6 only for patients enrolled in the study with an EDSS equal to 3 (Fig. 1B).

No statistically significant difference was detected in the probability of achieving EDSS 7 by disease course (Fig. 2A). The same features were observed when stratifying by EDSS level at study entry (Fig. 2B-E). Probability of achieving EDSS 7 was 40% for PPMS and 43% for SPMS at 10 years.

Table 1. Population characteristics.

Characteristic	PPMS (n = 274)	SPMS (n = 484)	All (N = 758)
Male, n (%)	129 (47.1)	213 (44.2)	342 (45.2)
Age at study entry (years)			
Mean ± SD*	49.0 ± 10.7	45.9 ± 10.1	47.0 ± 10.4
Median (Q_1-Q_3)*	50 (41-56)	45 (38-53)	47 (39-54)
EDSS at study entry, n (%)*			
3	91 (33.2)	76 (15.7)	167 (22.0)
4	40 (14.6)	92 (19.0)	132 (17.4)
5	29 (10.6)	82 (16.9)	111 (14.6)
6	85 (31.0)	181 (37.4)	266 (35.1)
7	29 (10.6)	53 (11.0)	82 (10.8)
Median (Q_1-Q_3)*	5 (3-6)	5 (4-6)	5 (4-6)
Pts with relapse before study entry, n (%)*	26 (9.49)	219 (45.25)	245 (32.32)
Pts with DMT before study entry, n (%)*	27 (9.85)	191 (39.46)	218 (28.76)
Follow-up time (years), median (Q_1-Q_3)	7.4 (2.9-12.9)	8.4 (4.1-14.1)	8.20 (3.6-13.7)
No. of visits with EDSS			
Mean ± SD*	12.8 ± 10.3	15.5 ± 13.1	14.5 ± 12.2
Median (Q1-Q3)*	9 (4-19)	12 (6-23)	11 (5-21)
Lag time between EDSS visits (months)			
Mean ± SD*	9.8 ± 11.0	9.4 ± 9.8	9.5 ± 10.2
Median (Q1-Q3)*	7.2 (5.9-9.2)	7.0 (5.6-9.2)	7.1 (5.7-9.2)
Pts with relapse, n (%)*	66 (24.1)	212 (43.8)	278 (36.7)
Pts with DA, n (%)*	112 (40.9)	244 (50.4)	356 (47.0)
Pts with DA or relapse, n (%)*	142 (51.8)	324 (66.9)	466 (61.5)
Relapse rate (95% CI)†	0.05 (0.04-0.06)	0.11 (0.10-0.12)	0.09 (0.08-0.10)
DA rate (95% CI)†	0.13 (0.11-0.14)	0.13 (0.12-0.14)	0.13 (0.12-0.14)
Pts with DMT, n (%)*	87 (31.8)	224 (46.3)	311 (41.0)
DMT type, n (%)*			
None	187 (68.3)	260 (53.7)	447 (59.0)
Interferon β 1a	13 (4.7)	39 (8.1)	52 (6.9)
Interferon β 1b	20 (7.3)	75 (15.5)	95 (12.5)
Teriflunomide	0 (0.0)	4 (0.8)	4 (0.5)
Fingolimod	8 (2.9)	8 (1.7)	16 (2.1)
Glatiramer	24 (8.8)	21 (4.3)	45 (5.9)
Dimetilfumarato	0 (0.0)	1 (0.1)	1 (0.1)
Cladribine	0 (0.0)	1 (0.1)	1 (0.1)
Natalizumab	2 (0.7)	9 (1.9)	11 (1.5)
> 1	20 (7.3)	66 (13.7)	86 (11.4)
Deaths, n (%)	27 (9.9)	55 (11.4)	82 (10.8)

Note. All events (relapse, DA, DMT) were observed during follow-up time.
CI indicates confidence interval; DA, disease activity; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; Pts, patients; Q, quartile; SPMS, secondary progressive multiple sclerosis.
*$P < .05$ PPM versus SPMS.
†Rates per person-year.

Mortality was similar between disease courses (Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.03.010), and approximately 11% of patients died during a median follow-up of 8 years.

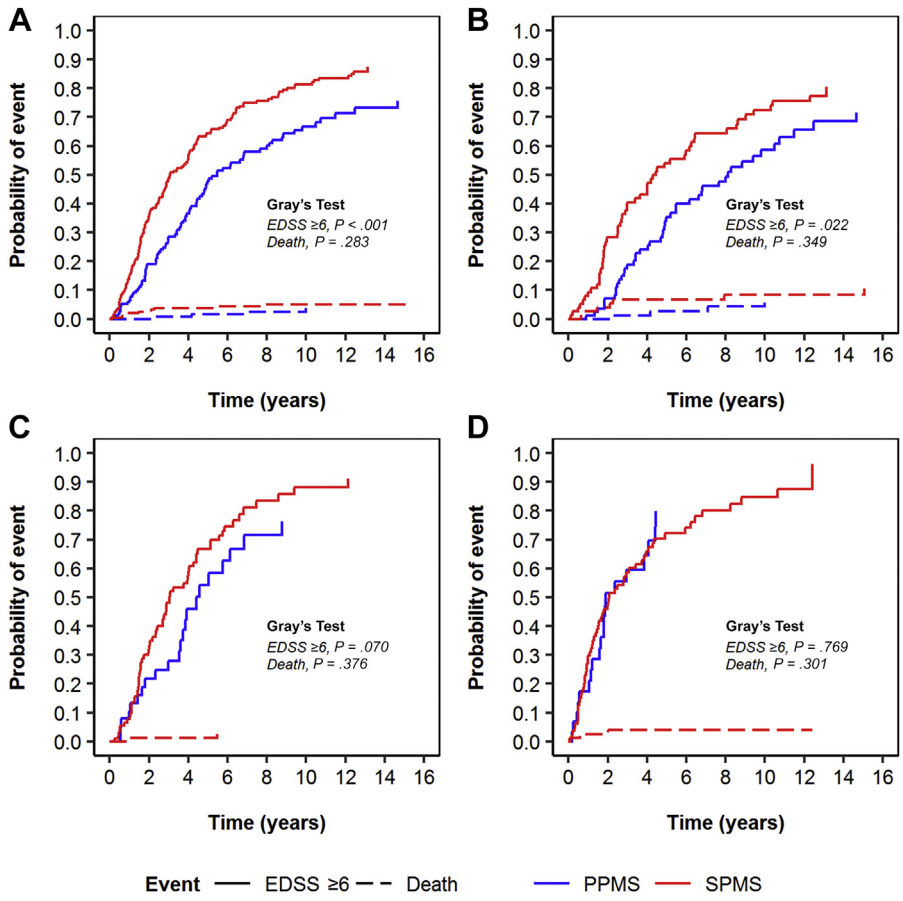
Annual Transition Probabilities Matrix

Annual transition probabilities (95% CI) among EDSS levels are presented in Table 2, as 2 separated matrices: one for PPMS and one for SPMS. Transition probabilities on the matrix diagonal are the annual probabilities of staying stable in an EDSS level. These probabilities are significantly lower in the SPMS groups than in the PPMS for EDSS level 3 and 4 and lower or similar for upper EDSS levels, except for EDSS 9 where the probability is higher even if the differences are not statistically significant. The annual probabilities of decreasing EDSS level of > 2 points are low, sometimes near to 0. Goodness of fit of the 2 models was good comparing expected and observed frequency of EDSS level in time (Appendix Figs. 2 and 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.03.010).

Annual Transition Probabilities Matrix: Sensitivity Analysis

Specific subgroup annual transition probability was estimated based on the factors affecting disability progression (reaching EDSS 6 and 7) in Cox proportion hazard regression models performed separately for PPMS and SPMS. In patients with PPMS, EDSS at study entry and relapse rate were positively associated to disability progression (Appendix Table 1 in Supplemental

Figure 1. Cumulative incidence functions for disability progression to EDSS 6 and death by disease course accounting for competing risks. (A) All patients. (B) Patients with EDSS 3 at study entry. (C) Patients with EDSS 4 at study entry. (D) Patients with EDSS 5 at study entry.



EDSS indicates Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Materials found at https://doi.org/10.1016/j.jval.2022.03.010). Factors influencing disability progression in patients with SPMS were EDSS at study entry, relapse rate, and use of DMTs (Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.03.010).

Transition matrices were estimated for subgroups of patients with PPMS and SPMS based on abovementioned factors and are graphically presented in Figures 3 and 4. More details on point estimate and 95% CIs for each specific subgroups transition matrix are presented in Appendix Tables 3 and 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.03.010. As shown in Figures 4 and 5, each subgroup presents different transition probability between EDSS states. When we exclude relapses or a patient with relapse, the annual probability of staying stable in an EDSS level increased in both disease courses even not significantly. In the SPMS group, the probability of staying stable slightly increased also in patients using DMTs.

Discussion

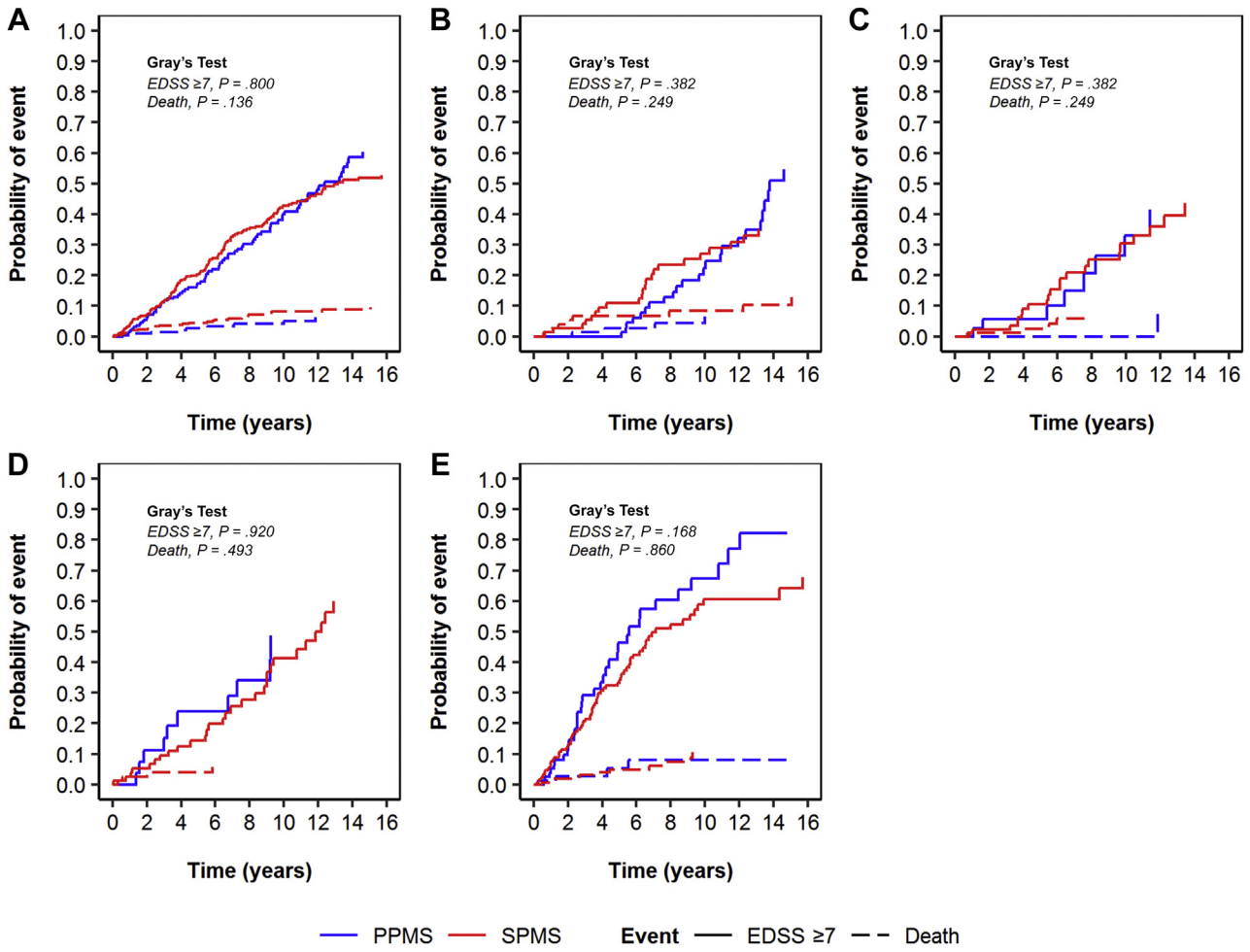
Defining disability progression within each MS course is a fundamental step to assess the impact of MS treatments and interventions. These data have been deeply studied and well defined for RRMS course.[15,16,20,22] Otherwise, assessment of PPMS and SPMS disability progression was less comprehensive and exhaustive.

Results of our study showed differences in disability progression to EDSS 6 between SPMS and PPMS courses, with SPMS reporting a faster progression. No differences were detected assessing progression to EDSS 7 and mortality. This is in line with the study by Cottrel et al[23] that reported comparable survival curves for the progression to EDSS 8 and death from disease onset. Our and Cottrell et al[23] results suggest a possible different progression in lower disability levels (EDSS 3-4) compared with more advance ones (eg, EDSS 5), which needs further investigation. In our study, disability progression to hard endpoints was confirmed at 24 weeks because it was largely recognized in clinician practice and scientific literature and also suggested by national health technology assessment agencies such as the National Institute for Health and Care Excellence.[12-14]

Based on the different course of PPMS and SPMS, we have defined the specific annual disability progression, providing for the first time a robust estimation of EDSS annual transition probabilities for progressive courses. This is an important result, reporting crucial reference information for assessing the effect of new DMTs and interventions on disability progression of PPMS and SPMS, as done in all economic evaluation of DMTs for RRMS.[9]

Some researchers have attempted to assess probabilities of reaching specific disability level over time in progressive

Figure 2. Cumulative incidence functions for disability progression to EDSS 6 and death by disease course accounting for competing risks. (A) All patients. (B) Patients with EDSS 3 at study entry. (C) Patients with EDSS 4 at study entry. (D) Patients with EDSS 5 at study entry. (E) Patients with EDSS 6 at study entry.



EDSS indicates Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

forms.[24-28] Nevertheless, no estimation of transition probabilities from each EDSS level was available so far in the literature, raising many concerns of the cost-effectiveness/value assessment of new DMTs, as reported by the National Institute for Health and Care Excellence for ocrelizumab assessment in patients with PPMS.[14]

The annual transition matrices obtained with our analyses give estimates of disability evolution from each EDSS level to the other EDSS levels, in patients with PPMS and SPMS. For example, based on our matrix, the annual probability of staying in EDSS level 3 was 76% in the PPMS group and 57% in the SPMS group. In the upper part of the matrix (above the diagonal), reporting annual probabilities of disability progression, the probability of moving from EDSS level 3 to 4 was 13% for primary course and 19% for secondary course. In the lower part of the matrix (under the diagonal), reporting annual probabilities of disability regression, the annual probabilities of moving from EDSS level 4 to 3 were 8% for both courses. The possibility to move to a lower EDSS level is another interesting result of our analyses, showing for the first time that PPMS and SPMS courses have the possibility of EDSS level decrease, as already shown for RRMS.[15,16] This is confirmed by the analysis on only patients without relapses.

The reliability of our transition matrix was assessed and validated comparing observed and expected prevalence of EDSS states by time. Furthermore, we performed a sensitivity analysis estimating transition matrices for patients subgroups defined by presence of relapses and use of DMTs, which were the main factors associated to disability progression in the multivariate Cox analysis. In our study, we also estimated transition matrices excluding the EDSS reported during the relapse to adjust for the relapse impact on the EDSS level variations. We think that these data could be a useful tool for assessment of clinical intervention and therapies in progressive MS courses subpopulations providing specific reference of EDSS progression probability data.

The supplementary Cox analysis of factors influencing disability progression revealed an association between relapse rate and disability progression, which is in contrast with findings of previous studies performed on London Ontario Database and Lyon MS Database between 1998 and 2006.[23-28] In these studies, relapses and relapse rate did not affect long-term outcomes of PPMS and SPMS.[23,26,27] Nevertheless, our results have the advantages to refer to a more updated cohort of patients (up to 2017) that cover a time period of 34 years.

Cox analysis also showed an association between DMTs use during the observational period and reduced disability progression in SPMS, even adjusting for confounding factors. Among the DMTs used in our cohort, only interferon beta-1b was approved in

Table 2. Annual transition matrices of EDSS state by disease course.

PPMS							
From EDSS	To EDSS						
	3	4	5	6	7	8	9
3	0.7625	0.1277	0.0410	0.0494	0.0094	0.0099	0.0002
	(0.6965-0.8019)	(0.0928-0.1706)	(0.0250-0.0765)	(0.0327-0.0831)	(0.0048-0.0361)	(0.0039-0.0316)	(0.0001-0.0007)
4	0.0755	0.6932	0.1147	0.1037	0.0080	0.0047	0.0001
	(0.0497-0.1102)	(0.6286-0.7393)	(0.0809-0.1562)	(0.0755-0.1486)	(0.0058-0.0129)	(0.0020-0.0270)	(0.0000-0.0009)
5	0.0347	0.0633	0.5697	0.2943	0.0318	0.0058	0.0003
	(0.0189-0.0640)	(0.0386-0.1045)	(0.4901-0.6309)	(0.2355-0.3556)	(0.0224-0.0633)	(0.0041-0.0103)	(0.0001-0.0024)
6	0.0020	0.0074	0.0248	0.8256	0.1113	0.0273	0.0015
	(0.0009-0.0121)	(0.0039-0.0163)	(0.0164-0.0377)	(0.7905-0.8471)	(0.0918-0.1366)	(0.0191-0.0416)	(0.0004-0.0123)
7	0.0001	0.0004	0.0015	0.0786	0.7791	0.1383	0.0021
	(0.0000-0.0006)	(0.0002-0.0009)	(0.0009-0.0031)	(0.0546-0.1114)	(0.7284-0.8181)	(0.1053-0.1801)	(0.0010-0.0044)
8	0.0001	0.0002	0.0031	0.0063	0.0422	0.9222	0.0260
	(0.0000-0.0006)	(0.0000-0.0010)	(0.0006-0.0180)	(0.0028-0.0364)	(0.0232-0.0730)	(0.8689-0.9442)	(0.0130-0.0525)
9	0.0000	0.0000	0.0002	0.0004	0.0028	0.1199	0.8766
	(0.0000-0.0000)	(0.0000-0.0001)	(0.0000-0.0021)	(0.0001-0.0033)	(0.0006-0.0125)	(0.0281-0.4285)	(0.5575-0.9711)

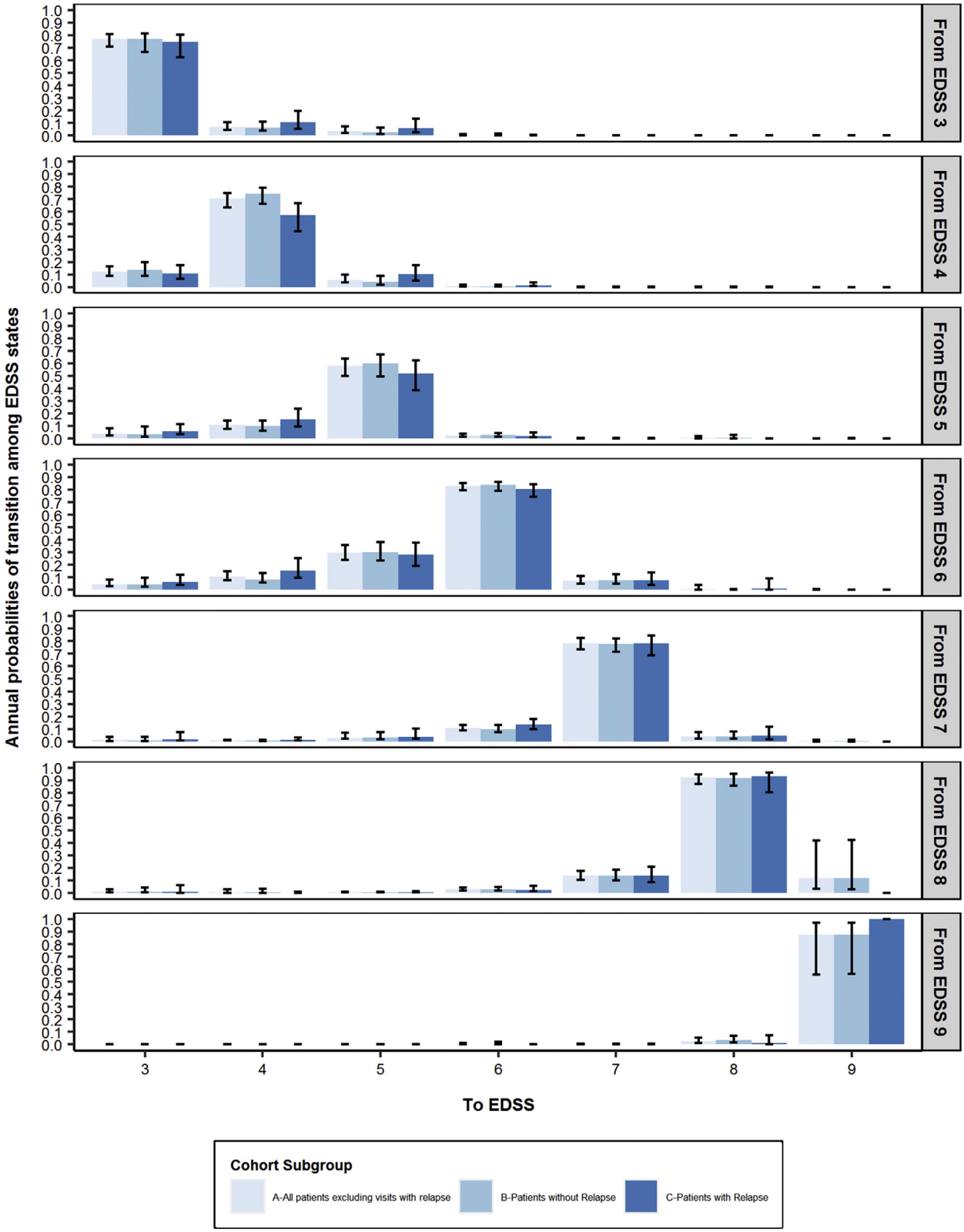
SPMS							
From EDSS	To EDSS						
	3	4	5	6	7	8	9
3	0.5648	0.1865	0.0881	0.1380	0.0141	0.0082	0.0003
	(0.4784-0.6185)	(0.1375-0.2412)	(0.0628-0.1363)	(0.1045-0.1915)	(0.0093-0.0562)	(0.0036-0.0357)	(0.0002-0.0010)
4	0.0754	0.5608	0.1584	0.1801	0.0195	0.0055	0.0003
	(0.0547-0.1023)	(0.5041-0.6021)	(0.1276-0.1960)	(0.1508-0.2204)	(0.0143-0.0370)	(0.0036-0.0245)	(0.0002-0.0008)
5	0.0340	0.0733	0.5122	0.3365	0.0346	0.0088	0.0006
	(0.0223-0.0535)	(0.0529-0.1002)	(0.4618-0.5562)	(0.2949-0.3771)	(0.0257-0.0525)	(0.0059-0.0236)	(0.0003-0.0014)
6	0.0063	0.0117	0.0434	0.8336	0.0829	0.0201	0.0020
	(0.0042-0.0110)	(0.0087-0.0177)	(0.0356-0.0538)	(0.8128-0.8474)	(0.0720-0.0953)	(0.0160-0.0271)	(0.0010-0.0055)
7	0.0016	0.0021	0.0072	0.0841	0.7277	0.1661	0.0112
	(0.0007-0.0194)	(0.0012-0.0281)	(0.0041-0.0207)	(0.0645-0.1104)	(0.6729-0.7555)	(0.1365-0.1990)	(0.0059-0.0240)
8	0.0013	0.0014	0.0005	0.0065	0.0393	0.9245	0.0265
	(0.0003-0.0116)	(0.0004-0.0103)	(0.0003-0.0019)	(0.0037-0.0167)	(0.0271-0.0565)	(0.8939-0.9392)	(0.0174-0.0422)
9	0.0001	0.0001	0.0000	0.0003	0.0018	0.0811	0.9167
	(0.0000-0.0005)	(0.0000-0.0006)	(0.0000-0.0001)	(0.0001-0.0009)	(0.0008-0.0042)	(0.0389-0.1793)	(0.8151-0.9599)

Note. p (95% CI).
CI indicates confidence interval (shaded lines); EDSS, Expanded Disability Status Scale; p, probability; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Italy. Nevertheless, based on published trials, interferon beta-1b does not affect disability progression.[29-31] The other DMTs used (empirically and with no specific and approved indication) have not shown efficacy in reducing the disability progression in clinical trials too. Based on this evidence, we cannot assume a protective role of DMTs on disability progression in patients with SPMS, suggesting a possible bias in patients keeping DMTs. Maybe, patients with a lower progression disability were selected to keep on DMTs. Nevertheless, further investigations on DMTs relapse frequency reduction and disability progression are needed.

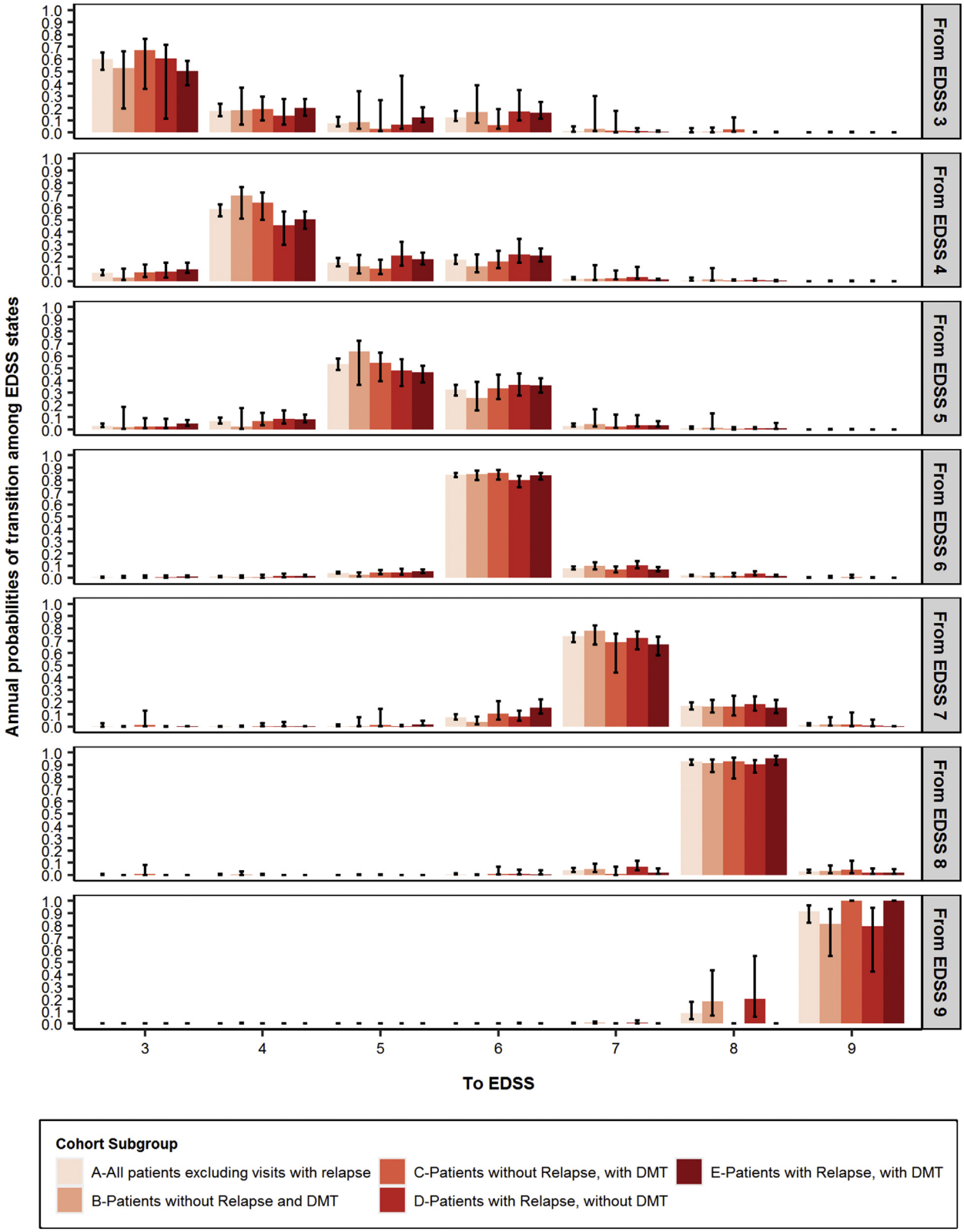
Our study presents some strengths. First, the use of MS disease registries allowed us access to original, "real-time" disability (EDSS) assessments recorded by MS specialist neurologists after a face-to-face consultation with patients and objective evaluation of functional scales.[17,18] Moreover, the availability of individual patient-level gave us the chance to apply the most appropriate approaches reported in literature to estimate disability progression probabilities.[15,16] We applied continuous Markov models which maximize data usage, including all valid disability assessments, regardless of their exact timing. This model allows to include clinically relevant patient-level data to identify the most accurate predictive model for PPMS and SPMS as performed in the RRMS studies.[15,16] The importance of this type of data set has already been shown in the study by Palace et al.[15]

Figure 3. Primary progressive multiple sclerosis. Annual transition matrices of EDSS state by subgroups. Annual transition probabilities and 95% CI.



CI indicates confidence interval; EDSS, Expanded Disability Status Scale.

Figure 4. Secondary progressive multiple sclerosis. Annual transition matrices of EDSS state by subgroups. Annual transition probabilities and 95% CI.



CI indicates confidence interval; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale.

Our study also presents some limitations. First, we used historical cohorts with data collected between 1983 and 2017. Different era of MS management (diagnostic instruments, supportive care, etc) included in our study could unbalance estimates of disability progression in comparison with what we could observe in a more recent cohort. Nevertheless, the disease duration and the time required to collect data for assessing the disability progression make our analyses the best approach for assessing the progression in MS courses. Our cohort is representative of 2 Italian provinces and can differ from MS populations in other countries; nevertheless, Italian guidelines for treatment of MS in Italy follow the European guidelines and the products available has been the same between main European countries and main market worldwide. Furthermore, as reported by Ghezzi et al,[32] European and American guidelines offer a similar view and similar recommendations for the most relevant and common questions of clinical practice, so results may be generalized in other countries. Different ways of EDSS assessment within the centers could have different time intervals between visits. Nevertheless, the use of continuous Markov models overtakes the issue related to time between visits. Some patients received DMTs during the observational period. Transition probabilities may be affected by treatment approaches and relapses, but we were able to estimate matrices also for cohort subgroups affected or not by treatment or relapses. Furthermore, stopping the observational time in 2017 has also excluded the risk of including patients with PPMS treated with ocrelizumab. Finally, mortality is not considered in the multistate model following the approach of a previous similar study.[15] Mortality is usually not included in the transition matrix of MS Markov model but it is included in health-economic models as independent probability estimated as relative risk based on age, sex, and EDSS applied to the general population mortality.[9,16,33]

Conclusions

This is the first study that provides a detailed assessment of disability progression of patients with PPMS and SPMS. In our study, we observed a different progression between PPMS and SPMS courses highlighting the impact of relapse rate in both courses. Furthermore, we estimated EDSS transition matrices providing essential data to estimate the long-term outcome and value of DMTs and healthcare intervention in PPMS and SPMS. These data are fundamental to help healthcare decision makers and health technology assessment national agencies in assessing new treatment options that are available or are approaching the market for the progressive course of MS.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.03.010.

Article and Author Information

Accepted for Publication: March 13, 2022

Published Online: April 25, 2022

doi: https://doi.org/10.1016/j.jval.2022.03.010

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Conflict of Interest Disclosures: Dr Cortesi reported receiving grants from Baxalta, now part of Shire, and reported receiving personal fees from Pfizer and Roche outside the submitted work. Dr Capra reported receiving personal fees from Novartis, Biogen, Roche, Celgene, and Merck outside the submitted work. Dr Patti reported receiving personal fees from Adienne, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, and Teva outside the submitted work. Mr Mantovani reported receiving grants from Biogen, Almirall, Roche, and Bayer and personal fees from Almirall, Roche, Biogen, and Bayer outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported by Roche S.p.A.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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