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ORIGINAL COMMUNICATION

Disease-modifying treatment, long-term outcomes and transition to progressive multiple sclerosis: data based on the New York State MS Consortium

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Abstract

Background The impact of disease-modifying treatments (DMTs) on multiple sclerosis (MS) long-term outcomes is continuously evolving. Retrospective analyses of large and long-term registries could provide information regarding general disease trajectories and risk factors that are commonly not investigated in shorter clinical trial settings.

Methods Retrospective observational study of people with MS (pwMS) registered in New York State MS Consortium (NYSMSC) since 1996. Disability outcomes of reaching sustained Expanded Disability Status Scale (EDSS) scores of 4.0, 6.0 and transition to secondary-progressive MS (SPMS) were confirmed at follow-up. Four DMT categories were determined (1) continuous DMT use, (2) discontinued DMT, (3) (re)started DMT and (4) never treated with DMT. Patient-reported outcomes (PRO) were acquired using LIFEware system. Kaplan–Meier survival curves and adjusted analysis of covariance (ANCOVA) were used to determine the rate and factors related to disability progression.

Results Total of 1893 pwMS were included with baseline average age of 43.2 years (SD = 10.4), 9.6 years of disease duration (SD = 8.8), median EDSS of 3.0 (IQR 2.0–3.5) and average follow-up time of 6.9 years (SD = 4.9). In addition to being male, older, more disabled and reporting worse PROs at baseline, pwMS who discontinued DMT had more than 5.5 times greater risk of reaching sustained EDSS of 4.0 (OR = 5.56, 95% CI 2.78–11.0, $p < 0.001$). Similarly, pwMS who discontinued DMT during the NYSMSC follow-up had 3.8- and 4.7-times greater risk to reach sustained EDSS 6.0 (OR = 3.86, 95% CI 2.12–7.02, $p < 0.001$), and to transition to SPMS (OR = 4.77, 95% CI 2.9–7.87, $p < 0.001$). Propensity matching analysis confirmed the worse clinical outcomes.

Conclusions In addition to known predictors of long-term clinical outcomes, pwMS who discontinue DMT have worse long-term disability trajectory when compared to both early and late DMT starters. PRO-based indicators may suggest worse clinical outcomes.

Keywords Multiple sclerosis · Disease-modifying therapy · Transition to SPMS · EDSS · Discontinuation

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Introduction

Multiple sclerosis (MS) is a chronic neuroinflammatory and neurodegenerative disease that affects more than 2.8 million people worldwide [13]. Over the course of the disease, people with MS (pwMS) accrue physical and cognitive disabilities that significantly impact the ability to earn income, decrease quality of life, and result in lower disability-adjusted life years [1]. Majority of pwMS are initially diagnosed with relapsing–remitting MS (RRMS), characterized by acute neurological worsening (relapse) that is followed by complete or partial recovery [13]. After variable time from symptom onset, RRMS transitions to a secondary-progressive MS (SPMS) phase, characterized with slow but continuous accumulation of disability progression [13].

Seminal data from the Lyon-based MS registry (European Database for Multiple Sclerosis; EDMUS) has outlined the natural history and long-term trajectories of the different phenotypes [2, 3]. Age at time of developing irreversible disability based on Expanded Disability Status Scale (EDSS) score of 4.0 (indicating walking limitations), EDSS 6.0 (indicating use of walking aid; cane), and EDSS 7.0 (indicating restricted mobility to a wheelchair) were 44.3 years, 54.7 years and 63.1 years, respectively [2]. These results were essentially similar whether the initial MS course was RR or progressive, and whatever the initial symptomatology [2]. Similar natural history trajectories were reported in Canada where up to 58.2% of RRMS transition into SPMS after 19 years from symptom onset, and Swedish-based data with median time to SPMS of 15 years [30, 33]. The clinical and demographic characteristics at the time of SPMS did not influence the time to EDSS of 8.0 (essentially restricted to bed or chair or perambulated in wheelchair) [33]. With introduction of the first disease-modifying therapy (DMT) of interferon-β in early 1990s, the incidence of SPMS significantly reduced by 62% when compared to untreated pwMS [34]. Moreover, the time to reach considerable disability with EDSS 4.0 and EDSS 6.0 milestones was significantly prolonged by 8.7 and 4.6 years from the date of birth [34].

The impact of modern DMTs on the MS course has been also investigated in a large prospective study that followed pwMS over a 10-year period [5]. Over follow-up, up to 55.3% of relapsing pwMS from all levels of baseline EDSS scores did experience disability progression, and 10.1% of RRMS transitioned into SPMS subtype [5]. Based on estimates, after 20 years from symptom onset, only 16.2% pwMS would reach EDSS of 6.0% and 24.2% would transition to SPMS [5]. While implementation of modern DMT arsenal resulted in more than 2.5-fold improvement in the natural history of the disease, a considerable number of pwMS still experience disease/disability worsening.

Based on this background, we aimed to determine the MS progression through retrospective analysis of the NYSMSC database. This analysis is part of a larger NYSMSC effort in determining early predictors of disability progression [12, 35]. In addition to confirming demographic and clinical predictors of long-term disability milestones, we also aimed at incorporating DMT use as an important disease modifier. Based on previous NYSMSC data, we hypothesized that pwMS that discontinue their DMT may be at risk for faster disability progression when compared to pwMS that are continuously treated with a DMT [11].

Materials and methods

Study population

This retrospective observational study utilized pwMS who were registered within the multicenter NYSMSC database since its inception in 1996. The inclusion criteria for the study were: (1) being diagnosed with MS based on the at the time current MS criteria (Poser [25] or any of the McDonald revisions [20, 23, 24, 31]), (2) Availability of at least three clinical visits with completed disability assessment using EDSS, (3) availability of the DMT status at the time of entry in the NYSMSC registry and throughout all aforementioned clinical visits. The exclusion criteria were: (1) other neuroinflammatory diseases, (2) lack of minimum clinical information required for the statistical analyses and (3) the pwMS has already reached the clinical outcome before baseline. Clinical visits that were at the time of relapse or within 3 months from a clinical relapse were not recorded in the NYSMSC as per registry design. The EDSS scores recorded in the database were acquired by NeuroStatus-certified investigators [16]. Limitations in lower extremity function was additionally determined using timed-25-foot walk (T25FW) test [22]. Disability outcomes of reaching sustained EDSS scores of 4.0 and 6.0 were confirmed at the following clinical visit. The clinical visits within the NYSMSC are recorded with minimal time difference of 6 months and most visits occur at yearly basis. The clinical course was determined based on clinical presentation and disease history and classified with the 2013 Lublin criteria [18]. Based on clinical history, the MS provider determined the transition from RRMS to SPMS as an additional clinical study outcome. The diagnosis of SPMS was made in retrospective fashion and at discretion of each of the MS providers within the NYSMSC. The general consensus was that the pwMS had to have disability worsening over 2 years with no evidence of clinical or radiological inflammatory activity.

If a DMT was reported, four groups were established: (1) those who entered the study while on DMT and remained on DMT for the duration of the study, (2) those who entered the

study while on DMT but stopped at some point during the follow-up, (3) those who were not on DMT when entering the study, but started at some points and (4) those who remained DMT naïve throughout the entire period of the study.

Patient-reported outcome (PRO) measures

At baseline, patient-reported outcome (PRO) measures were acquired through previously validated and standardized questionnaire called LIFEware system [6]. This questionnaire was implemented early in the data collection of the NYSMSC. Mobility, physical, and psychosocial scores reflect the sum of respective categorical subcomponents of the LIFEware system. Scores were Rasch-transformed, allowing for linear comparisons. Mobility scores ranged from 0 to 400, physical scores ranged from 0 to 800, and psychosocial scores ranged from 0 to 700, with higher scores indicating better outcomes.

Statistical analyses

Statistical analyses and visualization were performed using SPSS (IBM, Armonk, NY, USA). Data distribution was assessed using visual inspection of histograms and Q–Q plots. Parametric data were described as mean and standard deviations (SD), whereas non-parametric data were described as median and interquartile range (IQR). Comparison between categorical variables were performed using Chi-square, between parametric numerical variables with Student's *t* test and non-parametric with Mann–Whitney *U* test. Times to sustained EDSS of 4.0, 6.0 and transition to SPMS were visualized and compared using Kaplan–Meier survival curves and Mantel–Cox test. Logistics regression models were used to determine baseline predictors of sustained EDSS and transition to SPMS. The logistic regression models utilized all hypothesized baseline predictive measures together in "Enter" method. Given that some NYSMSC pwMS may have already reached the investigated outcome, for each of the analysis, we specify the number of pwMS included. Additional propensity-based matching was performed using R studio 4.2.0 and utilize 'MatchIt" library. The 1:1 matching used optimal Mahalanobis distance matching with sex, age, time of follow-up and baseline EDSS as covariates. Significant predictors were described using odds ratios (OR) and 95% confidence intervals (CI). *p* values lower than 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

Total of 1893 pwMS were included in the analyses (Table 1). The largest portion of pwMS ($n=777$, 41%) were treated with DMT throughout all study visits recorded within NYSMSC, followed by pwMS who (re)started DMT during the follow-up period ($n=692$, 36.6%), not treated during the follow-up ($n=228$, 12.0%), or discontinued their DMT ($n=196$, 10.4%). At baseline, pwMS who were not on any DMT were the oldest, followed by pwMS who discontinued, pwMS who were continuously on DMT, and the youngest were pwMS who (re)started DMT (49.5 vs. 43.2 vs. 42.3 vs. 42.0 years, $p<0.001$). The same distribution was seen for age of symptom onset as well (higher within the no DMT group $p=0.001$), baseline EDSS (highest disability within the no DMT group, $p=0.008$ and when compared to pwMS that restarted DMT; mean EDSS 3.0 vs. 3.2, post-hoc $p=0.005$), and percentage of progressive pwMS (highest among the no DMT group, $p<0.001$). There were no differences in baseline T25FW between the four groups as well.

Over the follow-up, significantly greater numbers of pwMS who discontinued DMT reached sustained EDSS of 4.0 when compared to continuously-treated pwMS, pwMS who (re)started a DMT, and pwMS who did not use any DMT (31.4% vs. 19.5% vs. 17.2% vs. 15.8%, $p<0.001$). Similarly, significantly greater numbers of pwMS who discontinued DMT reached EDSS 6.0 (45.6% vs. 27.0% vs. 26.7% vs. 21.0%, $p<0.001$). There were no differences in the % of pwMS who transitioned to SPMS over the follow-up ($p=0.228$).

Reaching sustained EDSS of 4.0 and DMT

The analysis investigating risk factors related to progression to sustained EDSS 4.0 included total of 1300 pwMS. Supplement Table 1 describes the demographic, clinical and PRO measures of the 926 pwMS who did not reach EDSS 4.0, and 374 pwMS who reached EDSS of 4.0 over 6.3- and 8.7-year follow-up period, respectively.

Based on regression analysis, being male resulted in a 92% greater risk to reach sustained EDSS 4.0 when compared to females (OR = 1.92, 95% CI 1.36–2.7, $p<0.001$) (Table 2). Older pwMS at baseline were at greater risk to reach EDSS 4.0 (OR = 1.03, 95% CI 1.01–1.05, $p=0.002$), being older at baseline for each 1 year conferred 3% additional risk. Higher baseline EDSS resulted in more than a threefold greater risk of reaching sustained EDSS 4.0 (OR = 3.23, 95% CI 2.46–4.38, $p<0.001$). For example, 1 point of higher baseline EDSS score conferred 3.23-times greater chance of reaching sustained EDSS of 4.0.

In terms of therapy, PwMS who discontinued DMT had more than a 5.5-times greater risk of reaching sustained EDSS 4.0 when compared to pwMS who were never on DMT (OR = 5.56, 95% CI 2.78–11.0, $p<0.001$). Contrarily, pwMS who (re)started DMT or were continuously treated had more than twofold lower risk of reaching EDSS 4.0 when compared to pwMS that were never on a DMT

Table 1 Demographic and clinical characteristics of the study population

	On DMT during all study visits $n=777$	On DMT at study baseline but stopped $n=196$	No DMT at baseline but (re)started during study $n=692$	No DMT during any study visits $n=228$	p value
Female, *n* (%)	559 (71.9)	164 (83.7)	495 (71.5)	171 (75.0)	**0.005**
Race, *n* (%)					
White/Caucasian	705 (90.8)	179 (91.4)	652 (94.2)	215 (94.3)	0.535
Black/African–American	47 (6.0)	13 (6.6)	34 (4.9)	10 (4.4)	
Other	13 (1.7)	3 (1.5)	5 (0.7)	3 (1.3)	
Unknown	12 (1.5)	1 (0.5)	1 (0.1)	–	
Age at baseline, mean (SD)	42.3 (10.0)	43.2 (10.7)	42.0 (9.5)	49.5 (11.6)	**< 0.001**
Time of follow-up, mean (SD)	6.8 (4.8)	8.1 (5.2)	7.4 (5.0)	5.3 (3.6)	**< 0.001**
Disease duration at baseline, mean (SD)	9.0 (8.3)	10.7 (8.8)	8.8 (8.3)	13.3 (10.7)	**< 0.001**
Age of symptom onset, mean (SD)	32.9 (10.0)	32.6 (10.7)	32.6 (9.7)	35.6 (11.6)	**0.001**
EDSS at baseline, mean (SD), median (IQR)	3.1 (1.0)	3.2 (1.0)	3.0 (0.9)	3.2 (1.0)	**0.008**
T25FW at baseline, mean (SD), median (IQR)	6.6 (3.4)	7.0 (3.6)	6.4 (3.5)	7.0 (5.1)	0.128
Disease course at baseline, *n* (%)					**< 0.001**
RRMS	647 (84.9)	150 (77.7)	528 (77.6)	122 (55.2)	
SPMS	82 (10.8)	28 (14.5)	95 (14.0)	50 (22.6)	
PPMS	33 (4.3)	15 (7.8)	57 (8.4)	49 (22.2)	
Diagnosis era, *n* (%)					
Pre Poser criteria	35 (5.0)	12 (7.3)	47 (7.0)	30 (13.6)	**< 0.001**
1982–2001 diagnosis	506 (71.8)	127 (77.0)	557 (82.8)	174 (79.1)	
2001 and onwards	164 (23.3)	26 (15.8)	69 (10.3)	16 (7.3)	
Disease outcomes, *n* (%)					
Reach sustained EDSS of 4.0	132 (19.5)	53 (31.4)	103 (17.2)	32 (15.8)	**< 0.001**
Reach sustained EDSS of 6.0	134 (27.0)	52 (45.6)	117 (26.7)	30 (21.0)	**< 0.001**
Reach SPMS	199 (28.3)	54 (32.9)	172 (28.7)	40 (22.9)	0.228

Group comparisons were analyzed using one-way analysis of variance (ANOVA) for continuous variables and Chi-squared for categorical variables. Statistically significant results ($p<0.05$) are displayed in bold

DMT use was determined at each visit. If a DMT was reported. Those who entered the study while on DMT and remained on DMT for the duration of the study are found in the first category, while those who stopped at some point during the study are found in the second category. Those who were not on DMT when entering the study, but started at some point are in the third category. Those who remained DMT naïve throughout the study are in the No DMT category. Disease duration, time of follow-up, and age are shown in years. T25FW scores are shown in seconds

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *T25FW* timed 25-foot walk, *RRMS* relapsing–remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *n* number, *SD* standard deviation, *IQR* interquartile range

(OR = 2.38, 95% CI 1.41–4.1, $p=0.001$ and OR = 2.44, 95% CI 1.43–4.17, $p=0.001$). The difference in risk of reaching sustained EDSS 4.0 between never and ever DMT users is shown in Supplement Fig. 1.

Reaching sustained EDSS of 6.0 and DMT

The analysis investigating risk factors related to progression to sustained EDSS 6.0 included total of 1802 pwMS. The clinical and demographic characteristics of pwMS utilized in the analysis regarding reaching sustained EDSS 6.0 is shown in Supplement Table 2. Out of the total 1802 pwMS, 363 (20.1%) reached sustained EDSS 6.0 over a follow-up time of 9.2 years. PwMS that reached sustained EDSS 6.0 had significantly worse baseline mobility and physical PRO-based scores (both $p<0.001$).

The same demographic and clinical factors were associated with EDSS 6.0, such as male (OR = 1.81, 95% CI 1.32–2.46, $p<0.001$), age (OR = 1.03, 95% CI 1.01–1.05, $p<0.001$) and higher EDSS (OR = 1.89, 95% CI 1.61–2.2, $p<0.001$) (Table 3). When interpreted, being older at baseline for each 1 year conferred 3% additional risk and 1 point of higher baseline EDSS score conferred 89% greater chance of reaching sustained EDSS of 6.0. When compared to pwMS who were never treated, pwMS who discontinued DMT had 3.8-times greater risk to reach sustained EDSS 6.0 (OR = 3.86, 95% CI 2.12–7.02, $p<0.001$). PwMS who were continuously on DMT, or (re)started

Table 2 Regression models predicting risk of reaching sustained EDSS score of 4.0

Demographic and clinical characteristics	B	OR	95% CI	*p* value
Male sex (female = reference)	0.65	1.92	1.36–2.70	**< 0.001**
Age at baseline	0.03	1.03	1.01–1.05	**0.002**
Disease duration at baseline	0.02	1.02	0.99–1.04	0.145
EDSS at baseline	1.19	3.23	2.46–4.38	**< 0.001**
Diagnosis era				
Pre Poser criteria	Ref	Ref	Ref	Ref
1982–2001 diagnosis	− 0.12	0.88	0.45–1.72	0.715
2001 and onwards	− 0.94	0.39	0.17–0.90	**0.027**
Never DMT	Ref	Ref	Ref	Ref
Started and remained	0.89	2.44	1.43–4.17	**0.001**
Started but stopped	1.71	5.56	2.78–11.0	**< 0.001**
No DMT at baseline but started	0.88	2.38	1.41–4.10	**0.001**
Patient reported outcomes (PRO)				
Mobility score	− 0.008	0.99	0.99–1.00	**< 0.001**
Physical score	0.001	1.18	0.99–1.002	0.845
Psychosocial score	0.002	1.00	1.00–1.00	**0.006**

Due to high collinearity with age at baseline and disease duration at baseline, age of symptom onset and time of follow-up in the study were excluded from the model. A logistic regression with enter criteria was conducted with reaching EDSS 4.0 as the dependent variable and sex, age, disease duration, baseline EDSS, diagnosis era, DMT use, and PRO measures of mobility, physical, and psychosocial as independent predictors. A p value of < 0.05 was considered statistically significant and is displayed in bold

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale

DMT during the follow-up, had significantly greater risk of sustained EDSS 6.0 when compared to pwMS who were never treated (OR = 2.06, 95% CI 1.26–3.37, $p = 0.004$ and

Table 3 Regression model showing baseline predictors of reaching sustained disability milestone EDSS 6.0

Demographic and clinical characteristics	*B*	OR	95% CI	*p* value
Male sex (female = reference)	0.59	1.81	1.32–2.46	**< 0.001**
Age at baseline	0.03	1.03	1.01–1.05	**< 0.001**
Disease duration at baseline	0.02	1.02	0.98–1.02	0.876
EDSS at baseline	0.63	1.89	1.61–2.20	**< 0.001**
Diagnosis era				
Pre Poser criteria	Ref	Ref	Ref	Ref
1982–2001 diagnosis	− 0.19	0.83	0.47–1.47	0.521
2001 and onwards	− 1.39	0.25	0.11–0.56	**< 0.001**
Never DMT	Ref	Ref	Ref	Ref
Started and remained	0.72	2.06	1.26–3.37	**0.004**
Started but stopped	1.35	3.86	2.12–7.02	**< 0.001**
No DMT at baseline but started	0.56	1.68	1.01–2.77	**0.044**
Patient reported outcomes (PRO)				
Mobility score	− 0.008	0.99	0.99–0.99	**< 0.001**
Physical score	0.002	1.00	1.00–1.00	**0.009**
Psychosocial score	− 0.001	1.00	1.00–1.00	0.858

Due to high collinearity with age at baseline and disease duration at baseline, age of symptom onset and time of follow-up in the study were excluded from the model. A logistic regression with enter criteria was conducted with reaching EDSS 6.0 as the dependent variable and sex, age, disease duration, baseline EDSS, diagnosis era, DMT use, and PRO measures of mobility, physical, and psychosocial as independent predictors. A p value of < 0.05 was considered statistically significant and is displayed in bold

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale

OR = 1.68, 95% CI 1.01–2.77, $p = 0.044$, respectively). The Kaplan–Meier survival plot regarding sustained EDSS 6.0 for DMT users and DMT naïve pwMS is shown in Supplement Fig. 2.

The differences in time to sustained EDSS 6.0 in pwMS that are being diagnosed within the three major MS criteria epochs are shown in Supplement Fig. 3. Finally, the Kaplan–Meier survival plot regarding the time to sustained EDSS 6.0 between the 4 DMT groups is shown in Fig. 1.

Transition to SPMS and DMT

The analysis investigating risk factors related to transition to SPMS included total of 1787 pwMS. The demographic and clinical characteristics of the pwMS who transition to SPMS, or do not do so, are shown in Supplement Table 3. PwMS who transition to SPMS reported worse baseline mobility and physical PRO-based scores when compared to those who did not (both $p < 0.001$) (Table 4).

PwMS who discontinued DMT had the highest 4.7-fold greater risk for SPMS transition (OR = 4.77, 95% CI 2.9–7.87, $p < 0.001$) when compared to pwMS who were never treated and had lowest risk of reaching SPMS status. Similarly, pwMS who were continuously treated or (re)started DMT had greater risk of reaching SPMS (OR = 3.94, 95% CI 2.62–5.92, $p < 0.001$, and OR = 3.78, 95% CI 2.49–5.74 $p < 0.001$, respectively) when compared to pwMS who were never treated. The Kaplan–Meier SPMS survival curve between DMT users and DMT naïve pwMS, is shown in Supplement Fig. 4.

Time to reach SPMS between pwMS that were diagnosed within the three major diagnostic epochs is shown in Supplement Fig. 5. PwMS diagnosed with McDonald criteria had the longest time to transition to SPMS, when compared to pwMS diagnosed with Poser or Schumacher MS criteria (Mantel–Cox $p < 0.001$). Finally, time to SPMS between pwMS who used DMT throughout the entire time, pwMS who (re)started DMT, pwMS who discontinued DMT, and pwMS who never used DMT, are shown in Fig. 2.

Propensity-based matching and DMT effect

To determine the stand-alone effect of DMT on disability milestones, 3 separate propensity-based matching procedures were employed. The first analysis aimed at matching pwMS who were continuously on DMT, and pwMS who discontinued their DMT, based on baseline characteristics, such as sex, age, time of follow-up and baseline EDSS scores. In three propensity matching procedures, the groups were well-balanced with standard differences in all variables below 0.1. After propensity matching, pwMS who discontinued their DMTs have significantly shorter time to EDSS

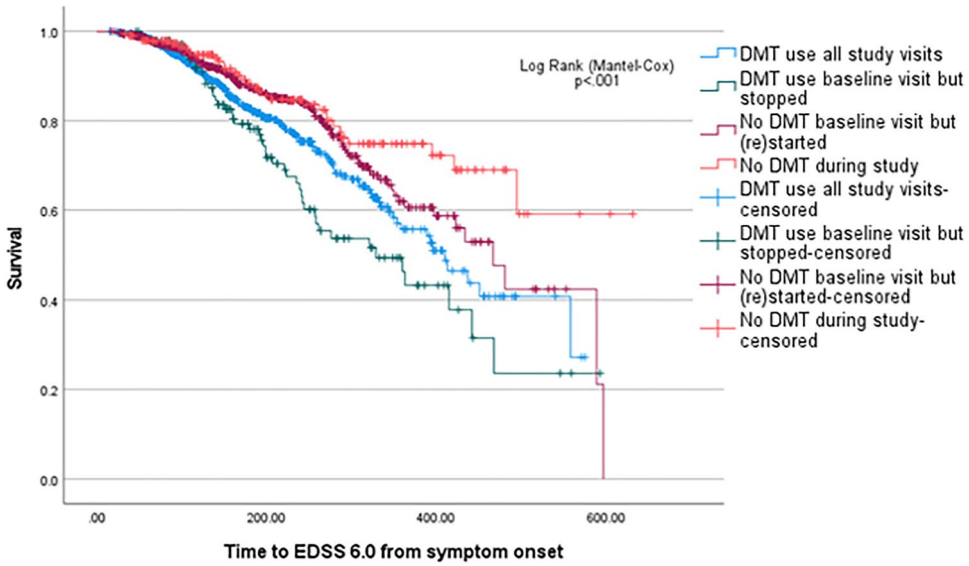

Fig. 1 Kaplan–Meier survival plot of four groups of therapy use/non-use reaching sustained disability milestone EDSS 6.0. First follow-up visit where EDSS 6.0 (or above) was reached was used to calculate time to EDSS 6.0 (in months) by subtracting date of first MS symptom onset. The subsequent follow-up visit was used to confirm that worsening was sustained. When EDSS 6.0 was not reached, the date of the most recent study visit was used to calculate censored time by subtracting date of first MS symptom onset. The independent predictor therapy status. It was divided into four categories (blue line—entered the study while on DMT and remained on DMT for the duration of the study, green line—entered the study while on DMT but stopped, purple line—entered the study not on DMT but started, orange line—entered the study not on DMT and remained DMT naïve throughout the study). Significance was determined through a log rank (Mantel–Cox) test. A p value of < 0.05 was considered statistically significant and the p value refers to the comparison of the two most different groups (pwMS that discontinued vs. pwMS not on any DMT)

Table 4 Regression model showing baseline predictors of reaching SPMS

Demographic and clinical characteristics	*B*	OR	95% CI	*p* value
Male sex (female = reference)	0.18	1.19	0.93–1.54	0.167
Age at baseline	0.02	1.02	1.00–1.00	**0.002**
Disease duration at baseline	0.03	1.03	1.02–1.05	**< 0.001**
EDSS at baseline	0.24	1.27	1.16–1.40	**< 0.001**
Diagnosis era				
Pre Poser criteria	Ref	Ref	Ref	Ref
1982–2001 diagnosis	0	1.0	0.64–1.56	1.56
2001 and onwards	− 1.24	0.29	0.16–0.54	**< 0.001**
Never DMT	Ref	Ref	Ref	Ref
Started and remained	1.38	3.94	2.62–5.92	**< 0.001**
Started but stopped	1.57	4.77	2.90–7.87	**< 0.001**
No DMT at baseline but started	1.33	3.78	2.49–5.74	**< 0.001**
Patient reported outcomes (PRO)				
Mobility score	− 0.002	1.00	0.996–0.999	**0.008**
Physical score	− 0.001	1.00	0.998–1.00	0.091
Psychosocial score	0.0	1.00	0.999–1.00	0.559

Due to high collinearity with age at baseline and disease duration at baseline, age of symptom onset and time of follow-up in the study were excluded from the model. A logistic regression with enter criteria was conducted with reaching SPMS as the dependent variable and sex, age, disease duration, baseline EDSS, diagnosis era, DMT use, and PRO measures of mobility, physical, and psychosocial as independent predictors. A *p* value of < 0.05 was considered statistically significant and is displayed in bold

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale

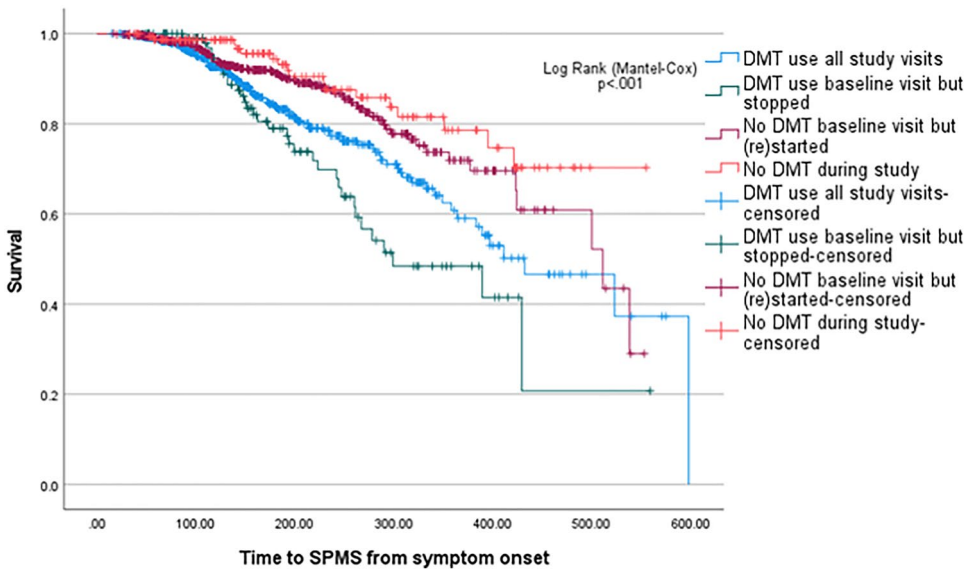

Fig. 2 Kaplan–Meier survival plot of time to SPMS status between the four groups of use/non-use of DMT. First follow-up visit when a physician reported an SPMS disease course was used to calculate time to SPMS (in months) by subtracting date of first MS symptom onset. When patient did not reach an SPMS disease course, the date of the most recent study visit was used to calculate censored time by subtracting date of first MS symptom onset. The independent predictor was therapy status. It was divided into four categories (blue line—entered the study while on DMT and remained on DMT for the duration of the study, green line—entered the study while on DMT but stopped, purple line—entered the study not on DMT but started, orange line—entered the study not on DMT and remained DMT naïve throughout the study). Significance was determined through a log rank (Mantel–Cox) test. A *p* value of < 0.05 was considered statistically significant and the *p* value refers to the comparison of the two most different groups (pwMS that discontinued vs. pwMS not on any DMT)

4.0 (Mantel–Cox $p = 0.024$), and shorter time to EDSS 6.0 (Mantel–Cox $p = 0.006$). Contrarily, pwMS who discontinued their DMTs were not statistically significant in their time to transition to SPMS (Mantel–Cox $p = 0.432$) compared to pwMS who remained on their DMT. The Kaplan–Meier survival curves in propensity-matched groups are shown in Fig. 3.

Propensity matching between 437 pwMS who were treated with DMT, and 437 pwMS who were never treated, demonstrated that untreated pwMS had significant better long-term clinical outcomes (EDSS 4.0, $p < 0.001$, EDSS 6.0, $p = 0.005$, and SPMS transition $p < 0.001$). There were no significant trajectory differences for any long-term disability outcomes between the 852 matched pairs of pwMS who remained on DMT vs. pwMS who(re)started DMT.

Discussion

The findings from this retrospective long-term analysis of the NYSMSC data are multifold. First, the rate of disability progression to EDSS 6.0, and transition to SPMS after 17 years from disease onset, occurs in less than 20% of total pwMS and mirrors similar modern disease trajectories. Second, it corroborates male sex, higher age, and higher disability early in the disease as important predictors of medium to long-term disability. Third, pwMS who discontinue their DMT during the follow-up have significantly worse long-term outcomes when compared to DMT-treated pwMS and late DMT starters. Finally, PRO measures acquired early in the disease are indicative of future long-term disease worsening.

Several factors can provide explanations for our finding that long-term MS outcomes improve based on which diagnostic criteria was utilized. First, newer MS criteria incorporate MRI-based measures of dissemination in time and space that allow early MS diagnosis and early start of appropriate DMT [12]. Early DMT treatment results with favorable long-term clinical outcomes and lower mortality rates [7, 14, 21]. The effect of changing classification on clinical outcomes is known as Will Rogers' phenomenon, and can substantially limit the ability to compare findings between different epochs and with other historical cohorts [29]. Despite Will Rogers' phenomenon, early treatment still

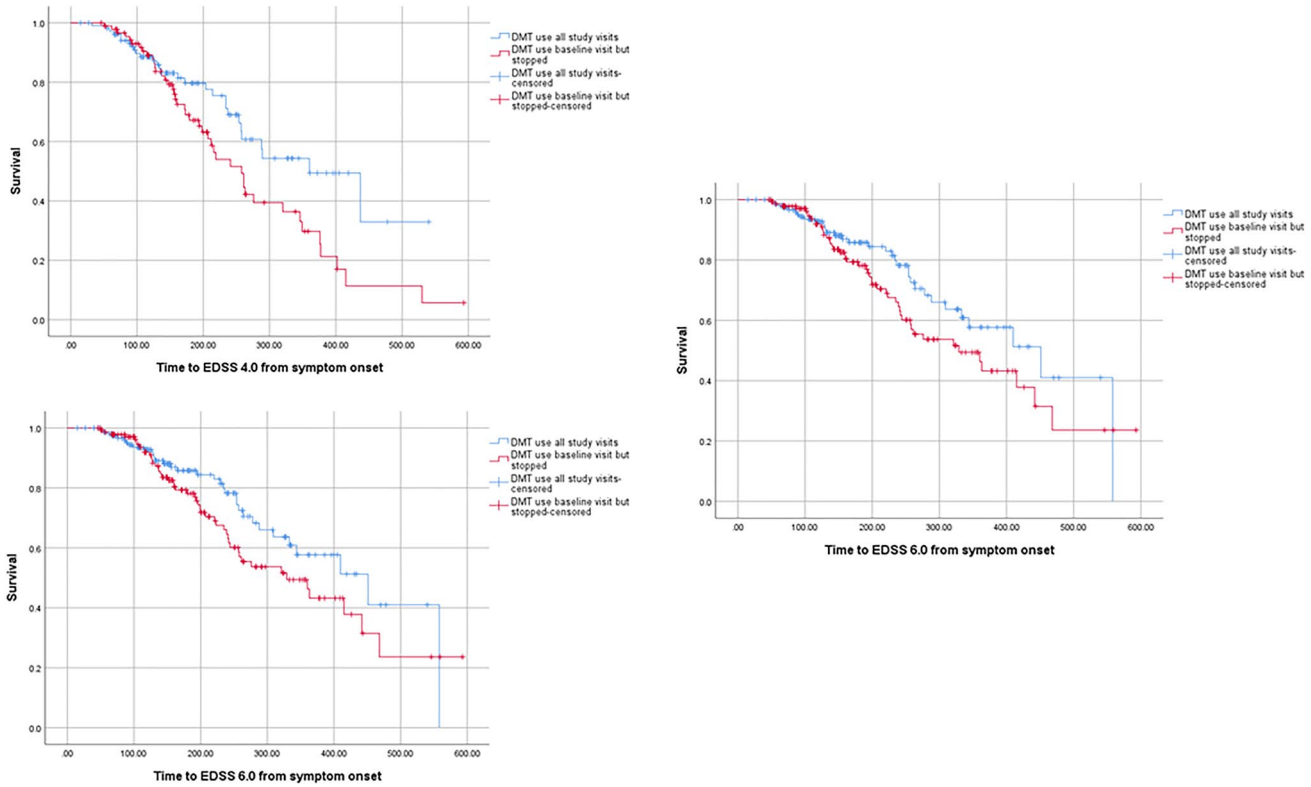

Fig. 3 Kaplan–Meier survival plot of time to SPMS status between the propensity-matched pwMS that remain on their DMT vs. pwMS that discontinued their DMT. First follow-up visit when a physician reported an SPMS disease course was used to calculate time to SPMS (in months) by subtracting date of first MS symptom onset. When patient did not reach an SPMS disease course, the date of the most recent study visit was used to calculate censored time by subtracting date of first MS symptom onset. Significance was determined through a log rank (Mantel–Cox) test. A p value of < 0.05 was considered statistically significant

remains a contributing factor towards better long-term clinical outcomes [32]. In a recent assessment of the Barcelona CIS group, pwMS diagnosed within different diagnostic epochs had significantly lower risk of reaching EDSS ≥ 3.0 with each new version of the MS criteria [32].

Outside of the established risk factors of male sex, higher age at symptom onset and higher disability levels in the early MS period, our analysis also demonstrated that early acquisition of PRO-based measures can help towards risk stratification [27]. Higher levels of patient-reported fatigue and lower limb limitations (both subcomponents of LIFEware System™) are already validated as predictors of future disability worsening [35, 37]. Moreover, pwMS commonly report worse PROs in the period shortly before the transition to SPMS status [8]. Based on these findings, the risk stratification process could utilize PRO measures either as a supplement to the existing clinical examination, or they could be utilized in circumstances when EDSS scores are not available.

At first glance the finding that untreated pwMS from NYSMSC have the best long-term clinical outcomes may be contra-intuitive. First, indication-to-treat bias, also known as confounding by indication, may be the biggest driving force that could describe the impact of "benign" MS on the interpretation of observational data [26]. PwMS with "benign" presentation may not fulfil the minimal threshold for therapeutic intervention [28]. Contrarily, pwMS with initially aggressive neuroinflammatory disease would receive prompt pharmacological intervention. The DMTs do not fully reverse the disease aggressiveness and will lead to a scenario, where DMT-treated pwMS would commonly have worse clinical outcomes. Propensity matching for baseline risk factors that also include MRI measures could partially correct for such biased findings. Alternatively, pwMS that satisfy predefined benign MS criteria can be excluded from the analyses [39]. Up to one-third of pwMS would satisfy such benign MS criteria (EDSS ≤ 2 and disease duration ≥ 10 years, or EDSS ≤ 3 and disease duration ≥ 15) [39]. Second, the nature of large registry-based observational data fundamentally differs from clinical trials. To enrich the study and extract greater effect size, clinical trials typically require disease activity as a main inclusion criterion (clinical relapse or MRI activity), and the majority of benign pwMS would not participate in such trials. Finally, a portion of pwMS in the registry may have already reached the study outcomes (EDSS 4.0, EDSS 6.0 or transitioned to SPMS) before their first ever recorded visit in the NYSMSC and would have not been included in the analyses. This will further tilt the favor of having greater proportion of less severe pwMS in our sample.

The effect of DMT discontinuation on disease reactivation, particularly in the aging MS population, is one particular topic that has been of recent special interest to the MS field. The consensus among the recent literature is that the current DMTs do not provide additional benefit after 50 or 60 years of age [38]. The lack of efficacy is additionally coupled with concerns regarding increased risk of adverse events from immunosuppressive therapy in an aging and vulnerable population [10, 36]. Most DMT discontinuation studies demonstrate that stopping therapy in older (age > 50 years) and clinically stable pwMS do not precipitate new disease activity in the form of elapses or inflammatory MRI activity [15]. Moreover, larger controlled clinical trial, such as the discontinuation of DMT in MS (NCT03073603), where pwMS would be continued or discontinue their DMT was not able to demonstrate that therapy cessation is not inferior when compared to DMT continuation [4]. It would be of particular importance to see the disability trajectory of pwMS that participated in DISCO–MS for the next 5–10 years. Currently the extension of the DISCO–MS only intends on following the pwMS for additional 12 months and investigate the clinical and radiological inflammatory outcomes. Fewer studies examine the effect of DMT discontinuation on the rate and time to disability worsening. Propensity analysis from the MSBase Registry suggested that DMT stoppers had significantly shorter time to new disability worsening (47% higher hazard ratio) when compared to pwMS who remained treated [15]. Similarly, previous NYSMSC analysis did suggest that up to 32.9% of clinically stable pwMS start to experience new disability worsening after they discontinue their DMT after an average follow-up of 2 years [11]. This disability worsening was equally present in both younger and older pwMS (cutoff of 55 years) [11].

The retrospective, observational nature of the study does come with several limitations. Despite the statistical correction, the different follow-up period between the groups may still contribute to some differences in study outcomes. The DMT data are significantly influenced by the individual decision-making process from both the MS care provider and the pwMS themselves. These can vary between tertiary centers with specialized MS centers, and community-based, general neurology providers, which were all represented in our sample. We agree that non-insured and pwMS with aggressive disease are at greater risk of being lost to follow-up, not complete the minimal 3 visit criteria and be excluded in such long-term analysis. Future analysis focused on socioeconomic status, distance to a specialized MS center, and differences in insurance plans could uncover targetable aspects that can improve the overall outcomes. Another major limitation is the lack of drug-specific analysis. At this stage, we did not consider performing drug-specific analysis due to the low sample size, particularly for medications that were recently introduced to the DMT repertoire. Moreover, our current DMT classifications do not incorporate information regarding

the indication for drug change or drug discontinuation. Progressing pwMS with similar clinical characterization may undergo either escalation of treatment, or discontinue their DMT due to presumed lack of efficacy. This limitation questions the study interpretation and the cause vs. effect for the DMT discontinuation. Moreover, our study population contained small number of people with primary-progressive MS (154 people with PPMS), a disease phenotype that traditionally has not responded to DMTs, where only ocrelizumab and mitoxantrone (progressive-relapsing forms) have FDA approval.

Another important aspect that should be considered when performing such studies is the subjective and ever-changing perception of the disease phenotypes and the transition to "SPMS". [9] We do acknowledge our definition for transition of SPMS was based on the individual classification provided by each MS provider in the NYSMSC and mostly assigned in a retrospective fashion. Recent studies have attempted at operationalizing the SPMS diagnosis which may standardize studies that explore the transition to the progressive phenotype. For example, MSBase-based registry has outlined a definition in which pwMS with baseline EDSS of 4.0 and pyramidal functional score of 2.0 that experience confirmed EDSS increase in absence of clinical/radiological activity remain having positive disability trajectory and 70% reach significant disability in the next 5 years (EDSS 6.0) [17]. This definition correctly aligned with the providers diagnosis and it was established approximately 4 years earlier than the physicians' diagnosis [17]. Unfortunately, the NYSMSC did not mandate collection of the functional scores and we were not able to test this particular definition. Another alternative approach in predicting SPMS diagnosis is through nomograms build based on survival models as ours [19]. The Swedish registry has utilized the long-term data of 8825 people with RRMS and created such model which reached 84% internal and > 77% external accuracy [19].

In conclusion, NY-based pwMS show similar global trends of improvement in long-term clinical outcomes as other recently published MS populations. After 17 years since symptom onset, less than 20% of pwMS experience disease progression to significant physical disability (use of unilateral support), and transition to SPMS. PwMS who discontinue DMT have worse disability trajectory when compared to early and late DMT starters. Finally, early PRO-based indicators may suggest worse clinical outcomes and should be considered during the process of risk stratification.

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Declarations

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Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research board (IRB) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the University at Buffalo IRB and all participants provided a written consent form.

References

1. Collaborators GBDMS (2019) Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 18:269–285
2. Confavreux C, Vukusic S (2006) Age at disability milestones in multiple sclerosis. Brain 129:595–605
3. Confavreux C, Vukusic S (2006) Natural history of multiple sclerosis: a unifying concept. Brain 129:606–616
4. Corboy JR, Fox RJ, Kister I, Cutter GR, Morgan CJ, Seale R, Engebretson E, Gustafson T, Miller AE, Investigators D (2023) Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): a multicentre, randomised, single-blind, phase 4, non-inferiority trial. Lancet Neurol 22:568–577
5. Cree BA, Gourraud PA, Oksenberg JR, Bevan C, Crabtree-Hartman E, Gelfand JM, Goodin DS, Graves J, Green AJ, Mowry E, Okuda DT, Pelletier D, von Büdingen HC, Zamvil SS, Agrawal A, Caillier S, Ciocca C, Gomez R, Kanner R, Lincoln R, Lizee A, Qualley P, Santaniello A, Suleiman L, Bucci M, Panara V, Papinutto N, Stern WA, Zhu AH, Cutter GR, Baranzini S, Henry RG, Hauser SL (2016) Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol 80:499–510
6. Granger C (1999) The LIFEware system. J Rehabil Outcomes Meas 3:63–69
7. Hartung HP, Graf J, Kremer D (2020) Long-term follow-up of multiple sclerosis studies and outcomes from early treatment of clinically isolated syndrome in the BENEFIT 11 study. J Neurol 267:308–316
8. Healy BC, Zurawski J, Chitnis T, Weiner HL, Glanz BI (2022) Patient-reported outcomes associated with transition to secondary progressive multiple sclerosis. Qual Life Res 31:1799–1805

9. Inojosa H, Proschmann U, Akgun K, Ziemssen T (2021) A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. J Neurol 268:1210–1221
10. Jakimovski D, Eckert SP, Zivadinov R, Weinstock-Guttman B (2021) Considering patient age when treating multiple sclerosis across the adult lifespan. Expert Rev Neurother 21:353–364
11. Jakimovski D, Kavak KS, Vaughn CB, Goodman AD, Coyle PK, Krupp L, Gottesman M, Edwards KR, Lenihan M, Perel A, Zivadinov R, Weinstock-Guttman B (2022) Discontinuation of disease modifying therapies is associated with disability progression regardless of prior stable disease and age. Multiple Scler Relat Disord 57:103406
12. Jakimovski D, Kavak KS, Zakalik K, Coetzee T, Gottesman M, Coyle PK, Zivadinov R, Weinstock-Guttman B (2022) Improvement in time to multiple sclerosis diagnosis: 25-year retrospective analysis from New York State MS Consortium (NYSMSC). Multiple Scler J 29:753–756
13. Jakimovski D, Bittner S, Zivadinov R, Morrow SA, Benedict RHB, Zipp F, Weinstock-Guttman (2023) Multiple sclerosis.The Lancet
14. Kappos L, Edan G, Freedman MS, Montalbán X, Hartung HP, Hemmer B, Fox EJ, Barkhof F, Schippling S, Schulze A, Pleimes D, Pohl C, Sandbrink R, Suarez G, Wicklein EM (2016) The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. Neurology 87:978–987
15. Kister I, Spelman T, Alroughani R, Lechner-Scott J, Duquette P, Grand'Maison F, Slee M, Lugaresi A, Barnett M, Grammond P, Iuliano G, Hupperts R, Pucci E, Trojano M, Butzkueven H (2016) Discontinuing disease-modifying therapy in MS after a prolonged relapse-free period: a propensity score-matched study. J Neurol Neurosurg Psychiatry 87:1133–1137
16. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33:1444–1452
17. Lorscheider J, Buzzard K, Jokubaitis V, Spelman T, Havrdova E, Horakova D, Trojano M, Izquierdo G, Girard M, Duquette P, Prat A, Lugaresi A, Grand'Maison F, Grammond P, Hupperts R, Alroughani R, Sola P, Boz C, Pucci E, Lechner-Scott J, Bergamaschi R, Oreja-Guevara C, Iuliano G, Van Pesch V, Granella F, Ramo-Tello C, Spitaleri D, Petersen T, Slee M, Verheul F, Ampapa R, Amato MP, McCombe P, Vucic S, Sanchez Menoyo JL, Cristiano E, Barnett MH, Hodgkinson S, Olascoaga J, Saladino ML, Gray O, Shaw C, Moore F, Butzkueven H, Kalincik T, Group MSS (2016) Defining secondary progressive multiple sclerosis. Brain 139:2395–2405
18. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, Bebo B Jr, Calabresi PA, Clanet M, Comi G, Fox RJ, Freedman MS, Goodman AD, Inglese M, Kappos L, Kieseier BC, Lincoln JA, Lubetzki C, Miller AE, Montalban X, O'Connor PW, Petkau J, Pozzilli C, Rudick RA, Sormani MP, Stüve O, Waubant E, Polman CH (2014) Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83:278–286
19. Manouchehrinia A, Zhu F, Piani-Meier D, Lange M, Silva DG, Carruthers R, Glaser A, Kingwell E, Tremlett H, Hillert J (2019) Predicting risk of secondary progression in multiple sclerosis: a nomogram. Multiple Scler 25:1102–1112
20. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 50:121–127
21. Miller AE, Vermersch P, Kappos L, Comi G, Freedman MS, Oh J, de Seze J, Truffinet P, Benamor M, Purvis A, Wolinsky JS (2019) Long-term outcomes with teriflunomide in patients with clinically isolated syndrome: results of the TOPIC extension study★★. Multiple Scler Relat Disord 33:131–138
22. Motl RW, Cohen JA, Benedict R, Phillips G, LaRocca N, Hudson LD, Rudick R (2017) Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler 23:704–710
23. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69:292–302
24. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 58:840–846
25. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13:227–231
26. Salas M, Hofman A, Stricker BH (1999) Confounding by indication: an example of variation in the use of epidemiologic terminology. Am J Epidemiol 149:981–983
27. Simmons SB, Schippling S, Giovannoni G, Ontaneda D (2021) Predicting disability worsening in relapsing and progressive multiple sclerosis. Curr Opin Neurol 34:312–321
28. Sorensen PS, Sellebjerg F, Hartung HP, Montalban X, Comi G, Tintoré M (2020) The apparently milder course of multiple sclerosis: changes in the diagnostic criteria, therapy and natural history. Brain 143:2637–2652
29. Sormani MP (2009) The Will Rogers phenomenon: the effect of different diagnostic criteria. J Neurol Sci 287(Suppl 1):S46-49
30. Tedeholm H, Skoog B, Lisovskaja V, Runmarker B, Nerman O, Andersen O (2015) The outcome spectrum of multiple sclerosis: disability, mortality, and a cluster of predictors from onset. J Neurol 262:1148–1163
31. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintore M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17:162–173
32. Tintore M, Cobo-Calvo A, Carbonell P, Arrambide G, Otero-Romero S, Río J, Tur C, Comabella M, Nos C, Arévalo MJ, Midaglia L, Galán I, Vidal-Jordana A, Castilló J, Rodríguez-Acevedo B, Zabalza de Torres A, Salerno A, Auger C, Sastre-Garriga J, Rovira À, Montalban X (2021) Effect of changes in MS diagnostic criteria over 25 years on time to treatment and prognosis in patients with clinically isolated syndrome. Neurology 97:e1641–e1652
33. Tremlett H, Yinshan Z, Devonshire V (2008) Natural history of secondary-progressive multiple sclerosis. Mult Scler 14:314–324
34. Trojano M, Pellegrini F, Fuiani A, Paolicelli D, Zipoli V, Zimatore GB, Di Monte E, Portaccio E, Lepore V, Livrea P, Amato MP (2007) New natural history of interferon-beta-treated relapsing multiple sclerosis. Ann Neurol 61:300–306
35. Vaughn C, Kavak KS, Jakimovski D, Qutab N, Avila R, Vignos M, Weinstock-Guttman B (2023) Patient-reported outcomes are the strongest predictors of disease disability in intramuscular interferon beta-1a users. Neurodegener Dis Manag 13:151–159
36. Vaughn CB, Jakimovski D, Kavak KS, Ramanathan M, Benedict RHB, Zivadinov R, Weinstock-Guttman B (2019) Epidemiology

and treatment of multiple sclerosis in elderly populations. Nat Rev Neurol 15:329–342
37. Vaughn CB, Kavak KS, Dwyer MG, Bushra A, Nadeem M, Cookfair DL, Ramanathan M, Benedict RHB, Zivadinov R, Goodman A, Krupp L, Motl RW, Weinstock-Guttman B, Kolb C, Robb JF, Jubelt B, Gerber A, Kister I, Ryerson LZ, Coyle P, Perel A, Gottesman M, Lenihan M, Edwards K, Garten L, Picone MA (2018) Fatigue at enrollment predicts EDSS worsening in the New York State Multiple Sclerosis Consortium. Mult Scler J 26:99–108
38. Zhang Y, Gonzalez Caldito N, Shirani A, Salter A, Cutter G, Culpepper W, Wallin M, Kosa P, Bielekova B, Lublin F, Stuve O (2020) Aging and efficacy of disease-modifying therapies in multiple sclerosis: a meta-analysis of clinical trials. Ther Adv Neurol Disord 13:1756286420969016
39. Zivadinov R, Cookfair DL, Krupp L, Miller AE, Lava N, Coyle PK, Goodman AD, Jubelt B, Lenihan M, Herbert J, Gottesman M, Snyder DH, Apatoff BR, Teter BE, Perel AB, Munschauer F, Weinstock-Guttman B (2016) Factors associated with benign multiple sclerosis in the New York State MS Consortium (NYSMSC). BMC Neurol 16:102