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Multiple sclerosis from onset to secondary progression: a 30-year Italian register study

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ABSTRACT

Background Three decades have passed since the initial approval of disease-modifying therapies (DMTs). Ongoing discussion is focused on fundamental aspects of the disease, highlighting a growing division between successes in managing relapsing multiple sclerosis (MS) and the persistent challenges posed by disease progression.

Methods A cohort study on prospectively acquired data from the Italian MS register. The primary outcome was to describe the MS disease course from onset to secondary progression (SP) defined according to a data-driven algorithm over 30 years follow-up and according to five different eras of disease onset.

Results A total cohort of 9958 patients was analysed; 1364 converted to SP after a mean of 8.5 (SD 5.5) years. A higher rate of patients converting to SP had never been exposed to DMTs (135, 9.9% vs 424, 5.2%) than non-converting ones. The treatment coverage was also lower in patients converting to SP than non-converting ones 58.4 (SD 31.5) vs 73.6 (SD 27.6).
The SP incidence rate was 1.26 (95% CI 1.19 to 1.32) overall. The rates showed a downward trend among the different eras: from 1st era 1.98 (95% CI 1.73 to 2.27) to 5th era 1.15 (95% CI 0.97 to 1.35).
In the multivariable Cox model, 10% increase of treatment coverage was associated to 19% lower risk to convert to SP (10%, HR 0.89, 95% CI 0.87 to 0.90).

Conclusions This 30-year analysis suggests that SP conversion rates have decreased over time, partially explained by improvements in therapeutic coverage. Future research should adopt a multifaceted approach to develop more comprehensive models of disease progression.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Three decades have passed since the initial approval of disease-modifying therapies (DMTs). Ongoing discussion is focused on fundamental aspects of the disease, highlighting a growing division between successes in managing relapsing multiple sclerosis (MS) and the persistent challenges posed by disease progression.

WHAT THIS STUDY ADDS

⇒ This population-based epidemiological investigation provides quantitative assessment of secondary progression (SP) conversion rates spanning from initial DMT authorisation (1993) through contemporary practice. Multivariable Cox proportional hazards modelling demonstrated that each 10-percentage-point increase in therapeutic coverage was associated with a 19% reduction in SPMS conversion hazard (adjusted HR 0.89, 95% CI 0.87 to 0.90).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further investigation is warranted to delineate the temporal dynamics between inflammatory and neurodegenerative pathophysiological processes in MS, with particular emphasis on DMT-mediated modification of disease trajectories. These findings could inform clinical algorithms and health policy development, underscoring the imperative for continued therapeutic innovation in MS management.

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INTRODUCTION

Multiple sclerosis (MS) represents a complex neurological disease characterised by a wide range of symptoms and challenges persist in understanding the intricacies of secondary progressive MS (SPMS), necessitating robust predictive markers and targeted interventions.[1]

The immunological basis of MS, crucial to the mechanisms of disease-modifying therapies (DMTs), remains pivotal, and ongoing research explores their impact on the conversion to SPMS.[2] In this context, neurodegenerative processes as axonal loss, grey matter atrophy and synaptic dysfunction play significant roles, contributing to irreversible disability highlighting the complexity of SPMS beyond the inflammatory phase.[2 3]

The definition of SP is not uniform, which may compromise the evaluation of risk factors—including the impact of DMTs and treatment adherence—and consequently affect assessment of disease course transition; furthermore, predictors of progression remain insufficiently defined amid

contradictory findings, with temporal trends in SP incidence and the influence of emerging therapeutic landscapes remaining poorly characterised.[4–11]

Three decades since the initial approval of DMTs have marked the dawn of MS treatment era,[12] with ongoing scientific debate increasingly highlighting a dichotomy between significant therapeutic advances in managing relapsing MS and the persistent challenges posed by disease progression, which remains a significant unmet need. Consequently, data from national and international registries constitute an essential resource for elucidating the long-term trajectory of the disease.

In this study, we aimed to characterise the MS disease course from onset to SP over 30 years follow-up in a large cohort of patients prospectively monitored in the Italian MS register (IMSR). Specifically, we sought to describe the incidence of SPMS defined using a previously validated data-driven algorithm (DDA)[4] across this period and to compare it among five different eras.

Furthermore, we investigated how treatment coverage and longitudinal trajectories, as measured by the Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Severity Scale (MSSS), have evolved over the past 30 years.

MATERIALS AND METHODS

Study design and setting

This is a cohort study using prospectively acquired data from the IMSR extracted in November 2023. At the time of data extraction, longitudinal data of 85 992 patients from 137 MS centres were available.

Participants

Subjects with a first symptom suggestive of MS onset, with age >18 years, at least six or more EDSS evaluations with functional system (Fs) score pyramidal available and 5 years or more of follow-up were included.

We excluded patients with a progressive course at the first evaluation and those enrolled in randomised clinical trials.

We then divided patients into five eras according to the year of the disease onset.

To ensure at least 5 years of follow-up for the last era, the interval 1993–2018 was considered. Five eras were established, each lasting 5 years, except for the second era, which was extended to 6 years to ensure a more homogeneous distribution following the approval of highly effective DMTs. The eras were distributed as follows: era I from 1 January 1993 to 31 December 1997, era II from 1 January 1998 to 1 January 2004, era III from 1 January 2004 to 1 January 2008, era IV from 1 January 2009 to 1 January 2013 and era V from 1 January 2014 to 1 January 2018.

Variables included in the dataset were date of birth, sex, date of disease onset, date of disease courses, dates of relapses, dates and values of EDSS evaluations, dates and values of pyramidal functional score evaluations, and start and end dates and name of all the administered DMTs.

Neurostatus certification was required at each participating centre. The relapse definition was standardised among Italian register centres.

In addition, the IMSR protocol stipulates annual updates of the minimum dataset, and this undergoes a rigorous quality assurance procedure[13] and has a coverage of about 70% with respect to the whole Italian MS population.

Outcomes and covariates definition

SPMS conversion was defined according to a previously reported DDA[4] modified from a previously published definition[5]: a three-strata progression magnitude (1.5 point increase if the baseline EDSS was 0, 1.0 point increase if the baseline EDSS was 1.0–5.5, 0.5 point increase if the baseline EDSS was >5.5) with a minimum EDSS score of 4.0 and a minimal pyramidal FS score of 2.0 at the time of conversion to SPMS confirmed at 3 months and at the end of follow-up (last EDSS score ≥4.0; last Fs pyramidal score ≥2) . In order to reduce the impact of transient EDSS modification due to relapses, all the EDSS scores collected during a relapse (±30 days) were excluded.

The MSSS was calculated by normalising EDSS relative to disease duration according to Roxburgh *et al*.[14] The MSSS score ranges from 0.01 to 9.9.

Baseline EDSS was defined as the first available within 2 years from MS onset. EDSS recorded within 30 days of a relapse were excluded.

Follow-up was defined as the time between the baseline EDSS and last available EDSS entry (non-converting patients) or SP occurrence (converting to SP patients), whichever occurred first.

Relapses were divided into seven phenotypes based on the presenting symptoms and signs: pyramidal, sensory, bowel/bladder, cerebellar, brainstem, visual and cognitive. The simultaneous involvement of multiple phenotypes was considered polyphenotypic.[15]

Treatment coverage was calculated as the total proportion of time spent treated with DMTs within the follow-up.

We classified DMTs into moderate efficacy (interferon beta products, glatiramer acetate, teriflunomide, dimethyl fumarate, azathioprine and methotrexate) and high-efficacy (fingolimod, cladribine, natalizumab, ocrelizumab, alemtuzumab, rituximab, mitoxantrone and cyclophosphamide) as previously defined.[16]

Source of bias and sample size

This observational study is subject to selection bias due to the non-random inclusion of patients from the IMSR. Information bias may persist despite the use of complete data for specific outcomes, as systematic errors in data recording, variability in coding practices. Confounding remains a concern, as unmeasured or residual confounders may influence the observed associations, even after statistical adjustments. The lack of randomisation limits causal inference, and findings should be interpreted within the context of these methodological constraints.

This study is a descriptive, registry-based observational analysis aimed at characterising the temporal evolution of SP conversion incidence in the IMSR. As no formal hypothesis testing was planned, a priori sample size calculation was not applicable. The study includes all eligible patients recorded in the registry during the study period, ensuring representativeness of the target population and reliability of the descriptive estimates.

Statistical analysis

Patients' baseline demographic and clinical characteristics are reported as mean±SD, or median along with quartiles (first and third), and as frequencies and percentages for continuous and categorical variables, respectively. The normality and asymmetry of continuous variables'distribution were assessed by skewness index and Q–Q plot.

Group comparisons were assessed by χ^2 or Fisher's exact tests as appropriate for categorical variables and by analysis of variance model or Kruskal-Wallis test as appropriate for continuous variables.

Overall and 10-year incidence rates (IRs) for SPMS conversion were reported as the number of events per 100 person-years

along with their 95% CIs. IRs were estimated also within each era.

Kaplan-Meier curves were used to represent time to SPMS conversion. Cox proportional hazards regression models were used to estimate the time to SPMS conversion, with the eras considered as the exposure. Potential confounders included in the multivariable model, as fixed effects, were sex, age at disease onset, time to diagnosis from onset, type of onset (monosymptomatic vs polysymptomatic), baseline EDSS, baseline pyramidal Fs score, total number of relapses and treatment coverage. Results were reported as HRs along with their 95% CIs. The proportionality of hazards assumption was assessed using scaled Schoenfeld residuals. Standard df (n–p–1) were applied to all statistical models, following conventional approaches for survival analyses and Cox proportional hazards models.

10-year EDSS and MSSS longitudinal trajectories were estimated using linear mixed effects model (restricted maximum likelihood, REML algorithm) with repeated measures over time and a spatial covariance matrix to account for unequally spaced time-visit observations. Continuous time and era as well as their interaction term, were included in the model as fixed effects. Random intercepts for centres was modelled using a compound symmetry covariance matrix. The intraclass correlation coefficient, measuring the centre effect was also estimated. Results were reported as estimated slopes, 95% CIs and SEs. To assess whether longitudinal trends vary between eras, the interaction term (era-by-time) was included into the model. Estimated EDSS and MSSS values were also displayed.

To address potential biases in registry coverage in the oldest era, we performed sensitivity analyses by running Cox proportional hazards models and 10-year EDSS and MSSS longitudinal trajectories with the REML algorithm removing era I.

The dataset was complete, and no imputation methods were applied. No adjustments for multiple comparisons were needed or performed. A two-sided $p<0.05$ was considered for statistical significance. All statistical analyses were performed using R (packages: 'survival', 'survminer', 'Hmisc', 'ggplot2', 'networkD3').

RESULTS

Characteristics of the whole cohort, patients non-converting versus converting to SP

From a total cohort of 85 992 patients, 9958 were included in the analysis, female 6524 (68%), mean age 33.2 years (SD 9.7). Flow chart of the study is shown in figure 1. The whole cohort baseline characteristics are shown in table 1.

Out of them, 1364 (13.7%) converted to an SP form according to DDA definition after a mean time of 8.5 (SD 5.5) years. The characteristics of patients converting to SP versus patients non-converting are detailed in table 1.

Generally, patients converting to SP were older than non-converting patients, mean age at onset 36.6 (SD 10.3) vs 32.7 (SD 9.5) and had a higher baseline EDSS (2.0, Q1–Q3 1.5–3.0 vs 1.5 (1.0–2.0) (table 1).

Furthermore, a higher rate of patients converting to SP had never been exposed to DMTs (135, 9.9% vs 424, 5.2%) than

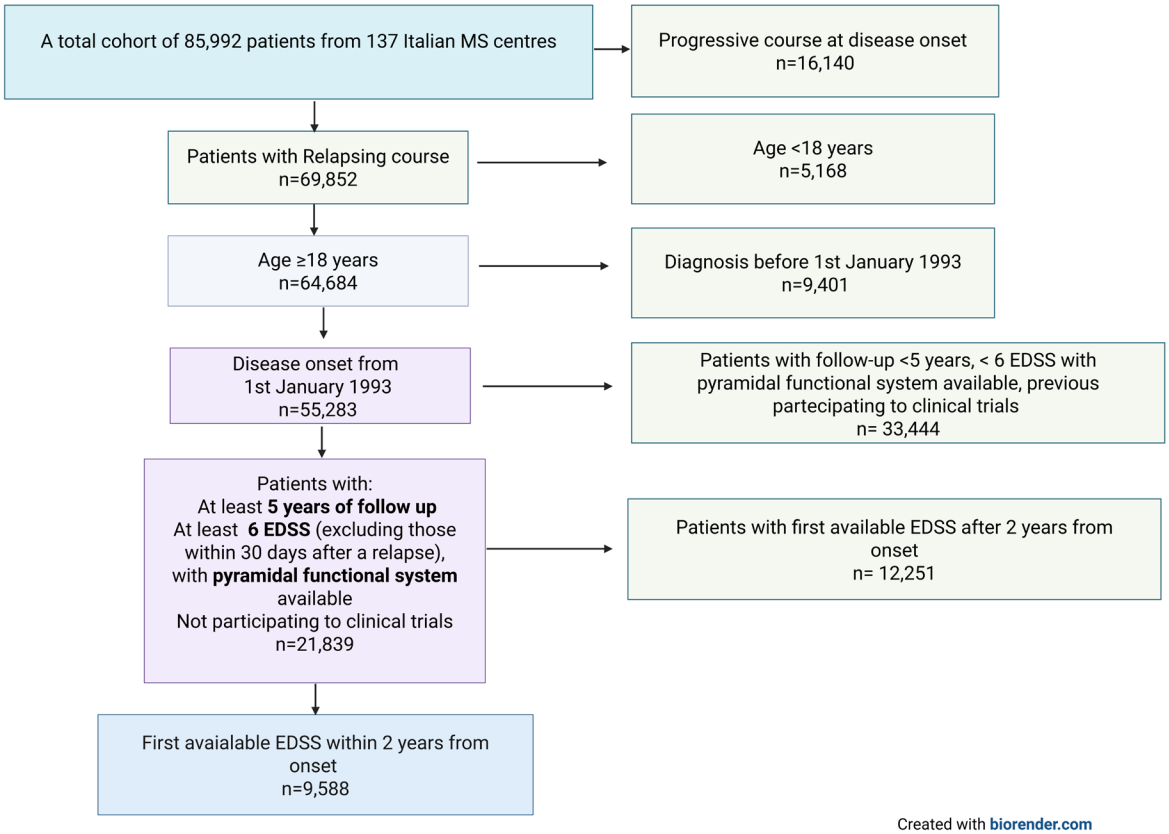

Figure 1 Flow chart of the study. Created in BioRender. D'Amico, E. (2025); https://BioRender.com/y48z519. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Table 1 Characteristics of the whole cohort, patients non-converting versus converting to SP

	Total (N=9588)	Patient non-converting to SP (N=8224)	Patients converting to SP (N=1364)
Sex, n (%)			
Female	6524 (68)	5652 (68.7)	872 (63.9)
Male	3064 (32)	2572 (31.3)	492 (36.1)
Age at disease onset, years			
Mean (SD)	33.2 (9.7)	32.7 (9.5)	36.6 (10.3)
Age at MS diagnosis, years			
Mean (SD)	33.9 (9.8)	33.4 (9.6)	37.4 (10.4)
Type of MS onset, n (%)			
Mono-symptomatic	283 (3)	244 (3)	39 (2.9)
Poly-symptomatic	9305 (97)	7980 (97)	1325 (97.1)
Baseline EDSS			
Median (Q1, Q3)	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)	2.0 (1.5, 3.0)
Baseline Pyramidal Fs score			
Median (Q1, Q3)	1 (1, 2)	(1, 2)	3 (2, 3)
Baseline MSSS			
Median (Q1, Q3)	4.3 (2.8, 5.0)	4.3 (2.8, 5.6)	5.6 (4.3, 7.6)
Total N.of relapses			
Mean (SD)	3.6 (3.3)	3.4 (3.2)	4.5 (3.9)
ARR			
Median (Q1, Q3)	0.3 (0.2, 0.5)	0.2 (0.1, 0.4)	0.5 (0.3, 0.9)
MS therapy, n (%)			
Patients never exposed to DMTs	559 (5.8)	424 (5.2)	135 (9.9)
Patients exposed to DMTs	9029 (94.2)	7800 (94.8)	1229 (90.1)
Treatment coverage (%)			
Mean (SD)	71.5 (28.7)	73.6 (27.6)	58.4 (31.5)
Time to first DMT prescription, years			
Mean (SD)	1.7 (2.4)	1.6 (2.4)	1.9 (2.3)
No of patients according to disease onset era, n (%)			
I	581 (6.1)	378 (4.6)	203 (14.8)
II	1772 (18.5)	1385 (16.8)	387 (28.4)
II	2462 (25.7)	2106 (25.6)	356 (26.1)
IV	2957 (30.8)	2678 (32.6)	279 (20.5)
V	1816 (18.9)	1677 (20.4)	139 (10.2)
Follow-up*, years			
Mean (SD)	11.8 (5.2)	8.5 (5.5)	8.5 (5.5)
Last* EDSS			
Median (Q1, Q3)	2.0 (1.0, 3.5)	1.5 (1.0, 2.0)	4.5 (4.0, 6.0)
Last* MSSS			
Median (Q1, Q3)	2.7 (1.5, 4.9)	2.3 (1.3, 3.8)	7.5 (6.2, 8.6)

*Last available follow-up (non-converting patients) or at the time of SP conversion (patients converting to SP).
ARR, annualised relapse rate; DMTs, disease-modifying therapy; EDSS, Expanded disability Status Scale; Fs, functional system; MS, multiple sclerosis; MSSS, Multiple Sclerosis Severity Scale; SP, secondary progressive.

non-converting ones. The treatment coverage was also lower in patients converting to SP than non-converting ones 58.4 (SD 31.5) vs 73.6 (SD 27.6) (table 1).

Additionally, time to first treatment was longer in patients converting to SP 1.9 (2.3) than non-converting ones 1.6 (SD 2.4) (table 1).

Online supplemental eTables 1–3 show baseline characteristics of the whole cohort, converting to SP patients and non-converting patients divided according to the disease onset era.

Table 2 Conversion to SP incidence rates

Disease onset era	Incidence rate* (95% CI)	10 years incidence rate* (95% CI)
Overall	1.26 (1.19 to 1.32)	1.12 (1.05 to 1.2)
I	1.98 (1.73 to 2.27)	1.66 (1.35 to 2.05)
II	1.39 (1.26 to 1.54)	1.24 (1.08 to 1.42)
III	1.14 (1.03 to 1.27)	1.02 (0.90 to 1.16)
IV	1.02 (0.91 to 1.15)	1.01 (0.89 to 1.14)
V	1.15 (0.97 to 1.35)	1.15 (0.97 to 1.35)

*For 100 person-years.
SP, secondary progression.

Notably, among patients converting to SP, the treatment coverage increased slowly with wider intervals between the first and third quartile among different eras than non-converting patients, although an upward trend in both groups (V era converting to SP 70.4%, Q1–Q3 38.2%–86.1%, vs V era non-converting patients 85.9%, Q1–Q3 72.8%–93.1%).

Incidence of secondary SPMS

The SP IRs and 10-year SP IRs are shown in table 2. The SP IR was 1.26 (95% CI 1.19 to 1.32) overall. The rates showed a downward trend among the different era: from 1st era 1.98 (95% CI 1.73 to 2.27) to 5th era 1.15 (95% CI 0.97 to 1.35) (table 2).

Kaplan-Meier curves for time to SPMS conversion, according to disease onset era, are shown in figure 2.

Univariable and multivariable Cox models confirmed the decreasing trend in SPMS conversion rates (table 3), with a role of disease onset eras on the risk of converting to SP.

Compared with the I era, the multivariable Cox models (table 3) showed that the risk of SP conversion is lower in era II (HR 0.78, 95% CI 0.66 to 0.93), in era III (HR 0.63, 95% CI 0.52 to 0.76), in era IV (HR 0.57, 95% CI 0.46 to 0.70) and in era V (HR 0.65, 95% CI 0.50 to 0.83). The confounding variables included into the model showed consistent associations (table 3). When the multivariable Cox model further included the treatment coverage, a 10% increase was associated to 19% lower risk to convert to SP (10%, HR 0.89, 95% CI 0.87 to 0.90).

DMTs and disease onset era

Details on DMTs prescription by disease onset era for the whole cohort, converting to SP and non-converting patients are reported in online supplemental eTables 1–3.

Noteworthy, the prescription rate of first high-efficacy DMT was systematically higher (in each disease onset era) in converting to SP versus non-converting patients (overall 111, 9.0% vs 592, 7.6%; era V 18.8% vs 13.2%; era I 4.2% vs 1.5%).

Number of DMTs prescribed did not differ between disease onset era and between converting to SP versus non-converting patients (overall 2 (SD 1.3) vs 2.7 (SD 1.2)).

Time to first DMT decreased over time from era I median 3.2 years (Q1, Q3 1.5–6.3) to era V median 0.6 years (Q1, Q3: 0.3–1.1), but this decreasing trend was common also in converting and non-converting patients (online supplemental eTables 2 and 3).

Treatment sequencing among different disease onset era in the whole cohort is shown in Sankey diagrams (online supplemental eFigures 1–5).

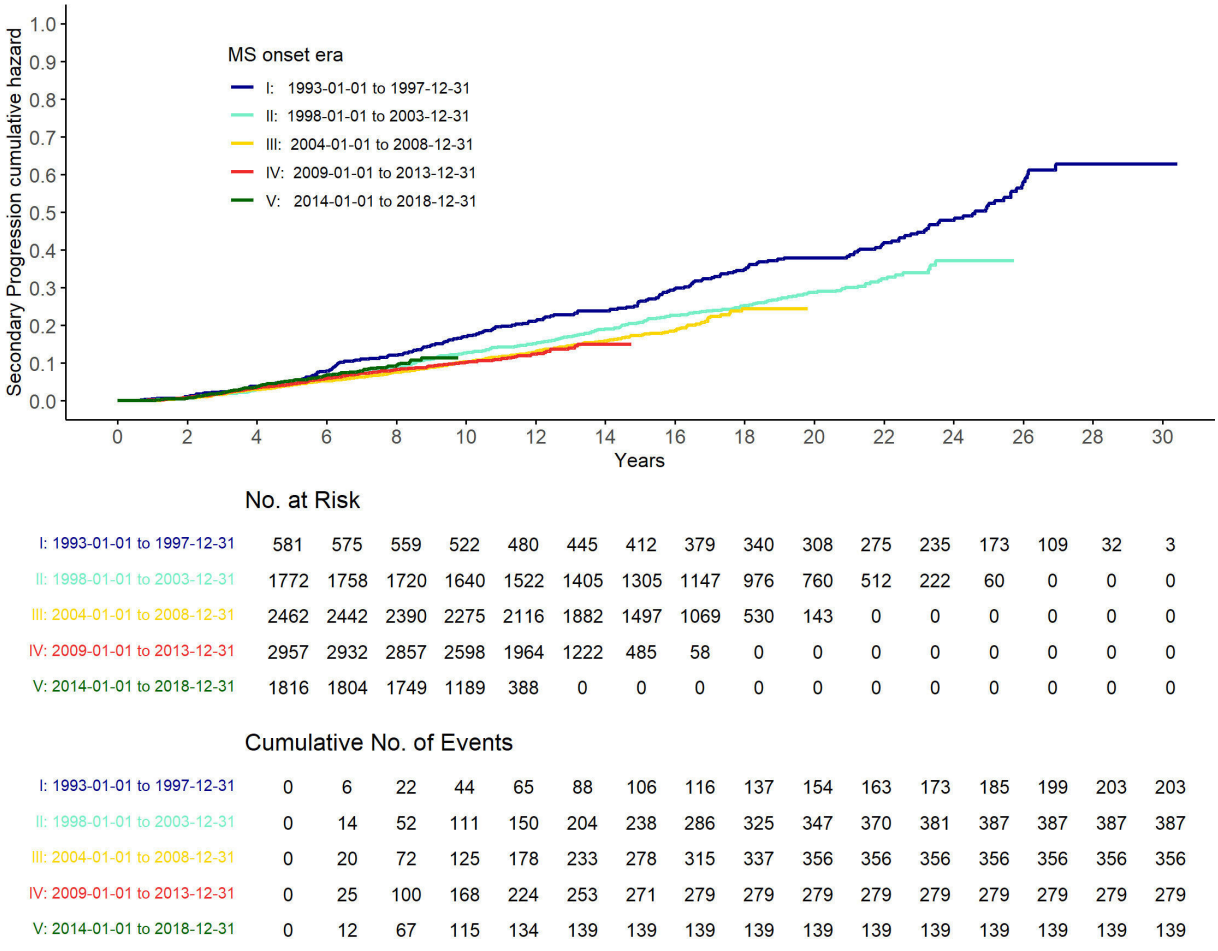

Figure 2 Kaplan-Meier curves for time to SPMS conversion according to disease-onset era. SPMS, secondary progressive multiple sclerosis. SPMS, secondary progressive multiple sclerosis.

EDSS and MSSS trajectories over time

The 10 years longitudinal trajectories of EDSS separately for non-converting patients versus converting to SP are shown in figure 3A,B. Details on estimated slopes, SEs and 95% CI for each era are reported in online supplemental eTable 4.

In the V disease onset era, there was a significant improvement of 10-year longitudinal trajectories of EDSS in the non-converting patients (p for interaction=0.0117) (online supplemental eTable 4).

Generally, in this cohort, EDSS increased over time with less steep slope in the last three disease onset era than first two (figure 3A).

Conversely, in converting to SP patients, we did not observe any difference in 10 years longitudinal trajectories between

Table 3 Univariable and multivariable Cox models for SP conversion

		Univariable HR (95% CI)	P value	Multivariable 1 (95% CI)	P value	Multivariable 2 (95% CI)	P value
Era	I	ref		ref		ref	
	II	0.75 (0.63 to 0.90)	0.0019	0.78 (0.66 to 0.93)	0.0066	0.96 (0.80 to 1.15)	0.6761
	III	0.65 (0.54 to 0.79)	<0.0001	0.63 (0.52 to 0.76)	<0.0001	0.84 (0.69 to 1.02)	0.0826
	IV	0.64 (0.52 to 0.78)	<0.0001	0.57 (0.46 to 0.70)	<0.0001	0.86 (0.70 to 1.07)	0.1785
	V	0.78 (0.62 to 0.99)	0.0378	0.65 (0.50 to 0.83)	0.0005	0.97 (0.76 to 1.25)	0.8313
Sex	Male vs female			1.28 (1.15 to 1.43)	<0.0001	1.29 (1.15 to 1.4)	<0.0001
Age at disease onset				1.04 (1.04 to 1.05)	<0.0001	1.04 (1.03 to 1.04)	<0.0001
Time to diagnosis from onset				0.98 (0.94 to 1.03)	0.4027	0.94 (0.89 to 0.98)	0.0027
Type of MS onset	Polysymptomatic versus monosymptomatic			1.30 (0.95 to 1.79)	0.1036	1.22 (0.89 to 1.68)	0.2225
Baseline EDSS				1.32 (1.25 to 1.40)	<0.0001	1.30 (1.23 to 1.38)	<0.0001
Baseline pyramidal Fs score				1.28 (1.18 to 1.38)	<0.0001	1.29 (1.19 to 1.39)	<0.0001
Total No of relapse				1.01 (1.00 to 1.03)	0.0377	1.02 (1.01 to 1.04)	0.0004
Treatment coverage (per 10%)						0.89 (0.87 to 0.90)	<0.0001

EDSS, Expanded Disability Status Scale; Fs, functional system; MS, multiple sclerosis; SP, secondary progression.

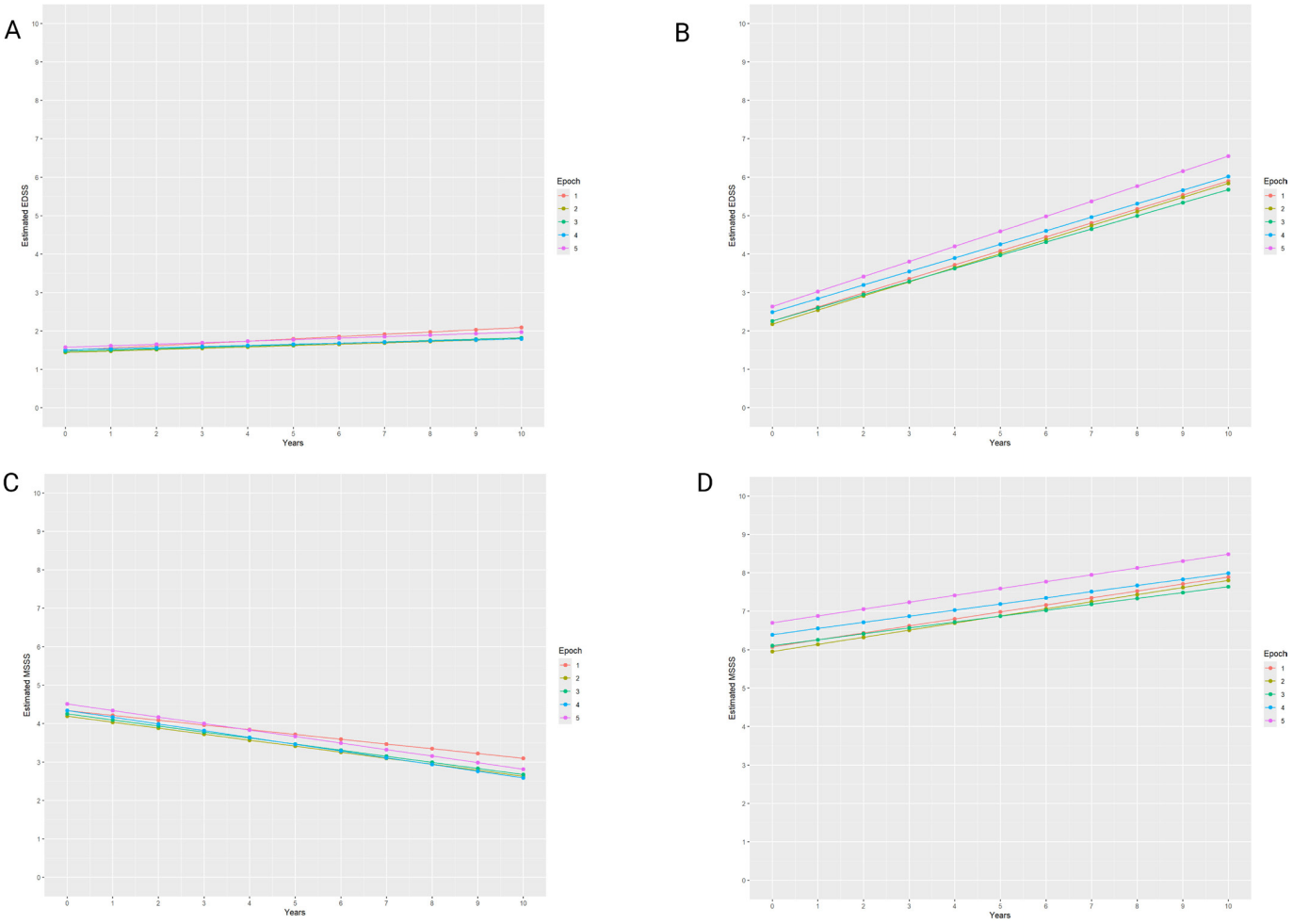

Figure 3 10 years longitudinal trajectories of EDSS and MSSS for converting to SP versus non-converting patients. (A) EDSS in non-converting patients. (B) EDSS in converting to SP patients. (C) MSSS in non-converting patients. (D) MSSS in converting to SP patients. EDSS, Expanded Disability Status Scale; MSSS, Multiple Sclerosis Severity Score; SP, secondary progression.

disease onset eras (p for interaction=0.4723) (figure 3B, online supplemental eTable 4).

The 10 years longitudinal MSSS showed similar results (figure 3C,D, online supplemental eTable 4).

In non-converting patients, the 10 years MSSS longitudinal trajectories decreased more remarkably in the latest disease onset eras (p for interaction=0.0035) (figure 3C, online supplemental eTable 4).

In converting to SP patients, the 10 years MSSS longitudinal trajectories increased over time, but without differential trends between disease onset eras (p for interaction=0.7096) (figure 3D, online supplemental eTable 4).

Sensitivity analyses

Sensitivity analysis confirmed the trends reported in principal analysis. The multivariable Cox model after era I removal confirmed that a 10% increase of treatment coverage was associated to 19% lower risk to convert to SP (10%,HR 0.89, 95% CI 0.87 to 0.91) (online supplemental eTable 5).

The 10 years longitudinal analyses of EDSS and MSSS separately for non-converting patients versus converting to SP are reported in online supplemental eTable 6. Here, no differences were found in converting and non-converting patients for 10 years longitudinal trajectories of EDSS. Conversely, in the V disease onset era, there was a significant improvement of 10 years longitudinal trajectories of MSSS in the non-converting patients (p for interaction=0.0208) (online supplemental eTable 6).

DISCUSSION

Our findings present an epidemiological analysis spanning 30 years, from the first DMT approval in 1993 to the present, examining the 10-year cumulative incidence of SPMS across this period. Overall, SPMS IRs significantly decreased over time and the era itself was associated with a progressive reduction in SPMS conversion. Notably, the delay from diagnosis to first DMT shortened by 75% from era I to V and 50% from era II to V.

When analysing the possible disease predictors, in the multivariable model, classical factors (age, sex, baseline EDSS, total number of relapses) were variably associated with a higher risk of SP incidence, but when treatment coverage was included in the model, it was found that a 10% increase of treatment coverage reduced the risk of SP conversion by 19%.

Additionally, patients converting to SP had a higher proportion of individuals who had never been exposed to DMTs (10% vs 5.9%).

Generally, according to the multivariable model, it appeared that the advent of DMTs played a role in reducing the SP incidence over time. These results align with previously published data that provided evidence that sustained exposure to DMTs

decreases the risk of disability accumulation, especially when considering different treatment strategies for relapsing MS.[17–19] The data indicated that escalation of treatment efficacy was inferior to using more efficacious DMT as initial treatment, particularly if started within 2 years from disease onset.[17–19]

Several studies have been focused on the definition of SPMS, possible early predictors of disease course, and the optimal sequence and timing of MS therapy.[4 7–9 20 21]

In our cohort, across different eras, the use of high-efficacy therapies increased only slightly for both non-converting and those who convert to SP. However, patients who converted to SP had a slightly higher percentage of high-efficacy therapy use, though still below 20%.

All these findings warrant further discussion. First, the 10 years SP incidence did not decline substantially from the second era onwards despite the earlier treatment initiation and high treatment coverage. This issue requires further investigation, particularly with regard to additional predictors of worse outcomes, such as smoking, socioeconomic factors and age-related comorbidities. Furthermore, it is quite possible that certain factors related to SP conversion are population-specific and time-specific, as previously suggested by the notable differences in MS survival rates across eras.[22 23]

Additionally, given that age and male sex were identified as independent predictors of SP conversion in our cohort, their influence should be further examined across different disease onset eras.[16 24 25] For the inflammatory component, the sex difference disappears after the age of 50 years, indicating that the differences between younger men and women may, to some extent, be attributable to sex hormones, but further investigations of their role are needed.[16 24]

According to previously published data, even milder patients—treated more frequently and earlier—convert at similar rates as before.[26] This suggests that preventing progression may depend on factors beyond the variables currently analysed. Changes in diagnostic criteria, stricter inclusion/exclusion standards and refined definitions of relapses and disease worsening might contribute to an apparently more favourable disease course with DMTs.[26] Additionally, focusing on achieving a stable disease state and reclassifying progressive MS from separate primary and secondary types to an integrated active/inactive model might also be influencing the disease course. Collectively, these aspects have contributed to a less severe MS progression over the past decade.

Considering that our cohort is based on a DDA definition of SPMS, which attempts to move beyond the evolving diagnostic criteria, this element needs to be better contextualised and discussed. As shown in a recent real-world Swedish study—even in settings with regular monitoring and low barriers to therapy switching—the impact of the initial DMT choice on disability accrual may be less pronounced than previously thought.[27] These observations add to an increasing body of evidence that disease burden cannot be explained solely by classical parameters of disease activity or by the rate of high-efficacy DMT use.[27]

Nevertheless, in our cohort, the overall use of high-efficacy therapies as a first-choice treatment remains limited. Although our Sankey diagram analysis, which examines treatment eras across all patients (rather than segregating into converting to SP versus non-converting groups to avoid statistical bias), does not capture precise timing of therapy switches, it consistently reveals a general trend: initial low-efficacy treatments predominate, and subsequent switching is infrequent. This trend may be influenced by two principal factors: therapeutic inertia and limited drug access.[28–32] The first, in the context of MS, may stem from clinical hesitancy, uncertainty over the optimal timing for escalation, or concerns about the risk–benefit profiles of high-efficacy agents; the second may be due to reimbursement policies and regulatory barriers that can restrict access to high-efficacy therapies, promoting a conservative approach during the early treatment phase.[28–32]

Another critical aspect highlighted is the 10 year longitudinal trends of EDSS and MSSS, which yield consistent results. Both scores exhibited a slower growth trend with advancing onset era among non-converting patients, whereas this trend was absent among patients who converted to SP.

The sensitivity analysis confirmed similar trends for MSSS but not for EDSS, which may be explained by the reduced sample size and exclusion of era I, during which EDSS slopes increased at a higher rate compared with the more homogeneous subsequent eras.

As previously noted regarding baseline cohort differences, data on differing percentages of untreated individuals and treatment approach (eg, percentage of high-efficacy therapies, their trends and the timing of their introduction) alone are insufficient to justify the aforementioned.

Maybe our results may suggests that findings observed are strictly related to outcomes definition and patients selection in real world setting, and, while clinical phenotyping was essential for organising the pivotal clinical trials that allowed MS treatment 30 years ago, the field now struggles with how classifying patient cohorts by clinical phenotype alone may obscure the diverse biologic, pathologic and modulatory factors that underlie the spectrum of disease and its heterogeneous outcomes.[33]

These elements have led to the necessity of viewing MS as a spectrum and avoiding dichotomous concepts in patient management, such as ‘progression versus relapsing’ or, as long debated, whether disability accumulation could be attributed to progression independent of relapse activity or relapses associated worsening.[15 34 35] An integrated approach using increasingly refined tools at onset to identify differential elements for predicting disease course is imperative.[36]

This study possesses strengths, notably in its cohort selection criteria, which ensure uniformity and the absence of data imputation, with all used data being complete and unimputed.

The novelty of the inquiry and the extended follow-up period, aimed to elucidate the temporal progression of the phenomenon as an epidemiological datum. The definition of progression according to DDA criteria provides an objective measure independent of varying diagnostic criteria over time or individual neurologists’ perspectives, as validated in other register studies.

Study limitations

The primary limitations of this investigation derive from its retrospective, observational design, as detailed in the methods section. The use of register-based data introduces potential sources of bias and confounding factors, which have been acknowledged and addressed in our analytical approach. In particular, the limitations of our study belong to the following aspects.

Data availability constraints

Data on key factors such as ethnicity, family history, socioeconomic status (including education and income), regional differences in clinical practices and procedures, comorbidities, body mass index, smoking history, access to DMTs, therapeutic adherence, timing of switches, systematic MRI data were not available.

Methodological challenges

The standardised definition of therapeutic eras, while necessary for temporal comparisons, resulted in heterogeneous follow-up periods across cohorts. Differential censoring across eras also poses analytical challenges that may impact the interpretation of long-term outcomes. Moreover, the DDA is based solely on EDSS changes over time, which may introduce bias by selecting patients with more aggressive disease courses due to the EDSS 4.0 cut-off. To mitigate this, we included MSSS, a linear variable, in our model.

Sample selection and generalisability

Our rigorous selection criteria, while enhancing data quality and homogeneity, led to a substantial reduction in sample size and potential loss of informative data points. The absence of a comparison with excluded patients further limits the generalisability of our findings. The trade-off between data quality and sample representation should be considered when interpreting the results.

Causal inference and study design

Although our results align with those from previous studies, the observational nature of our study does not allow us to establish a causative link between DMT exposure and SP conversion. The post hoc division of the cohort into converting and non-converting SP groups, based on outcomes rather than predefined criteria, may lead to non-random assignment and an increased risk of overfitting the model to the data, thereby limiting the applicability of our findings to other populations.

Nevertheless, our approach was undertaken to apply homogeneous and modern criteria, generating insights that are directly relevant to current clinical practice, stimulating new hypotheses about disease progression and treatment effects and enabling tailored analysis of subgroups for more personalised insights.

CONCLUSIONS

This 30-year analysis suggests that SPMS conversion rates have decreased over time, partially explained by improvements in therapeutic coverage and earlier treatment initiation. However, our findings suggest that DMT utilisation alone cannot fully account for these changes. Additional factors likely contribute to this evolution, including shifts in diagnostic criteria, more stringent definitions of disease progression, changes in patient selection and evolving clinical practices. The complex interplay between these elements, alongside therapeutic advances, collectively shapes the observed disease trajectories. Future research should adopt a multifaceted approach that considers both treatment strategies and these contextual factors to develop more comprehensive models of disease progression and more effective interventions for patients with MS.

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