Multiple Sclerosis from onset to secondary progression: a 30-years Italian register study

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INTRODUCTION

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.**

AIM

This study aimed to:

characterise the MS disease course from onset to secondary progression (SP) over 30 years of follow-up in a large cohort of patients, prospectively monitored in the Italian MS register;

describe the incidence of Secondary Progressive MS (SPMS) across this period using a previously validated data-driven algorithm (DDA) and compare it among five different eras.

METHODS

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

The main outcomes included the overall and 10-years incidence rates (IR) for SP conversion. IRs were estimates 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 expanded disability status scale (EDSS), baseline pyramidal functional system score, total number of relapses and treatment coverage.

RESULTS

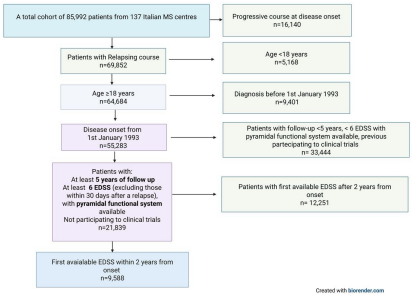
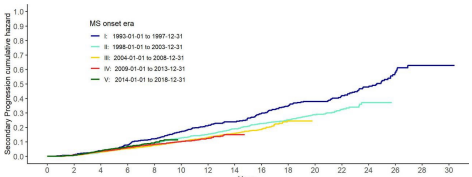


Figure 1. Flow chart of the study. Created in BioRender. D'Amico, E. (2025); https://BioRender.com/y48z519. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

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) (fig. 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.



No. at Risk

I: 1993-01-01 to 1997-12-31	581	575	559	522	480	445	412	379	340	308	275	235	173	109	32	3
II: 1998-01-01 to 2003-12-31	1772	1758	1720	1640	1522	1405	1305	1147	976	760	512	222	60	0	0	0
III: 2004-01-01 to 2008-12-31	2462	2442	2390	2275	2116	1882	1497	1069	530	143	0	0	0	0	0	0
IV: 2009-01-01 to 2013-12-31	2957	2932	2857	2598	1964	1222	485	58	0	0	0	0	0	0	0	0
V: 2014-01-01 to 2018-12-31	1816	1804	1749	1189	388	0	0	0	0	0	0	0	0	0	0	0

Cumulative No. of Events

I: 1993-01-01 to 1997-12-31	0	6	22	44	65	88	106	116	137	154	163	173	185	199	203	203
II: 1998-01-01 to 2003-12-31	0	14	52	111	150	204	238	286	325	347	370	381	387	387	387	387
III: 2004-01-01 to 2008-12-31	0	20	72	125	178	233	278	315	337	356	356	356	356	356	356	356
IV: 2009-01-01 to 2013-12-31	0	25	100	168	224	253	271	279	279	279	279	279	279	279	279	279
V: 2014-01-01 to 2018-12-31	0	12	67	115	134	139	139	139	139	139	139	139	139	139	139	139

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.

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 10-years 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).

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 1), with a role of disease onset eras on the risk of converting to SP. 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).

		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

Table 1. Univariable and multivariable Cox models for SP conversion. EDSS, Expanded Disability Status Scale; Fs, functional system; MS, multiple sclerosis; SP, secondary progression.

CONCLUSIONS

This 30-year analysis suggests that **SP conversion rates have decreased over time**, partially explained by **improvements in therapeutic coverage.**

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

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DISCLOSURES

The authors have nothing to disclose.

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