BMC Health Services Research

RESEARCH

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Economic burden of secondary progressive multiple sclerosis: DISCOVER study

Celia Oreja-Guevara[1,2*†], José E. Meca-Lallana[3], Irene Gómez-Estévez[1], José-Ramón Ara[4], Miguel Ángel Hernández Pérez[5], Julia Gracia Gil[6], Ana María Alonso Torres[7], Belén Pilo de la Fuente[8], Lluís Ramió-Torrentà[9], Sara Eichau Madueño[10], Francisco Gascón-Giménez[11], Bonaventura Casanova[12], Sergio Martínez-Yélamos[13], Marta Aguado Valcárcel[14], Maria Luisa Martínez Ginés[15], Yasmina El Berdei Montero[16], Ana María López Real[17], Vicente González-Quintanilla[18], Carlos Lopez de Silanes[19], José Enrique Martínez-Rodríguez[20], Lucienne Costa-Frossard[21], Moisés Garcés Redondo[22], Andrés Labiano Fontcuberta[23], Fernando Castellanos-Pinedo[24], Juan Antonio García Merino[25], Carmen Muñoz Fernández[26], Tamara Castillo-Triviño[27], Virginia Meca-Lallana[28], Joaquín Peña Martínez[29], Alfredo Rodríguez-Antigüedad[30], José María Prieto González[31], Eduardo Agüera Morales[32], Inmaculada Pérez Molina[33], Dulce M. Solar Sánchez[34], Nicolás Herrera Varo[35], Marta Aguirre Vázquez[36], José Manuel Rodríguez Barrios[36] and Jordi Río[37†]

Abstract

Background To estimate the socioeconomic burden of people with secondary progressive multiple sclerosis (pwSPMS), considering direct health care, direct non-health care, and indirect costs, and to evaluate the relationship between costs and patients' functional outcomes.

Methods Observational, cross-sectional, multicenter study with retrospective real-life clinical practice data collection from pwSPMS visiting the neurology services of 34 hospitals during 2019–2020. Clinical data included Expanded Disability Status Scale scores, number of relapses, magnetic resonance imaging, disease-modifying treatment (DMT), symptoms, and comorbidities from 24 months before the study visit. Resource use and allied costs were collected 12 months before the study visit. Patient-reported outcomes, functional and cognitive scales were also collected.

Results 70% of pwSPMS used primary care services, and nearly 50% needed assistance in a daycare or rehabilitation center. Almost 60% of the participants were receiving DMT at the study visit, and 80% needed support for domestic/housekeeping tasks. More than 90% were inactive at work, with nearly 80% taking early retirement. The estimated total annual cost per pwSPMS in Spain was almost €41,500, of which more than 50% (€21,400) were indirect costs, followed by direct health care costs (30%, €11,300), and, finally, direct non-health care costs (about 20%, €8,800). Older patients with severe disabilities and worse functional outcomes incurred higher costs.

†Celia Oreja-Guevara and Jordi Río contributed equally to the study and manuscript process.

*Correspondence:
Celia Oreja-Guevara
orejacbn@gmail.com

Full list of author information is available at the end of the article

Conclusions SPMS is a major burden on health care systems, patients, and society as a whole. Health care and societal policies should be aimed at improving the SPMS care pathway and minimizing patients' funding of direct non-health care costs.

Trial registration The trial is a non-interventional study. The NCC code is CBAF312AES01/NOV-EMS-2019–01.

Keywords Secondary progressive multiple sclerosis, Disability, Patient-reported outcomes, Socioeconomic burden, Indirect costs, Direct costs

Introduction

Multiple sclerosis (MS) places a pronounced burden on patients, national health systems (NHS), and society. As evidenced in previous studies, the direct costs of MS, mainly treatment costs, as well as indirect costs, have a positive correlation with the progression of the disease [1]. People with MS (pwMS) with severe disabilities use more health resources per year than those with mild or moderate illness [1]. An economic evaluation of different European countries conducted in 2015 estimated a total annual mean cost in pwMS with mild disabilities of €12,600–27,300, whereas in those with severe disabilities, it was in the range of €27,500–77,600 [2]. In Spain, results from the cited study estimated a mean annual total cost of €20,600 for mild disabilities versus €68,700 for severe disabilities [3].

Secondary progressive multiple sclerosis (SPMS) is a disabling progressive disease reached by about 70% of relapsing–remitting multiple sclerosis (RRMS) patients, leading to irreversible impairment. The prevalence of SPMS among pwMS in Europe is in the range of 15%–38%, whereas in Spain, it is around 15%–25% [1, 4–7]. It is estimated that 60% of pwMS will have a severe disability score in 20 years [8], and that it will take 10 years for all people with SPMS (pwSPMS) to reach this condition [9]. SPMS is accompanied by a worsening of physical function, cognitive impairment, psychological burden, and pain, all leading to a negative impact on patients' quality of life and a major economic burden despite the introduction of disease-modifying treatments (DMTs) [10, 11].

The economic burden of SPMS reported across studies may be an underestimate owing to the challenges of definitive diagnosis in this group of patients [12]. Uncertainty surrounding diagnosis may also contribute to the small sample sizes of patients with SPMS seen in the majority of studies and the observation that a number of studies reported costs for MS as a whole [12]. In this sense, different studies in Europe highlight that pwSPMS have much higher total annual costs than people with RRMS. A Finnish study conducted in 2015 estimated a cost of €71,177 for SPMS versus €36,492 for RRMS [13]. In this study and another carried out in Sweden in 2019, indirect MS costs were responsible for a higher proportion of SPMS costs versus RRMS costs [13, 14]. Similarly, in a large international multicenter study, the International MultiPlE Sclerosis Study (IMPrESS), severe SPMS was associated with higher total costs versus RRMS, with a higher proportion of indirect costs [15]. In Spain, data on the economic burden of SPMS are quite limited, with most studies focusing on MS and not SPMS specifically [1, 3]. However, a literature review study of MS costs in Spain found that higher costs for progressive MS were associated with indirect and direct non-health costs [16].

The aims of the present study are to estimate the socioeconomic burden of pwSPMS considering direct health care, direct non-health care, and indirect costs and to evaluate costs in relation to patients' functional outcomes.

Methods

Study design

DISCOVER was an observational, cross-sectional, multicenter study with retrospective data collection conducted according to real-world clinical practice conditions in Spain. Participants were consecutively included when they visited the neurology services of 34 Spanish public hospitals between 1 April 2019 and 6 March 2020 and met all the selection criteria. Information was collected at a single visit (inclusion visit or study visit) with no follow-up visits.

Eligible patients were ≥ 18 years old with SPMS, according to established definition criteria [11], diagnosed a minimum of 12 months before the study visit, with a score of 3–6.5 on the Expanded Disability Status Scale (EDSS) during the study visit, being an EDSS score of 3–3.5 indicative of moderate disability while EDSS scores ≥ 6 indicate severe disability, without relapses in the last 3 months before the study visit, who had been followed up in the same hospital for the last 12 months, and who had all the information required by the protocol in their clinical history. PwSPMS participating in any other clinical trial in the last 12 months, institutionalized patients, and those with severe cognitive impairment or psychological disorders that did not allow them to complete the study questionnaires were excluded. Before being included in the study, participants were required to provide informed consent.

The perspective identifies the relevant costs and health outcomes. Ideally, the most comprehensive is the

societal perspective, as it includes all costs and health outcomes. However, when using the societal perspective, it is important to also present the results achieved using the NHS and patient perspectives, as each piece of information can be valuable. To collect all types of costs associated with a chronic disease (direct health care and non-health care and, also, indirect costs), societal perspective is showed in the present study [17].

Demographic and clinical variables

The following demographic characteristics were collected during the study visit: age, gender, educational level, and current family situation (living alone or living with relatives: partner, children, or other relatives).

Clinical data were obtained during the study visit and from medical records. The main variables collected were the date of diagnosis of MS and SPMS; EDSS score (at MS and SPMS diagnosis and the study visit); the number of relapses from 3 to 12 months and 12 to 24 months before the study visit; the date of last magnetic resonance imaging (MRI); the presence and number of T1 black holes, gadolinium (Gd+)-enhancing lesions in T1 and T2 hyperintense lesions; and SPMS-related symptoms (at the study visit) and comorbidities (at the study visit).

Resource use and costs

One of the objectives of the study was to identify and quantify the use of the different resources related to the management of SPMS, which was done as follows:

- Direct healthcare resources used during the 12 months prior to the study visit were collected from medical records. They included: number of outpatient visits associated with MS, number of days per week in day/occupational centers or rehabilitation sessions for MS-related reasons, number of medical tests performed due to MS, hospitalizations (number and length of stay), number of emergency room visits associated with MS and MS/SPMS treatments (including rituximab, beta 1a-interferon, fingolimod, glatiramer acetate, beta 1b-interferon, dimethyl fumarate, natalizumab, teriflunomide, azathioprine, cladribine, ocrelizumab, beta 1a-interferon + azathioprine, and beta 1a-peginterferon). Unit costs were obtained from the e-SALUD database [18], and treatment costs were extracted from the Botplus database (General Pharmaceutical Council of Spain) [19].
- Direct non-healthcare resources used during the previous 12 months were collected at the study visit through questions from the researcher to the patient and/or the caregiver. They included the following: mobility aids, vehicle/home adaptations, domestic/housekeeping help, a formal caregiver, and transport to medical appointments. Unit costs were obtained from the literature [20] or reported by patients.
- Indirect resources used during the 12 months prior to the study visit were identified at this visit by questions from the researcher to the patient and/or the caregiver. Indirect costs included patient and caregiver (when needed) short- and long-term work absence and unemployment, permanent disability, reduction or early retirement, work absenteeism and presenteeism, reduction in working hours, loss of leisure time, activities, and expenditures. Unit costs were extracted from the Spanish National Statistics Institute (INE) [21] and the literature [22].

All costs were calculated per patient per year and valued in 2020 euros using the Spanish Consumer Price Index (IPC). Direct health care and non-health care resources were estimated from the Spanish NHS, patient, and societal perspectives. Indirect costs were estimated from the societal perspective, and the human-capital method was used to estimate productivity costs [23].

Patient-reported outcomes, functional and cognitive scales

During the study visit, different questionnaires were answered by patients to assess the physical and psychological impact of SPMS (Multiple Sclerosis Impact Scale-29 [MSIS-29]) [24]; health-related quality of life (HRQoL; EuroQoL-5 Dimensions-5 Levels [EQ-5D-5L]) [25]; fatigue (Modified Fatigue Impact Scale [MFIS]) [26]; cognitive impairment (Symbol Digit Modalities Test [SDMT]) [27]; anxiety and depression (Hospital Anxiety and Depression Scale [HADS]) [28]; and pain (Visual Analog Scale [VAS]).

Ethical considerations

The study was performed according to the guidelines on observational post-authorization studies for medicinal products for human use specified in Order SAS/3470/2009 of the Spanish Agency of Medicines and Medical Devices and conducted according to Good Clinical Practice (International Conference of Harmonization) guidelines, the Declaration of Helsinki, and local regulations—including privacy laws—at the time of the study's initiation. The study protocol, informed consent forms, and information for patients were approved by the Ethical and Clinical Research Committee of the Principado de Asturias.

Statistical methods

A sample size of 311 patients was calculated to estimate the annual cost of SPMS in Spain. A descriptive analysis was conducted for continuous variables, including the number of patients, mean, standard deviation (SD), median, minimum, and maximum, and quartiles were

presented according to their distribution. For categorical variables, frequencies and percentages were presented. The imputation of missing data was not performed.

Due to the expected non-normal distribution of the total cost, the first analysis approach included a logarithmic transformation. To compare resource use and patients' clinical profiles, Spearman correlations (r) were performed in the case of continuous variables, and Kruskal–Wallis test was performed to compare continuous and qualitative variables. The chi-square test was used to compare qualitative variables.

A multiple regression analysis was performed to assess the relationship between significant variables obtained in the bivariant analysis and SPMS costs. Independent variables included in the regression model were age, EDSS score at study visit, employment situation, MS evolution time, T2 lesions on MRI, comorbidities, and SPMS-related symptoms.

Data were analyzed with Statistical Analysis Software (SAS®) Enterprise Guide version 7.15. The significance level was set at 0.05 ($p < 0.05$).

For analysis purposes, resources were grouped by type (direct health care, non-health care and indirect resources) and estimated according to the 3 perspectives collected in the study (Spanish NHS, pwSPMS, and societal perspectives).

Results

A total of 314 pwSPMS were included in the study: 297 (94.6%) were evaluable and 17, non-evaluable due to not meeting the inclusion and/or exclusion criteria (Fig. 1).

Baseline characteristics

The participants were mainly female (185 [62.3%]), with a mean (SD) age of 54.6 (9.4) years, ranging from 32 to 82 years. Regarding the current familial situation, 263 (88.6%) participants were living with relatives, mostly with one partner and children. Concerning education level, 212 participants (71.4%) had secondary or higher education. The mean (SD) time between the MS diagnosis and the study visit was 19.1 (9.0) years, and the mean (SD) time from the SPMS diagnosis to the study visit was 5.9 (5.3) years. The mean EDSS (SD) score at diagnosis was 2.0 (1.2), whereas at SPMS diagnosis it was 5.1 (1.1), and at the study visit it was 5.9 (0.8). One hundred twenty-six patients (42.4%) showed EDSS scores ≥ 6, indicating severe disabilities (Table 1).

A total of 166 pwSPMS (55.9%) presented comorbidities, the most frequent of which were metabolic (28.6%), cardiovascular (18.5%), and musculoskeletal and soft tissue (14.8%) diseases. Regarding treatment, 170 patients (57.2%) were receiving DMT at the study visit, while during the 12 months before the study visit, 203 (68.4%) patients had been treated with DMT (Table 1).

Functional, patient-reported, and HRQoL outcomes of the DISCOVER study's population are shown in supplemental data (Supplementary Information, Table S1).

Resource use

During the year preceding the study visit, 196 participants (66.0%) required at least one primary care visit, with a mean (SD) of 4.9 (5.8) visits, whereas 297 (100%) saw a neurologist, with a mean (SD) of 1.5 (0.7) visits, and 176 (59.3%) saw a neurology nurse, with a mean (SD) of 4.1 (3.3) visits. One hundred forty-three (48.1%) participants needed daycare/occupational or rehabilitation center services, which they usually paid for themselves, with a mean (SD) of 120.4 (56.8) and 104.7 (71.3) visits, respectively, during the previous year.

At least one hospital admission (excluding emergency room) was required by 19 pwSPMS (6.4%), with a mean (SD) of 1.3 (0.5) admissions and a mean (SD) length of stay of 6.5 (8.5) days for these patients. Concerning emergency room visits, 55 patients (18.5%) were admitted during the 12 months before the study visit, 9 (3%) related to MS, with a mean (SD) of 2.4 (2.2) visits per year.

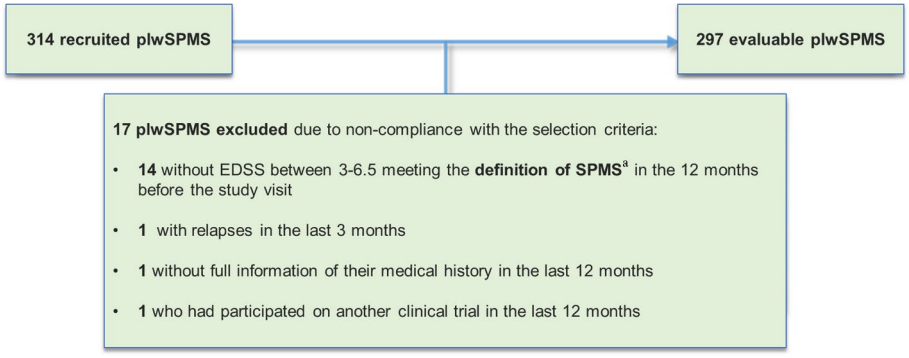

Fig. 1 DISCOVER study flow diagram. EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; pwSPMS: people with multiple secondary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis. [a]Definition of SPMS: an EDSS score increase of at least 1 point sustained for ≥ 6 months in MS patient with baseline EDSS score < 6.0 (minimum baseline EDSS score = 3.0); an EDSS score increase of at least 0.5 point sustained for ≥ 6 months in MS patient with baseline EDSS score ≥ 6.0

Table 1 Baseline demographic and clinical characteristics

Variable		Total (*N* = 297)
Gender	Male, n (%)	112 (37.7)
	Female, n (%)	185 (62.3)
Age (years)	Mean (SD)	54.6 (9.4)
Education level	Without studies, n (%)	4 (1.3)
	Primary education, n (%)	81 (27.3)
	Secondary education, n (%)	107 (36.0)
	Higher education, n (%)	105 (35.4)
Current familiar situation	Living alone (excluding caregiver, if it applies), n (%)	34 (11.4)
	Living with a relative, n (%)	263 (88.6)
Time from MS diagnosis to the study visit (years)	Mean (SD)	19.1 (9.0)
	Valid n	296
Time from SPMS diagnosis to the study visit (years)	Mean (SD)	5.9 (5.3)
EDSS score at MS diagnosis	Mean (SD)	2.0 (1.2)
	Valid n	147
EDSS score at SPMS diagnosis	Mean (SD)	5.1 (1.1)
	Valid n	296
EDSS score at the study visit	Mean (SD)	5.9 (0.8)
	Valid n	147
EDSS score at the study visit (grouped). n (%)	EDSS: 0–2.5	-
	EDSS: 3–4.5	35 (11.8)
	EDSS: 5–5.5	37 (12.5)
	EDSS: 6	99 (33.3)
	EDSS: 6.5	126 (42.4)
Comorbidities at the study visit. n (%)	Metabolic	85 (28.6)
	Cardiovascular	55 (18.5)
	Musculoskeletal and soft tissues	44 (14.8)
	Urinary	29 (9.8)
	Neurological	23 (7.7)
	Autoimmune	15 (5.1)
	Respiratory	14 (4.7)
	Gastrointestinal	12 (4.0)
	Neoplasia	9 (3.0)
	Infections	3 (1.0)
Prescribed DMT at the study visit. n (%)	Any DMT	170 (57.2)
	Rituximab	72 (24.2)
	Beta 1a-interferon	19 (6.4)
	Fingolimod	18 (6.1)
	Glatiramer acetate	15 (5.1)
	Beta 1b-interferon	13 (4.4)
	Dimethyl fumarate	8 (2.7)
	Natalizumab	8 (2.7)
	Teriflunomide	7 (2.4)
	Azathioprine	3 (1.0)
	Cladribine	3 (1.0)
	Ocrelizumab	2 (0.7)
	Beta 1a-interferon + azathioprine	1 (0.3)
	Beta 1a-peginterferon	1 (0.3)

DMT disease-modifying treatments, *EDSS* Expanded Disability Status Scale, *MS* multiple sclerosis, *SD* standard deviation, *SPMS* secondary progressive multiple sclerosis

Of note, 217 patients (73.1%) required support and adaptation devices at home or in the vehicle, with the majority paying for them themselves; the most common were bathroom adjustments (30.6%), the use of crutches or canes (30.0% and 20.2%), and the use of bath chairs (22.2%). Two hundred twenty-nine pwSPMS (77.1%) patients needed support for domestic/housekeeping tasks. One hundred twenty-four (41.8%) patients were helped by caregivers who received economic remuneration in return and 123 (41.4%) by unpaid caregivers, with a mean (SD) of 97.8 (129.6) and 26.2 (29.6) hours per month, respectively. Regarding daily tasks, 193 participants (65.0%) needed help, 28 (9.4%) from paid caregivers and 184 (62%) from unpaid caregivers. Unpaid caregivers provided a mean (SD) of 134.6 (154.8) hours per month, and paid caregivers provided 136.3 (170.2) hours per month (Table 2, Supplementary Information, Table S2).

At the study visit, 31 pwSPMS (10.4%) were actively employed, 8 of them (25.8%) with working time reduction, and 14 (45.2%) with incapacity for work due to SPMS/MS. For active participants, the mean (SD) time of work absenteeism due to SPMS/MS was 2.4 (3.0) hours per week, and work presenteeism was estimated at 14.1 (11.2) hours per week. Six (19.4%) active participants were on sick leave due to SPMS for a total of 46.2 (66.2) days on average during the last 6 months. For pwSPMS inactive at work, 41 (15.4%) took early retirement due to SPMS/MS. Loss of leisure time was estimated at a mean (SD) of 12.1 (17.4) hours per week in the study population. Unpaid caregivers reported a mean (SD) work absenteeism of 8.6 (11.9) hours per week and a loss of leisure time of 10.3 (15.6) hours per week (Table 2 and Supplementary Information, Table S2).

Costs

From the Spanish NHS perspective, annual costs amounted to €11,420.36 and, from the patient perspective, €8,698.14.

From a societal perspective, the total mean annual cost of SPMS per patient was €41,480.87, with €11,343.16 (27.3%) being direct health care costs, €8,775.34 (21.2%) being direct non-health care costs, and €21,362.37 (51.5%) being indirect costs (Fig. 2). Regarding direct health care costs, they were mainly attributable to SPMS treatments (€8,055.38, 71.0%), with €6.436,21 (56.7%) accounting for MS treatments. Of note, 89.2% of total direct health care costs were financed by the Spanish NHS, and the remaining 10.8% were paid by patients themselves. Regarding direct non-health care costs, €6,465.12 was attributable to adaptation devices at home/vehicle costs. PwSPMS paid 85.2% of all direct non-health care costs. Finally, most indirect costs were related to patients' work disabilities due to SPMS (€13,371.87, 62.6%) (Table 3).

SPMS patients' profiles and costs

PwSPMS with higher disability (EDSS score = 6.5) had a total mean cost of €46,262.76, in contrast to €34,851.49 for patients with moderate disability (EDSS score 3–3.5). This difference was mainly related to the increase in indirect costs (work disability and loss of leisure), from €16,680.27 (EDSS score 3–3.5) to €24,289.50 (EDSS score = 6.5) (Fig. 3). Moreover, older pwSPMS had lower total mean annual costs compared to younger pwSPMS, with costs being €42,570.28 in the < 45 years group versus €30,188.80 in the ≥ 65 years group ($p < 0.001$). These results and other statistically significant differences in the total mean cost by sociodemographic and clinical variables are shown in the supplementary data (Supplementary Information, Table S3).

By cost type, higher direct health care costs were estimated in younger participants (€14,687.69) versus older participants (€7,974.73) ($p < 0.001$) and in the SPMS group with a short time since diagnosis (≤ 2 years) (€13,217.70) versus the group with > 10 years since diagnosis (€10,113.22) ($p = 0.02$). Regarding direct non-health care costs, higher costs were observed in the group with the most severe disabilities (EDSS score = 6.5) versus the group with moderate disabilities (EDSS score 3–3.5), at €10,485.10 versus €4,053.10 ($p < 0.001$). Indirect costs were higher in the group with the most severe disabilities (EDSS score = 6.5) versus the group with moderate disabilities (EDSS score 3–3.5), as well as in young participants versus older participants, with costs of €22,755.7 in the < 45 years group versus €12,296.9 in the ≥ 65 years group ($p < 0.001$) (Supplementary Information, Tables S4, S5, and S6).

Considering functional and HRQoL outcomes, in the correlation analysis, higher total mean annual costs were related to higher physical impact ($r = 0.254$ in MSIS-29), fatigue ($r = 0.155$ in MFIS), cognitive and physical affectation by fatigue ($r = 0.157$ and $r = 0.144$ in MFIS), and worse general health status ($r = -0.211$ in EQ-5D-5L index value) (Supplementary Information, Table S7).

In addition, multiple regression analysis also showed higher total annual costs for older patients, those not actively working, those with EDSS scores of 6–6.5, and those without cardiovascular comorbidities (Supplementary Information, Table S8).

Discussion

The DISCOVER study analyzed the burden of SPMS on the Spanish NHS, patients, and society. As expected, the total annual costs for SPMS are higher than those for other mild/moderate forms of MS [3]. The study cohort covered all Spanish regions, with participants from 34 hospitals and a sufficiently representative sample size of Spanish pwSPMS. The proportion of women was higher (62.3%), which is consistent with other

Table 2 Direct health care, non-health care, and indirect resource use of pwSPMS in Spain

Variable	NHS perspective	PwSPMS' perspective	Societal perspective
Direct health resource use[a]			
Visits/admissions in the last 12 months (at least once)			
Primary care. n (%)	194 (65.3)	3 (1.0)	196 (66.0)
Mean (SD)	4.8 (5.7)	12.7 (9.5)	4.9 (5.8)
Neurology nursing. n (%)	176 (59.3)	-	176 (59.3)
Mean (SD)	4.1 (3.3)	-	4.1 (3.3)
Speech therapy. n (%)	6 (2.0)	6 (2.0)	12 (4.0)
Mean (SD)	36.7 (30.2)	29.2 (22.5)	32.9 (25.7)
Neurology. n (%)	297 (100.0)	2 (0.7)	297 (100.0)
Mean (SD)	3.3 (1.4)	1.5 (0.7)	3.3 (1.4)
Ophthalmology. n (%)	59 (19.9)	9 (3.0)	66 (22.2)
Mean (SD)	1.5 (0.8)	1.3 (0.7)	1.5 (0.9)
Psychology. n (%)	44 (14.8)	14 (4.7)	55 (18.5)
Mean (SD)	2.9 (3.9)	13.6 (13.1)	5.8 (8.7)
Other specialties. n (%)	139 (46.8)	14 (4.7)	149 (50.2)
Mean (SD)	4.4 (5.2)	9.1 (16.6)	4.9 (7.3)
Daycare/occupational center. n (%)	9 (3.0)	19 (6.4)	28 (9.4)
Mean (SD)	114.7 (43.7)	123.2 (63.0)	120.4 (56.8)
Rehabilitation center. n (%)	42 (14.1)	100 (33.7)	135 (45.5)
Mean (SD)	100.0 (78.6)	99.4 (57.7)	104.7 (71.3)
Hospital admissions. n (%)	18 (6.1)	1 (0.3)	19 (6.4)
Mean (SD)	1.3 (0.5)	1.0 (0.0)	1.3 (0.5)
Length of hospital stay (days), mean (SD)	6.6 (8.8)	5.0 (0.0)	6.5 (8.5)
Emergency room visits. n (%)	-	-	55 (18.5)
Emergency room visits, MS related. n (%)	9 (3.0)	-	9 (3.0)
Mean (SD)	2.4 (2.2)	-	2.4 (2.2)
Tests related to SPMS/MS. N (%)	297 (100.0)	297 (100.0)	297 (100.0)
Direct non-health resource use			
Support and adaptation devices at home/vehicle. n (%)	71 (23.9)	208 (70.0)	217 (73.1)
Support for domestic/housekeeping tasks. n (%)			
- Support for domestic/housekeeping tasks (unpaid caregivers)	-	-	19 (6.4)
- Support for domestic/housekeeping tasks (paid caregivers)	17 (5.7)	78 (26.3)	90 (30.3)
Support for daily tasks. n (%)			
- Unpaid caregiver	-	-	101 (34.0)
- Paid caregiver	12 (4.0)	17 (5.7)	26 (8.8)
Transport to appointments. n (%)			
- Ambulance	25 (8.4)	-	25 (8.4)
- Private vehicle	2 (0.7)	214 (72.1)	216 (72.7)
- Adapted collective transport	3 (1.0)	1 (0.3)	4 (1.3)
- Taxi	3 (1.0)	45 (15.2)	48 (16.2)
- Public transport	4 (1.3)	37 (12.5)	41 (13.8)
Indirect resource use			
Actively employed pwSPMS, $N=31$			
- Patients with reduction of working hours. n (%)	-	-	8 (25.8)
- Absenteeism due to SPMS/MS (hours/week). Mean (SD)	-	-	2.4 (3.0)
- Presenteeism (hours/week), Mean (SD)	-	-	14.1 (11.2)
- Work disability due to SPMS/MS. n (%)	-	-	14 (45.2)
- Permanent partial disability due to SPMS/MS. n (%)	-	-	9 (29.0)
- Permanent total disability due to SPMS/MS. n (%)	-	-	5 (16.1)
- Sick leave due to SPMS/MS in last 6 months. n (%)	-	-	6 (19.4)
Inactive pwSPMS, $N=266$			
- Early retirement due to SPMS/MS. n (%)	-	-	41 (15.4)
Retirement age (years). Mean (SD)	-	-	48.7 (8.2)

Table 2 (continued)

Variable	NHS perspective	PwSPMS' perspective	Societal perspective
- Loss of work due to SPMS/MS. N (%)	-	-	4 (1.5)
- Work disability due to SPMS/MS. N (%)	-	-	183 (68.8)
Actively employed and inactive pwSPMS, *N* = 290			
- Loss of leisure time (hours/week). Mean (SD)	-	-	12.2 (17.4)
Unpaid caregivers, *N* = 121			
- Actively employed. n (%)	-	-	49 (39.8)
- Patients with reduction of working hours. N (%)	-	-	6 (12.2)
- Absenteeism due to SPMS/MS (hours/week). Mean (SD)	-	-	8.6 (11.9)
- Inactive. N (%)	-	-	74 (60.2)
- Loss of leisure time (hours/week). Mean (SD)	-	-	(15.6)

DMT disease-modifying treatments, *MS* multiple sclerosis, *NHS* National Health System, *pwSPMS* people with secondary progressive multiple sclerosis, *SD* standard deviation

[a]DMT direct health resources use showed in Table 1

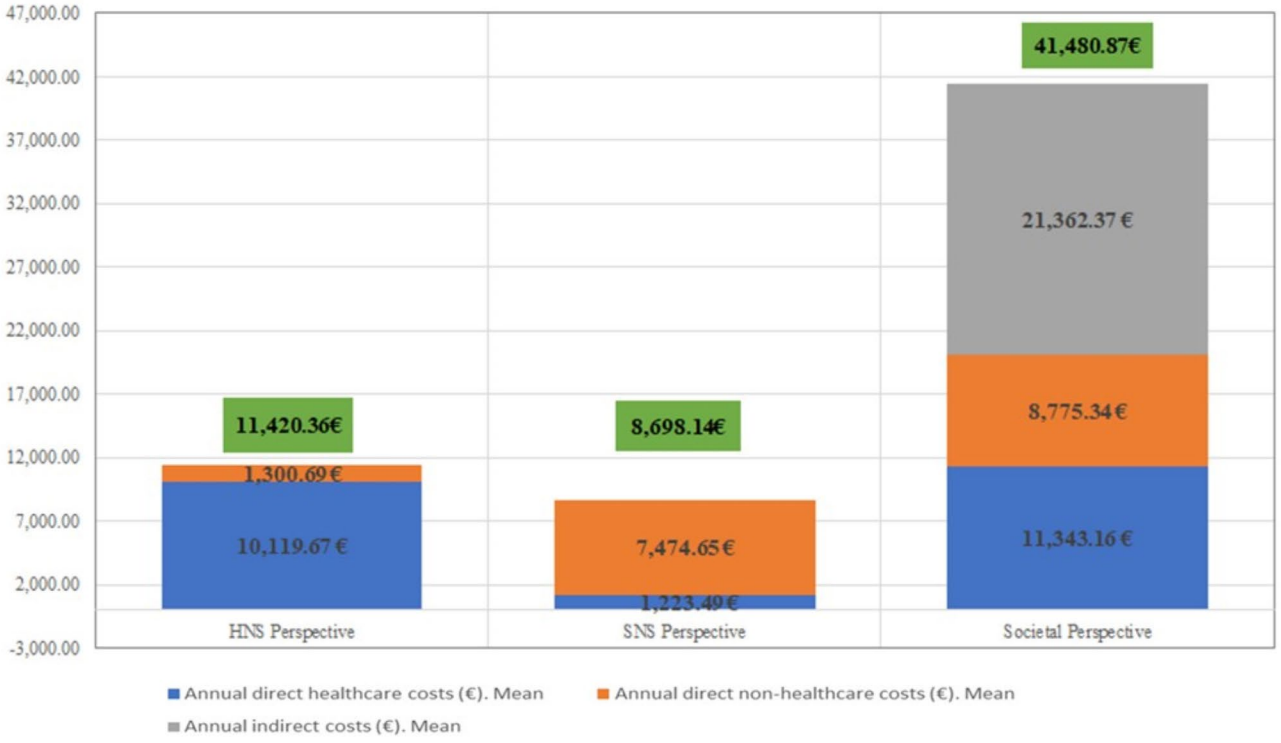

Fig. 2 Distribution of total annual costs by cost type and perspective[a]. [a]At the top of the columns: total annual costs

SPMS observational studies (63% in a French study) [9]. PwSPMS showed a similar mean age (54.6) to patients from other European countries, such as Finland and Sweden (55.6 years in Finland) [13, 14]. Of note, participants in this study were older compared with participants in a recently published cross-sectional Spanish study focused on all MS forms and conducted among Spanish patients' associations (42.6 years) [3]. It is important to note that most participants in the DISCOVER study were living with relatives, in contrast to other studies in Nordic countries with fewer participants having such an arrangement (e.g., 89% vs. 69% in Finland), probably due to cultural differences. Regarding educational level, the proportion of pwSPMS with secondary or higher education was similar to that noted in other studies (36% with secondary education vs. 35% in Sweden) [14]. Participants predominantly received their MS diagnosis in their thirties, and the SPMS diagnosis occurred six years before the study visit, in the early fifties, crucially impacting the functioning and careers of participants.

Regarding the clinical profiles of pwSPMS, more than 42% showed ambulatory severe disabilities (EDSS score = 6.5) at the study visit. Other studies in Europe, such as those in Nordic countries, also included non-ambulatory pwSPMS (EDSS ≥ 7), making direct comparisons difficult [13, 14]. More than half of patients

Table 3 Description of total annual costs by perspective

Variable	NHS perspective	PwSPMS' perspective	Societal perspective
Annual direct health care costs (€). Mean (SD)			
- DMT	6,435.90 (7,027.76)	0.32 (2.47)	6,436.21 (7,027.50)
- Other treatments	1,517.84 (1,664.82)	101.33 (343.90)	1,619.17 (1,845.28)
- Medical visits	829.50 (617.98)	110.09 (493.67)	939.59 (786.16)
- Specific attention (daycare/rehabilitation)	435.70 (2,627.92)	987.92 (4257.15)	1423.62 (4915.84)
- Hospital admissions	307.49 (2,429.37)	9.10 (156.82)	316.59 (2433.28)
- Emergency room visits	19.09 (143.98)	0.00 (0.00)	19.09 (143.98)
- Other costs (Tests)	561.87 (553.81)	14.73 (128.89)	576.60 (556.20)
Total costs	10,119.67 (8,576.25)	1,223.49 (4,471.58)	11,343.16 (9,519.40)
Annual direct non-health care costs (€). Mean (SD)			
- Support and adaptation devices at home/vehicle	264.28 (767.10)	6,200.84 (2,5687.02)	6,465.12 (2,5677.34)
- Support for domestic/housekeeping tasks	136.69 (848.65)	816.86 (2,188.18)	953.56 (2,310.81)
- Support for daily tasks (paid/unpaid caregiver)	859.51 (8,345.12)	386.42 (1,828.80)	1,245.93 (8,711.34)
- Other costs (transport)	40.21 (325.90)	70.52 (137.71)	110.73 (34.36)
Total cost	1,300.69 (8,520.16)	7,474.65 (2,6276.65)	8,775.34 (2,7810.01)
Annual indirect costs (€). Mean (SD)			
- PwSPMS work disability due to SPMS/MS	-	-	13,371.87 (11,349.50)
- PwSPMS sick leave due to SPMS/MS	-	-	137.03 (1,706.01)
- PwSPMS unemployment due to SPMS/MS	-	-	139.46 (1,195.60)
- Reduction of working hours due to SPMS/MS	-	-	287.07 (1,879.70)
- Early retirement due to SPMS/MS	-	-	2,501.65 (7,398.57)
- PwSPMS absenteeism due to SPMS/MS	-	-	39.74 (211.87)
- PwSPMS presenteeism due to SPMS/MS	-	-	6.43 (23.69)
- PwSPMS loss of leisure time	-	-	1793.86 (2,605.51)
- Work termination of unpaid caregiver	-	-	1,492.68 (4,667.94)
- Unpaid caregiver reduction of working hours	-	-	97.35 (578.78)
- Unpaid caregiver absenteeism	-	-	232.04 (707.59)
- Unpaid caregiver loss of leisure time	-	-	1,400.23 (2,560.84)
Total costs	-	-	21,362.37 (12,769.34)
Total annual costs (€). Mean (SD)	11,420.36 (12,502.82)	8,698.14 (26,541.37)	41,480.87 (31,668.28)

DMT disease-modifying treatments, *MS* multiple sclerosis, *NHS* National Health System, *pwSPMS* people with progressive multiple sclerosis, *SD* standard deviation

had comorbidities, with metabolic diseases (mainly dyslipidemia) being the most frequent (28.6%), followed by cardiovascular diseases (18.8%). This distribution of comorbidities was similar to that in an Italian study (17.8% had dyslipidemia in our cohort vs. 16% in the Italian study) [29].

Regarding direct health care resource use, during the year before the study visit, all pwSPMS attended neurologists, and nearly 70% used primary care services. The number of hospitalizations was low, but almost 20% of participants visited the emergency room, and nearly 50% needed assistance in a daycare or rehabilitation center, mostly paying for it themselves. Inpatient resource use was relatively lower compared with other studies on primary progressive multiple sclerosis [30]. Almost 60% of pwSPMS received MS treatments, with nearly a quarter of the whole cohort being treated with rituximab. In patients with worse EDSS scores, rituximab was less commonly prescribed than interferons, whereas rituximab was more commonly prescribed during an early SPMS diagnosis with low EDSS scores, as evidenced in other studies in France, Finland, and Sweden [9, 13, 31]. More than 40% of the DISCOVER study's population did not receive any DMT. This last result is in line with the lack of treatment options in SPMS that are limited to patients with persistent inflammatory activity [32]. In this sense, the present study included reimbursed MS/SPMS treatments, although many of them were used off label, since they did not have this indication at the time of the study. Concerning direct non-health care resource use, we estimated that nearly three-quarters of the study cohort needed support and adaptation devices at home/vehicle, and almost 80% needed support for domestic/housekeeping tasks, provided in equal parts by paid and unpaid caregivers. Of note, 65% of pwSPMS required assistance with daily tasks, which was mostly provided by close caregivers (family members, neighbors, or volunteers). The use of non-health care resources is greater than in other countries, such as Ireland [32]. Regarding indirect resources, more than 90% of participants were inactive at the study visit due mainly to work disabilities due to SPMS, with nearly 80% opting for early retirement.

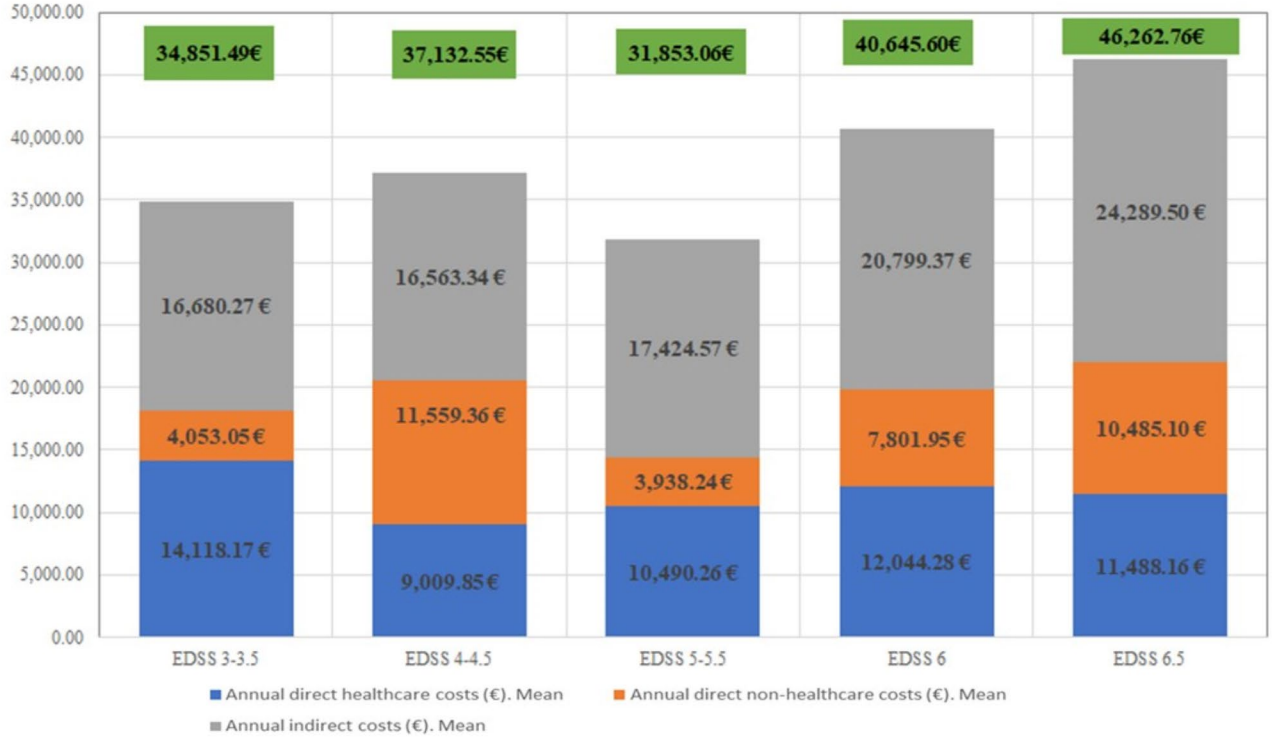

Fig. 3 Total annual costs by EDSS score[a]. EDSS: Expanded Disability Status Scale. [a]At the top of the columns: total annual costs

Unpaid caregivers showed a high level of work absenteeism and loss of leisure time.

We estimated a total annual cost per pwSPMS in Spain of almost €41,500, of which more than 50% (€21,400) were indirect costs, followed by direct health care costs (30%, €11,300), and, finally, direct non-health care costs (about 20%, €8,800). This predominance of indirect costs in SPMS was also evidenced in other studies in Finland or Ireland, but with a higher total amount (about €70,000), probably due to the inclusion of pwSPMS with EDSS scores of ≥ 7 in these last studies [13, 32]. However, in the pooled analysis of SPMS costs in the United Kingdom, France, Germany, and the United States of the IMPrESS study, the distribution of costs was similar to that in the present study, with a major contribution from indirect costs and close total annual costs for SPMS [15]. It is interesting to observe that in other forms of MS, such as RRMS, direct costs (mainly DMTs) contribute more to overall costs than indirect costs [15]. In the above-mentioned cross-sectional Spanish study by Oreja-Guevara et al. [3], the overall cost for MS patients with moderate disease severity (EDSS 4–6.5) was €48,000. This difference versus our data is explained by the increase in direct costs due to the increased use of DMTs in the Oreja-Guevara et al. study (mainly in the second line).

In our cohort, major indirect cost drivers were work disabilities (€13,400), whereas direct health care cost drivers were DMT and other related treatments (€8,000), and direct non-health care cost drivers were adaptations at home/vehicle (nearly €6,500). These cost drivers are like those highlighted in the IMPrESS study [15].

It is also worth noting that the annual cost of SPMS per patient in Spain is higher than that of other chronic diseases. Thus, chronic heart failure patients had an estimated annual cost of more than €18,000, owing primarily to indirect costs [33], while other common diseases such as stroke had an estimated annual cost of more than €27,500, owing primarily to indirect costs [34].

Therefore, SPMS costs per patient in Spain are higher than those for other, more prevalent diseases, indicating a high patient burden for this type of MS. This increased burden could be attributable to SPMS' long duration, and its high incidence in young people, with the subsequent early work disability, the greater need for domestic/housekeeping help and the higher costs of health care resources versus stroke or Alzheimer's disease [35].

Disability is an important factor in the SPMS burden. In the DISCOVER study, more severe disease (EDSS score = 6.5) was associated with a higher total annual cost (€46,200) versus moderate disease (€34,900). This difference can be explained by the increase in indirect costs with advancing disability [36, 37]. Older participants also had higher total costs, while younger participants had higher direct costs due to DMT [13]. Worse functional and HRQoL outcomes were also factors for higher total annual costs in the context of SPMS, especially regarding

physical and psychological impact, cognitive impairment, and worse general health status [13].

The limitations of the present study stem from its design. Among other things, the cross-sectional design and the retrospective revision of clinical and resource use data are worth highlighting. A prospective cohort design could have been more robust, considering that the current design could have led to a memory bias in the recollection of variables reported by the participant themselves. This limitation was minimized by a fully designed and implemented case report form and the exhaustive revision of data. Another limitation is the inclusion criterion of EDSS scores up to 6.5, which did not allow the inclusion of pwSPMS with non-ambulatory severe disability for the purpose of assessing ambulatory pwSPMS in a hospital sample. This could have led to a greater underestimation of total costs versus other studies that included these patients, but it must be noted that pwSPMS with EDSS scores ≥ 7 represent a limited population for this MS form (e.g., 7% in a Swedish cohort) [14] and that the DISCOVER study was focused on ambulatory SPMS patients. Similarly, the fact that only 5 patients with an EDSS score of 3–3.5 were included is a limitation when making estimates or comparisons of this group with the rest. Although the results of the study detect data with non-linear trends (probably due more to clinical than methodological reasons), these data faithfully reflect those collected in the study, so additional studies would be needed to clarify the specific reasons for these trends. The strengths of the study are that it is the first study in a Spanish setting focused on SPMS that is hospital based, nationally representative, and offers complete information on patient profiles, the burden of cost, and functional and HRQoL data.

Conclusions

In conclusion, SPMS represents an important burden from the NHS, quality-of-life, and societal perspectives in Spain, with associated costs of more than €41,000 per patient per year. SPMS is associated with higher costs per patient versus other, more prevalent chronic diseases. PwSPMS show a high level of disability and impact on HRQoL, with physical impact, fatigue, and cognitive impairment. Indirect costs play an important role, with patients' work disabilities being the major cost driver of SPMS. The high societal impact of SPMS must be highlighted considering the ramifications for working careers, economic and family setting disruption, and caregiver involvement in the health care setting. However, further analyses comparing costs across different demographic groups could uncover any cost disparities and offer policy-relevant insights.

Cost-of-illness studies allow health authorities to obtain valuable data to plan health policies. Taking into consideration the results of the DISCOVER study, the management of pwMS should focus on delaying MS progression to more severe disability types by implementing therapeutic strategies specific to pwSPMS during the early stages of progression. Furthermore, health care and societal policies should aim to reduce patients' funding of direct non-health care costs and address work disability in pwSPMS.

Abbreviations

DMT	Disease-modifying treatment
EDSS	Expanded Disability Status Scale
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
Gd +	Gadolinium
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
IMPrESS	International MultiPlE Sclerosis Study
INE	Spanish National Statistics Institute
IPC	Spanish Consumer Price Index
MFIS	Modified Fatigue Impact Scale
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale-29
NHS	National health systems
pwMS	People with multiple sclerosis
pwSPMS	People with secondary progressive multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SAS	Statistical Analysis Software
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SE	Standard Error
SPMS	Secondary progressive multiple sclerosis
VAS	Visual Analog Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12913-025-12592-1.

Supplementary Material 1: Table S1. Results on patient-reported outcomes, functional and cognitive scales scores in pwSPMS. Table S2. Direct non-health care and indirect resource use of pwSPMS in Spain (supplementary data). Table S3. Total annual costs by sociodemographic and clinical variables (only statistically significant results). Table S4. Annual direct health care costs by sociodemographic and clinical variables (only statistically significant results). Table S5. Annual direct non-health care costs by sociodemographic and clinical variables (only statistically significant results). Table S6. Annual indirect costs by sociodemographic and clinical variables (only statistically significant results). Table S7. Correlation between annual mean costs and functional and HRQoL scores. Table S8. Multiple regression analysis of total annual cost and independent variables

Acknowledgements

The authors would like to thank IQVIA and Carmen Barrull for providing medical editorial assistance for this manuscript.

Authors' contributions

Conceptualization, methodology, supervision and visualization: COG, MAV, JMRB, JR. Investigation and resources: COG, JEML, IGE, JMA, MAHP, JGG, AMAT, BPdF, LRT, SEM, FGG, BC, SMY, MAV, MLMG, YEBM, AMLR, VGQ, CLS, JEMR, LCF, MGR, ALF, FCP, JAGM, CMF, TCT, VML, JPM, ARA, JMPG, EAM, IPM, DMSS, NHV, JR. Writing-original draft: COG, JR. All authors contributed to the validation of the results and reviewed and approved the final version of the manuscript.

Funding

This study was funded by Novartis Farmacéutica, S.A. The funder had the following involvement with the study: study design, data collection and analysis, decision to publish and preparation of the manuscript.

Data availability
The data that support the findings of this study and other related documents, such as the protocol and amendments, can be shared upon reasonable request through a data sharing agreement.

Declarations

Ethics approval and consent to participate
The study protocol, informed consent forms, and information for patients were approved by the Ethical and Clinical Research Committee of Principado de Asturias. Also, the study was conducted according to the guidelines of the Spanish Agency of Medicines and Medical Devices, with the post-marketing study code NOV-EMS-2019-01. Before being included in the study, participants were required to provide informed consent.

Consent for publication
No individual data included in the manuscript.

Competing interests
COG has received speaker and consultation fees from: Alexion, Biogen Idec, Bristol-Myers-Squibb, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. JEML has received grants or contracts from: Sanofi, Biogen, Novartis, Roche, Bristol Myers Squibb, Merck, Janssen, and Alexion; consulting fees from: Biogen, Sanofi, Bristol Myers Squibb, Merck, Janssen, and Alexion; payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events and Support for attending meetings and/or travel from: Sanofi, Biogen, Novartis, Roche, Bristol Myers Squibb, Merck, and Janssen. MAHP has received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events and support for attending meetings and/or travel from: Biogen, Merck, Novartis, and Sanofi. JGG has received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from: Biogen, Merck, Sanofi, Roche, Teva, Janssen, and Novartis; payment for expert testimony from: Roche, and Sanofi; support for attending meetings and/or travel from: Biogen, Merck, Sanofi, Roche, Teva, Janssen, Almirall, and Novartis; participation on a Data Safety Monitoring Board or Advisory Board: Sanofi. AMAT has received consulting fees from: Novartis, Biogen, Janssen, Roche, and Sanofi; payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from: Merck, Sanofi, Janssen, Almirall, Roche, Novartis, Biogen, and BMS; support for attending meetings and/or travel: Biogen. BPF has received speaker honoraria from: Novartis and Almirall; travel honoraria from: Merck and Sanofi; training honoraria from: Sanofi and Merck. LRT has received consulting fees from: BMS and Sanofi; payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from: BMS, Sanofi, Novartis, Merck, Janssen, Biogen, and Horizon; support for attending meetings and/or travel from: BMS, Sanofi, Novartis, Merck, Janssen, and Biogen. SEM has received speaker honoraria and consultant fees from: Janssen, Bristol-Meyers-Squibb, Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva. FGG has received funding for research grants, travel support and honoraria for speaking engagements from: Bayer, Biogen, Roche, Merck, Novartis, Almirall, Teva, Bristol-Meyers-Squibb, and Genzyme-Sanofi. BC has received grants for advisory boards from: Sanofi, Roche, Merck, Horizon, and Novartis. SMY has participated as Principal Investigator in clinical trials promoted by industry from: Roche, Sanofi, Biogen, Merck, and Novartis; support for attending meetings and/or travel from: Biogen, BMS, Janssen, Merck, Novartis, Roche, and Sanofi. MAV has been consulting for: Novartis, Biogen, Sanofi, and Merck; payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from: Novartis, Biogen, Sanofi, Merck, and Roche. Grants or contracts from: Novartis, Biogen, Sanofi, Merck, and Teva; support for attending meetings and/or travel from: Novartis, Biogen, Sanofi, Merck, Teva, and Roche. MLMG has received compensation for consulting services and speaking fees from: Merck, Biogen, Novartis, Sanofi, Almirall, Roche, BMS, Janssen-Cilag, and Viatris. YEBM has received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from: Novartis, Roche, Sanofi-Genzyme, Almirall, Bayer, Merck, and Biogen. AMLR has acted as a speaker for Roche, Biogen Idec, Genzyme-Sanofi, Janssen, and Novartis. JEMR has participated as consultant and has received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from: Novartis, Biogen Idec, Sanofi, and Merck Serono. LCF has received honoraria for lecturing, travel expenses for attending meetings from: Merck, Bayer, Biogen, Novartis, Sanofi Genzyme, Almirall, Roche, Celgene, Biopas, Ipsen, and Teva. MGR has received honoraria as a lecturer from: Sanofi-Aventis, Novartis, Biogen, and Merck. TCT has received speaking/consulting fees and/or travel funding from: Almirall, Biogen, Bristol-Myers-Squibb, Janssen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva. VML has received consulting or speaking fees from: Almirall, Biogen, Genzyme, Janssen, Merck Serono, Novartis, Roche, Terumo, Sanofi, Teva, Celgene, and Bristol-Myers-Squibb. JPM has received speaker and consultation fees and congress travel support from: Biogen, Bristol-Myers-Squibb, Janssen, Merck, Novartis, Roche, and Sanofi. ARA has participated as a medical adviser/speaker for: Merck, Biogen, Novartis, Roche, Sanofi, Sandoz, Teva, and Bristol-Myers-Squibb. JMPG has been a consultant for Bayer Pharmaceuticals, Biogen Spain S.L., Daiichi Sankyo Spain, Genzyme Corporation, Janssen Spain, Merck Serono, Novartis Pharmaceuticals Corporation, Sanofi, Sandoz Iberia, Teva Pharmaceutical Industries, Roche Pharma, Almirall Prodesfarma S.A., and Celgene Spain S.L. He has participated as a speaker/moderator in meetings and/or symposiums organized by Almirall Prodesfarma S.A., Bayer Pharmaceuticals, Biogen Spain S.L., Genzyme Corporation, Merck Serono, Novartis Pharmaceuticals Corporation, Sanofi, Teva Pharmaceutical Industries, and Roche Pharma. EAM has received speaker honoraria from: Roche, Novartis, Merck, Sanofi, and Biogen. IPM has received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from: Novartis. DMSS has participated as a medical adviser/speaker for Biogen, Novartis, Sanofi, Almirall, Roche, Merck, and Bristol-Myers-Squibb. MAV and JMRB are Novartis employees. JR has received speaking honoraria and support for attending meetings and/or travel in advisory boards from: Biogen-Idec, Genzyme, Merck-Serono, Novartis, Teva, Roche, Janssen, and Sanofi-Aventis. IGE, JRA, VGQ, ALF, FCP, JAGM, CMF and NHV: no disclosures reported.

Author details
[1]Neurology Department, CSUR Multiple Sclerosis, Hospital Universitario Clínico San Carlos, IdISCC, Planta Sexta Norte, Calle del Prof. Martín Lagos, Madrid 28040, Spain
[2]Medical Department, Medicine Faculty, Complutense University of Madrid (UCM), Madrid, Spain
[3]Neurology Department, CSUR Multiple Sclerosis and Clinical Neuroimmunology Unit, Virgen de La Arrixaca Clinical University Hospital, IMIB-Arrixaca, Murcia, Spain
[4]Neurology Department, Miguel Servet University Hospital, Zaragoza, Spain
[5]Neurology Department, Nuestra Señora de La Candelaria University Hospital, Santa Cruz de Tenerife, Spain
[6]Neurology Department, Albacete University Hospital Complex, Albacete, Spain
[7]Neurology Department, CSUR Multiple Sclerosis, Málaga Regional University Hospital, Málaga, Spain
[8]Neurology Department, Getafe University Hospital, Madrid, Spain
[9]Neurology Department, Neuroimmunology and Multiple Sclerosis Unit, Department of Medical Sciences, Dr. Josep Trueta University Hospital, IDIBGI, University of Girona, Girona, Spain
[10]Neurology Department, Virgen Macarena University Hospital, Seville, Spain
[11]Neurology Department, Hospital Clínico de Valencia, Valencia, Spain
[12]Neuroinmunology Unit, University and Polytechnic La Fe Hospital, Valencia, Spain
[13]Neurology Department, Hospital Universitari de Bellvitge-IDIBELL, Hospitalet De Llobregat, Spain
[14]Neurology Department, Hospital Álvaro Cunqueiro, Vigo, Spain
[15]Neurology Department, Hospital Gregorio Marañón, Madrid, Spain
[16]Neurology Department, Salamanca University Hospital, Salamanca, Spain
[17]Neurology Department, A Coruña University Hospital Complex, A Coruña, Spain
[18]Neurology Department, Marqués de Valdecilla University Hospital, Cantabria, Spain
[19]Neurology Department, Torrejón University Hospital, Madrid, Spain
[20]Neurology Department, Hospital del Mar, Barcelona, Spain
[21]Neurology Department, Ramón y Cajal University Hospital, Madrid, Spain
[22]Neurology Department, Lozano Blesa Clinical University Hospital, Zaragoza, Spain

[23]Neurology Department, 12 de Octubre University Hospital, Madrid, Spain
[24]Neurology Department, Hospital Virgen del Puerto Plasencia, Caceres, Spain
[25]Neurology Department, Puerta de Hierro University Hospital, Madrid, Spain
[26]Neurology Department, Torrecardenas University Hospital, Almería, Spain
[27]Neurology Department, Donostia University Hospital, San Sebastián, Spain
[28]Neurology Department, La Princesa University Hospital, Madrid, Spain
[29]Neurology Department, San Agustín University Hospital, Avilés, Asturias, Spain
[30]Neurology Department, Cruces-Biocruces Bizkaia University Hospital, Barakaldo-Bizkaia, Spain
[31]Neurology Department, Santiago Clinical University Hospital, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[32]Neurology Department, Reina Sofia University Hospital, Córdoba, Spain
[33]Neurology Department, Hospital Virgen de La Salud, Toledo, Spain
[34]Neurology Department, Cabueñes University Hospital, Gijon, Spain
[35]Neurology Department, Burgos University Hospital, Burgos, Spain
[36]Novartis Farmacéutica, S.A., Barcelona, Spain
[37]Neurology Department, CEMCAT, Vall d'Hebron University Hospital, Barcelona, Spain

Received: 2 April 2024 / Accepted: 17 March 2025
Published online: 10 April 2025

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