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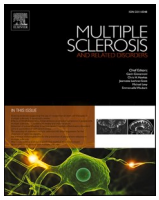

Socioeconomic burden of multiple sclerosis: Insights from a cohort in Coimbra, Portugal

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ABSTRACT

Introduction: Multiple Sclerosis (MS) is the leading cause of non-traumatic disability in young adults, burdening patients, caregivers, and healthcare systems. In Portugal, annual direct healthcare costs for MS are estimated between €12,303 and €16,451, with total costs reaching €34,400 per patient. This study aims to characterize MS patients in Coimbra, focusing on demographic, clinical, and economic aspects to assess the disease's socioeconomic impact.

Methods: A cost-of-illness study with cross-sectional and retrospective components was conducted between 2021 and 2022 at the single referral center for MS in Coimbra. Patients completed a survey assessing sociodemographic, clinical, and economic data. Descriptive and comparative non-parametric analyses stratified by MS severity (mild EDSS 0–3.5, moderate 4–6.5, severe above 6.5) were performed.

Results: Among 163 patients (69.9 % female, mean age 48), 87.1 % had relapsing-remitting MS. Higher education was common (69.3 %), 45.4 % were married. Employment declined with disease severity; 9.4 % of mild EDSS patients were unemployed, while severe EDSS patients were retired. Average annual direct healthcare costs were €12,406, increasing with severity (€12,267 in mild MS to €16,020 in severe MS). Disease-modifying therapies accounted for most direct costs, although these declined in advanced stages, with hospitalization costs rising. Total costs per patient were €14,954 (mild MS), €28,289 (moderate MS), and €35,557 (severe MS), with relapses adding €3277 annually.

Conclusion: This study underscores the substantial economic burden of MS, particularly as disease severity progresses. Rising hospitalization and relapse costs highlight the need for cost-effective strategies and policies reducing MS-related socioeconomic impacts. Effective management could help mitigate these costs while improving outcomes.

1. Introduction

Multiple Sclerosis (MS) is the leading cause of non-traumatic disability in young adults (Filippi et al., 2018), significantly impacting patients (pwMS) and their caregivers. Typically presenting in early adulthood, MS disrupts personal plans for family, career, and life goals. While there is no cure, prompt recognition, appropriate treatment, and adequate social support are essential to improve outcomes (Weideman et al., 2017).

The socioeconomic consequences of MS are substantial. Studies reveal 15 %–30 % lower employment rates, reduced earnings, higher absenteeism, and increased work disability among pwMS (Kavaliunas et al., 2021). MS also negatively affects family dynamics, with higher divorce rates reported, especially among men (Landfeldt et al., 2018).

Before the introduction of disease-modifying therapies (DMT), MS-related healthcare costs were primarily driven by hospitalizations (Kobelt et al., 2017). However, DMTs have drastically shifted the cost burden, now representing the largest portion of MS healthcare expenses (Kobelt et al., 2017).

In Europe, annual disease costs (direct and indirect) range from €22,800€ to €57,500 in 2015 (Kobelt et al., 2017). In the United States, 2019 data showed average annual medical costs of $65,612 per PwMS,

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Table 1
Distribution of clinical variables in the population and according to MS severity.

Variables		Population	Mild MS (EDSS 0–3.5)	Moderate MS (EDSS 4–6.5)	Severe MS (EDSS 7–9)	*p* value
Number of patients, n (%)		163 (100)	132 (81)	26 (16)	5 (3)	<0.001
Sex, n (%)	Female	114 (69.9)	92 (69.7)	19 (73.1)	3 (60)	0.836
	Male	49 (30.1)	40 (30.3)	7 (26.9)	2 (40)	
MS type, n (%)	RRMS	142 (87.1)	130 (98.5)	12 (46.2)	0 (0)	<0.001
	SPMS	17 (10.4)	2 (1.5)	11 (42.3)	4 (80)	
	PPMS	4 (2.5)	0 (0)	3 (11.5)	1 (20)	
Age, y (SD)	Present	48 (12.8)	46 (11.1)	62 (9.9)	66 (12.2)	<0.001
	First symptoms	33.4 (11.9)	32.1 (10.8)	39.2 (14.3)	37.8 (17.8)	0.039
	Diagnosis	36.7 (11.6)	35.1 (10.2)	43.7 (14.5)	41.8 (16.6)	0.01
MS duration, y (SD)		11.6 (9.1)	9.9 (8)	18.6 (10.7)	18.6 (8.1)	<0.001
Family history of MS, n (%)	Yes	20 (12.3)	15 (11)	5 (19)	0 (0)	0.376
Other autoimmune diseases	Yes	6 (3.7)	5 (3.8)	1 (3.8)	0 (0)	0.3
	• *Alopecia areata and inflammatory bowel disease*	1 (17)	1 (20)	0 (0)	0 (0)	
	• *Myasthenia gravis*	1 (17)	0 (0)	1 (100)	0 (0)	
	• *Psoriasis*	2 (33)	2 (40)	0 (0)	0 (0)	
	• *Thyroiditis*	2 (33)	2 (40)	0 (0)	0 (0)	
Relapses over the past year, n (%)	0	131 (80.4)	109 (83)	20 (77)	2 (40)	0.069
	1	29 (17.8)	20 (15)	6 (23)	3 (60)	
	2	3 (1.8)	3 (2.3)	0 (0)	0 (0)	
Current DMT, n (%)	Interferon 1α or 1β	16 (9.8)	14 (11)	1 (3.8)	1 (20)	0.2
	Glatiramer acetate	5 (3.1)	5 (3.8)	0 (0)	0 (0)	
	Teriflunomide	34 (20.9)	23 (17)	11 (42)	0 (0)	
	Dimethyl fumarate	21 (12.9)	20 (15)	0 (0)	1 (20)	
	Fingolimod	23 (14.1)	20 (15)	3 (12)	0 (0)	
	Natalizumab	22 (13.5)	20 (15)	1 (3.8)	1 (20)	
	Ocrelizumab	14 (8.6)	12 (9.1)	2 (7.7)	0 (0)	
	Rituximab	6 (3.7)	2 (1.5)	3 (12)	1 (20)	
	Ofatumumab	1 (0.6)	1 (0.8)	0 (0)	0 (0)	
	Cladribine	7 (4.3)	7 (5.3)	0 (0)	0 (0)	
	Alemtuzumab	1 (0.6)	0 (0)	1 (3.8)	0 (0)	
	Off-label	5 (3.1)	2 (1.5)	2 (7.7)	1 (20)	
	Clinical trial	4 (2.5)	4 (3)	0 (0)	0 (0)	
	None	4 (2.5)	2 (1.5)	2 (7.7)	0 (0)	
Previous use of approved DMT for MS, n (%)	Interferon β 1α/1b or glatiramer acetate	83 (50.9)	63 (47.7)	17 (65.4)	3 (60)	0.9
	Teriflunomide	11 (6.7)	3 (2.3)	6 (23.1)	2 (40)	<0.001
	Dimethyl fumarate	10 (6.1)	10 (7.6)	0 (0)	0 (0)	0.2
	Fingolimod	22 (13.5)	11 (8.3)	10 (38.5)	1 (20)	0.003
	Natalizumab	38 (23.3)	24 (18.2)	12 (46.2)	2 (40)	0.051
	Cladribine	1 (0.6)	0 (0)	1 (3.8)	0 (0)	0.2
	Alemtuzumab	3 (1.8)	0 (0)	2 (7.7)	1 (20)	0.007
	Clinical Trial	5 (3.1)	5 (3.8)	0 (0)	0 (0)	0.7

Abbreviations: MS – Multiple sclerosis; EDSS - expanded disability Status Scale; RRMS—relapsing–remitting multiple sclerosis; SPMS—secondary progressive multiple sclerosis; PPMS—primary progressive multiple sclerosis; SD – standard deviation, DMT - disease modifying therapy; IVIg - intravenous immunoglobulin.

with an additional $22,875 in indirect and nonmedical costs, primarily due to lost earnings, absenteeism, and presenteeism (Bebo et al., 2022).

In Portugal, the mean annual cost per patient by disease severity (mild, moderate and severe MS) has been estimated between €16,500 and €34,400, with DMTs being the largest contributor. However, family support plays a significant role, reflecting insufficient public support systems. Direct healthcare costs ranged from €12,303 to €16,451, and unemployment rates were high, with employment dropping from 75 % at EDSS 1–2 to 40 % at EDSS 3 (Diário da República 2017). These findings, based on data from 2015 to 2016, may now be outdated due to the availability of newer DMT (Sa et al., 2017).

Coimbra is a city in central Portugal, part of a region comprising 18 other municipalities. CHUC, the city's only public tertiary referral hospital and the largest hospital in Portugal, serves patients from Coimbra and surrounding districts. Unlike previous Portuguese studies, which relied on questionnaires or Delphi panels without linkage to hospital records, this cohort provides comprehensive real-world data, highlighting its unique value for understanding disease patterns and management in the region.

This study aims to characterize the demographic, social, clinical, and economic features of MS patients in Coimbra, providing an updated estimate of the socioeconomic burden of the disease.

2. Methods

We conducted a cost-of-illness study using a bottom-up and prevalence-based approach, incorporating both cross-sectional and retrospective observational components to assess socioeconomic characteristics.

2.1. Study area and population

Coimbra is a municipality in central Portugal, part of the Coimbra region (a Level III region according to the European Nomenclature of Territorial Units for Statistics), situated at 40°12′41″ N latitude. The city has a population of 140,816 (Census 2021) and covers an area of 319.40 km^2. The Coimbra region includes 18 additional municipalities (Thompson et al., 2018; Termos de Referência 2022). In this study, references to "Coimbra" pertain specifically to the city itself. CHUC is Portugal's largest hospital, serving patients from the Coimbra region and surrounding districts, reaching a population of over 1.8 million. It is the only public hospital in Coimbra, functioning as the region's tertiary referral center, and uniquely provides a permanent neurology team in the emergency department. In Portugal, the costs of neurological consultations for MS, related diagnostic tests, and other disease-related appointments conducted in public hospitals are fully covered by the

Table 2
Distribution of socioeconomic variables in the population and according to MS severity.

Variables		Total	Mild MS (EDSS 0–3.5)	Moderate MS (EDSS 4–6.5)	Severe MS (EDSS 7–9)	*p* value
Nationality, n (%)	Portuguese	157 (96.3)	126 (95.5)	26 (100)	5 (100)	0.833
	Brazilian	5 (3.1)	5 (3.8)	0 (0)	0 (0)	
	Angolan	1 (0.6)	1 (0.8)	0 (0)	0 (0)	
School degree, n (%)	Up to Middle School	22 (13.5)	14 (10.6)	6 (23.1)	2 (40)	0.002
	High School	28 (17.2)	23 (17.4)	2 (7.7)	3 (60)	
	Higher Education	113 (69.3)	95 (72)	18 (69.2)	0 (0)	
Civil Status, n (%)	Married	74 (45.4)	57 (43.2)	14 (53.8)	3 (60)	0.022
	Divorced	17 (10.4)	12 (9.1)	5 (19.2)	0 (0)	
	Single	52 (31.9)	47 (35.6)	4 (15.4)	1 (20)	
	Union	16 (9.8)	15 (11.4)	1 (3.8)	0 (0)	
	Widower	4 (2.5)	1 (0.8)	2 (7.7)	1 (20)	
Smoking habits, n (%)	Ex-smoker	39 (23.9)	32 (24.2)	5 (19.2)	2 (40)	0.3
	Smoker	35 (21.4)	32 (24.2)	3 (11.5)	0 (0)	
	Non-smoker	89 (54.6)	68 (51.5)	18 (69.2)	3 (60)	
Alcohol Consumption, n (%)	No	136 (83.4)	111 (84.1)	20 (76.9)	5 (100)	0.2
	1–2 glasses per day	26 (16)	21 (15.9)	5 (19.2)	0 (0)	
	>3 glasses per day	1 (0.6)	0 (0)	1 (3.8)	0 (0)	
Physical Activity, n (%)	No	67 (41.1)	52 (39.4)	12 (46.2)	3 (60)	0.7
	<150 min of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity per day	54 (33.1)	45 (34.1)	7 (26.9)	2 (40)	
	At least 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity per day	42 (25.8)	35 (26.5)	7 (26.9)	2 (40)	
Employment Status in patients of working age, n (%)	Total	143 (87.7)	127 (96.2)	14 (53.8)	2 (40)	<0.001
	Student	3 (2.1)	3 (2.4)	0 (0)	0 (0)	<0.001
	Worker	105 (73.4)	101 (79.5)	4 (28.6)	0 (0)	
	Unemployed	12 (8.4)	12 (9.4)	0 (0)	0 (0)	
	Retired	23 (16.1)	11 (8.7)	10 (71.4)	2 (100)	

Abbreviations: MS – Multiple sclerosis; EDSS - expanded disability Status Scale; SD – standard deviation.

National Health Service (NHS). Additionally, DMTs for MS are administered almost exclusively in public hospitals and are also fully funded through the NHS.

2.2. Patients recruitment

Patients meeting the 2017 revised McDonald criteria for MS (Thompson et al., 2018) followed in our Neurology Department and residing in Coimbra on December 31, 2021 were selected for inclusion in the study.

Selected patients were invited to participate during Demyelinating Diseases consultations or Neurology Day Hospital sessions between December 1, 2021, and October 31, 2022. After agreeing, patients or caregivers completed a questionnaire specifically developed for the purposes of this research, collecting data retrospectively for 12 months. The questionnaire covered six categories: demographics, social and economic data, clinical information, and pharmacovigilance. Clinical data were later supplemented by investigators using hospital records.

2.3. Costs calculation

Healthcare costs were assessed based on the resources used by patients over the previous 12 months, excluding those in clinical trials since their costs are not hospital-covered. Costs were calculated per patient according to standard rates defined by the Portuguese National Health System and medication costs were based on national regulatory data (Diário da República 2017; Termos de Referência 2022). The costs of blood tests were determined using information from our hospital. Cost components included: Specialty consultations; General Practitioner consultations; Day-hospital medical sessions; DMT; emergency room visits; hospitalizations; diagnostic tests (MRI scans and blood tests). For each category, costs were calculated based on the frequency of use and standard unit cost. Total annual direct costs per patient were determined by summing these components, excluding patients not on DMT.

Services and informal care costs included community services like ambulance transportation (Diário da República 2023), patient investments, and costs associated with informal caregiving.

Indirect costs included expenses related to short- and long-term absences, as well as invalidity and early retirement (Portugal, 2022).

2.4. Statistical analysis

We performed a descriptive analysis of all the variables included. Variables were assessed for normality. For consistency with prior literature and to facilitate comparisons, for continuous variables, the mean and standard deviation were used even for variables that did not strictly follow a normal distribution. For categorical variables, absolute and relative frequencies were presented.

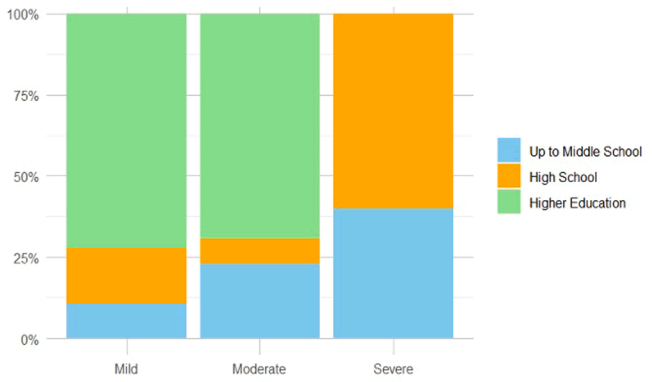

Fig. 1. Education levels by MS severity. As disease severity increases, there is a shift in educational levels with a decrease of the proportion of individuals with Higher Education and an increase of the proportion of individuals with Up to Middle School in the severe category.

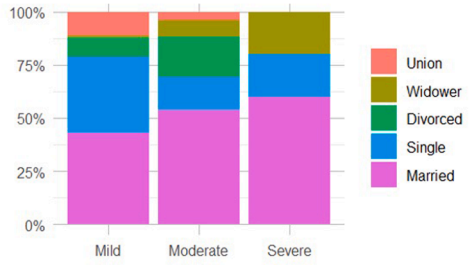

Fig. 2. Civil status by MS severity. Civil status distributions shift slightly as disease severity increases, with an increasing proportion of divorced patients with moderate disease category.

We performed a comparative analysis to evaluate differences between groups stratified by MS severity. MS was classified as mild if the EDSS was between 0 and 3.5, moderate if EDSS was between 4 and 6.5, and severe if EDSS was 7 or higher (Kobelt et al., 2017). Non-parametric tests were conducted because the variables did not follow a normal distribution, particularly the Kruskal–Wallis rank-sum test was used for quantitative variables, and Fisher's exact test was used for nominal variables. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical overview

A total of 163 patients were included. The complete clinical characterization of the population is available in Table 1. Analysis showed that 69.9 % ($n = 114$) of the patients were female, with a mean age of 48 years (SD 12.8, range 23–80). Patients with mild EDSS were younger (46 vs. 62 and 66 years, $p < 0.001$). Most patients (87.1 %, $n = 142$) had RRMS, followed by 10.4 % ($n = 17$) with SPMS and 2.5 % ($n = 4$) with PPMS. The median EDSS was 2.0 (IQR 1.5), with 81 % ($n = 132$) classified as mild MS, 16 % ($n = 26$) as moderate, and 3 % ($n = 5$) as severe. Mild MS was primarily RRMS (98.5 %, $n = 130$), while moderate and severe MS included more SPMS (42.3 % and 80 %, respectively) and PPMS (11.5 % and 20 %). The mean age at symptom onset was 33.4 (SD 11.9) years, with diagnosis at 36.7 (SD 11.6) years. MS duration was longer in moderate and severe cases (18.6 years). Family history of MS was present in 12.3 % ($n = 20$), and 3.7 % ($n = 6$) had other autoimmune diseases. In the past year, 19.6 % ($n = 32$) experienced relapses, leading to an MS diagnosis in 15.6 % ($n = 5$) of these cases. At the time of the survey, 58.3 % ($n = 95$) were on moderate- or high-efficacy DMT, based on the classification used by Singer et al. (2024) (Singer et al., 2024), and only 2.5 % ($n = 4$) were not on any DMT.

3.2. Socioeconomic characterization of the population

The complete socioeconomic characterization of the population is shown in Table 2. Most patients (96.3 %, $n = 157$) were born in Portugal, with 62.6 % ($n = 102$) from the Coimbra District, and 84 % ($n = 137$) were living in Coimbra at diagnosis. A majority (69.3 %, $n = 113$) had higher education, except for severe EDSS patients (0 %, $n = 0$), with disease severity associated with lower education levels, as shown in Fig. 1.

Less than half (45.4 %, $n = 74$) were married, while the divorce rate was highest among those with moderate EDSS (19.2 %, $n = 5$), as shown

Table 3
Resource utilization in the previous 12 months.

Variables	Population		Mild MS (EDSS 0–3.5)		Moderate MS (EDSS 4–6.5)		Severe MS (EDSS 7–9)		*p* value
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	
Consultations and Hospitalization									
Specialist Consultation	163 (100)	4.4 (2.9)	132 (100)	4.2 (2.7)	26 (100)	4.4 (2.2)	5 (100)	8.0 (7.2)	0.354
• MS consultation	163 (100)	2.3 (1.1)	132 (100)	2.3 (1.2)	26 (100)	2.2 (1.0)	5 (100)	2 (0)	0.696
• Other Specialties consultation	108 (66.3)	2.1 (2.7)	84 (0.6)	1.9 (2.5)	20 (76.9)	2.2 (1.7)	4 (80)	6 (7.2)	0.136
General Practitioner consultation	98 (60.1)	1.3 (2.0)	81 (61.4)	1.2 (1.9)	15 (57.7)	1.6 (1.8)	2 (40)	2.4 (4.3)	0.708
Day-Hospital session	125 (76.7)	4.2 (5)	102 (77.3)	4.4 (5.3)	20 (76.9)	3.1 (3.2)	4 (80)	5 (4.4)	0.694
Emergency room visits	45 (27.6)	0.4 (0.9)	30 (22.7)	0.4 (0.8)	9 (34.6)	0.7 (0.9)	3 (60)	1.6 (1.8)	0.015
Hospitalization	16 (9.8)	1.37	10 (7.6)	0.5 (2.5)	3 (11.5)	1.3 (3.7)	3 (60)	24.4 (29.6)	<0.001
• Inpatient admission	15 (9.2)	1.1 (5.1)	9 (6.8)	0.5 (2.5)	3 (11.5)	1.3 (3.7)	3 (60)	17 (20.8)	<0.001
• Rehabilitation centre	3 (1.8)	0.2 (2.4)	1 (0.8)	0 (0.1)	0 (0)	0 (0)	2 (40)	7.4 (13)	<0.001
Tests									
MRI (brain and/or spine)	114 (69.9)	1 (0.9)	100 (75.8)	1.14 (0.9)	12 (46.2)	0.6 (0.7)	2 (40)	0.6 (0.9)	0.005
Blood tests	137 (84)	1.9 (1.8)	110 (83.3)	1.8 (1.6)	24 (92.3)	2.5 (2.3)	3 (60)	1.8 (0.9)	0.122
Equipment, aids, modifications									
Walking aids	12 (7.4)	-	2 (1.5)	-	8 (30.8)	-	2 (40)	-	<0.001
House modifications	11 (6.7)	-	4 (3.0)	-	5 (19.2)	-	2 (40)	-	<0.001
Car modifications	6 (3.7)	-	4 (3)	-	2 (7.7)	-	0 (0)	-	0.468
Community services									
Transportation (trips)	12 (6.1)	-	3 (2.3)	-	5 (19.2)	-	4 (80)	-	<0.001
Home help	59 (36.2)	-	43 (32.6)	-	15 (57.7)	-	2 (40)	-	0.039
• Housemaid	57 (35.0)	-	43 (32.6)	-	13 (50)	-	1 (20)	-	0.184
• Hired caregiver	2 (1.2)	-	0 (0)	-	2 (7.7)	-	0 (0)	-	0.005
Nursing home	2 (1.2)	-	0 (0)	-	1 (3.8)	-	1 (20)	-	<0.001

Abbreviations: MS – Multiple sclerosis; EDSS - expanded disability Status Scale; SD – standard deviation.

Table 4
Total costs per patient stratified according to MS Severity.

Costs (euros)	Population Mean (SD)	Mild MS (EDSS 0–3.5) Mean (SD)	Moderate MS (EDSS 4–6.5) Mean (SD)	Severe MS (EDSS 7–9) Mean (SD)	*p* value
Healthcare Costs	12,454 (4984)	12,311 (4293)	12,451 (6265)	16,066 (11,731)	0.4
• **Specialist Consultation**	324 (211)	311 (194)	332 (166)	600 (543)	0.354
• **General Practitioner consultation**	41 (62)	39 (59)	47 (55)	74 (134)	0.823
• **Day-Hospital**	88 (106)	92 (112)	65 (68)	105 (92)	0.694
• **Emergency room**	50 (99)	40 (90)	73 (100)	179 (204)	0.018
• **Hospitalization**	447 (1729)	246 (908)	440 (1244)	5649 (6868)	<0.001
• **MRI scan**	130 (115)	144 (116)	74 (90)	77 (114)	0.006
• **Blood tests**	47 (41)	44 (36)	64 (57)	46 (52)	0.088
• **DMT**	11,312 (4308)	11,390 (3951)	11,309 (5781)	9 336 (5434)	0.661
Services and informal care costs	97 (221)	58 (117)	241 (395)	365 (503)	<0.001
• ***Community services***	6.4 (36.2)	1.9 (19.1)	12.0 (52.7)	94.9 (110.8)	<0.001
• **Investments**	893 (7225)	587 (5682)	2554 (12,743)	72 (102)	<0.001
• ***Informal care***	91 (213)	56 (116)	229 (376)	270 (524)	0.011
TOTAL DIRECT COST	13,144 (8855)	12,772 (7215)	14,328 (14,348)	16,503 (11,402)	0.283
Short-term and long-term absence	204 (732)	246 (809)	37 (131)	0 (0)	0.036
Invalidity and early retirement	4434 (8077)	1935 (5778)	13,924 (8619)	19,054 (0)	<0.001
TOTAL INDIRECT COST	4638 (7997)	2182 (5752)	13,961 (8558)	19,054 (0)	<0.001
TOTAL COSTS	17,782 (12,481)	14,954 (9251)	28,289 (17,605)	35,557 (11,402)	<0.001

Abbreviations: MS – Multiple sclerosis; EDSS - expanded disability Status Scale; SD – standard deviation; DMT - disease modifying therapy.

in Fig. 2.

Smoking was reported by 21.4 % ($n = 35$) but decreased with greater EDSS severity. Most patients had low or no alcohol consumption, and 58.9 % ($n = 96$) engaged in physical activity. Although 87.7 % ($n = 143$) were of working age, only 73.4 % ($n = 105$) were employed. Unemployment was 9.4 % ($n = 12$) among mild EDSS patients, while retirement rates were high in moderate (71.4 %, $n = 10$) and severe EDSS (100 %, $n = 2$)) groups, even among those of working age. All patients beyond working age were retired. Employed patients worked an average of 39.8 h (SD 8.9) per week, with 6.7 % ($n = 7$) reducing hours and 10.5 % ($n = 11$) changing roles, negatively impacting income for 27.3 % ($n = 3$). Patients missed an average of 2.13 days (SD 3.9) over the past year due to MS, with 40 % ($n = 42$) taking time off work. Sick leave was required by 18.1 % ($n = 19$), averaging 4.84 days (SD 18.8). The average retirement age was 50.3 years (SD 8.4).

3.3. Resource utilization

The resource utilization data for the previous year is summarized in Table 3. All patients attended Specialist consultations, with 66.3 % ($n = 108$) also consulting other Specialties and 60.1 % ($n = 98$) seeing General Practitioners. Day-hospital visits were reported by 76.7 % ($n = 125$) of patients, averaging 4.2 (SD 5) visits each. Emergency room visits were required by 27.6 % of patients ($n = 45$), rising to 60 % ($n = 3$) in severe MS cases, while 9.8 % ($n = 16$) required hospitalization, also 60 % ($n = 3$) in severe MS. Most underwent MS-related tests. Walking aids were acquired by 7.4 % of patients ($n = 12$), with few needing home or car modifications. Home assistance was required by 36.2 % ($n = 59$), while nursing home care was needed by only 1.2 % ($n = 2$). Ambulance transportation was used by 6.1 % ($n = 12$), with all resource use increasing alongside higher EDSS scores.

3.4. Economic burden

For the cost evaluation, 159 patients were included, excluding 4 patients involved in clinical trials. For the analysis of DMT and total costs, 155 patients were included, as 4 patients not receiving DMT were excluded. The average total annual costs per patient are summarized in Table 4. The average total annual direct healthcare cost per patient was €12,454 (SD 4984), increasing with MS severity, from €12,311 (SD 4293) in mild MS to €16,066 (SD 11,731) in severe MS. Most costs were attributed to DMT, which decreased with higher severity, while hospitalization costs, minimal in mild MS (€246, SD 908), became the second-largest expense in severe MS (€5649, SD 6868). A similar pattern was observed for consultation, day-hospital session, and emergency room costs, as shown in Fig. 3, as well for the majority of services and informal care costs. Total indirect costs increased from €2182 (SD 5752) in mild MS to €19,054 in severe MS, mostly due to the remarking increase in Invalidity and early retirement costs. The mean total cost per patients was €17,782 (SD 12,481), increasing from €14,954 (SD 9251) in mild MS, to €28,289 (SD 17,605) in moderate MS, and €35,557 (SD 11,402) in severe MS.

Relapses in the previous year significantly increased the economic burden, adding an average healthcare cost of €3277 per patient. This increase was driven by higher expenses across all categories, with DMT costs rising by €2154 and hospitalization costs by €870, as shown in Table 5 and Fig. 4. The difference in total costs were €2467.

4. Discussion

MS is prevalent in Portugal, with a reported prevalence of 143.45 cases per 100,000 in Coimbra (Correia et al., 2024). This study highlights the social, clinical, and economic challenges faced by individuals with MS, providing crucial insights to inform healthcare policies.

This cohort included patients across all MS subtypes, with a distribution consistent with the regional epidemiology of Coimbra. The low proportion of PPMS cases mirrors our previous prevalence study, suggesting near-complete regional coverage of this subgroup (Correia et al., 2024). Most patients presented with mild disability, reflecting both the regional clinical profile and the widespread access to specialized care, and allowing meaningful comparison with previous studies using similar EDSS-based classifications (Sa et al., 2017; Ernstsson et al., 2016). The prevalence of family history of MS and concomitant autoimmune diseases was in line with prior national and international reports, reinforcing the representativeness of the cohort, (Harirchian et al., 2018; Roshanisefat et al., 2012; Edwards and Constantinescu, 2004; Marrie et al., 2017; Fellner et al., 2014; Niederwieser et al., 2003) while rarer associations were also identified, such as myasthenia gravis and alopecia areata, the latter having only two cases reported in the literature (Dehbashi et al., 2019; Rossi et al., 2020). The high proportion of treated patients reflects the availability of newer DMTs within the Portuguese public healthcare system (Sa et al., 2017). Relapse rates observed over the past year were closer to European averages than to earlier Portuguese reports, suggesting evolving disease management patterns in this regional setting (Kobelt et al., 2017; Sa et al., 2017).

Beyond the characterization of the study population, the primary contribution of this study lies in the estimation of the socioeconomic burden of multiple sclerosis (MS) in a real-world regional cohort. Our findings provide an updated and comprehensive assessment of direct

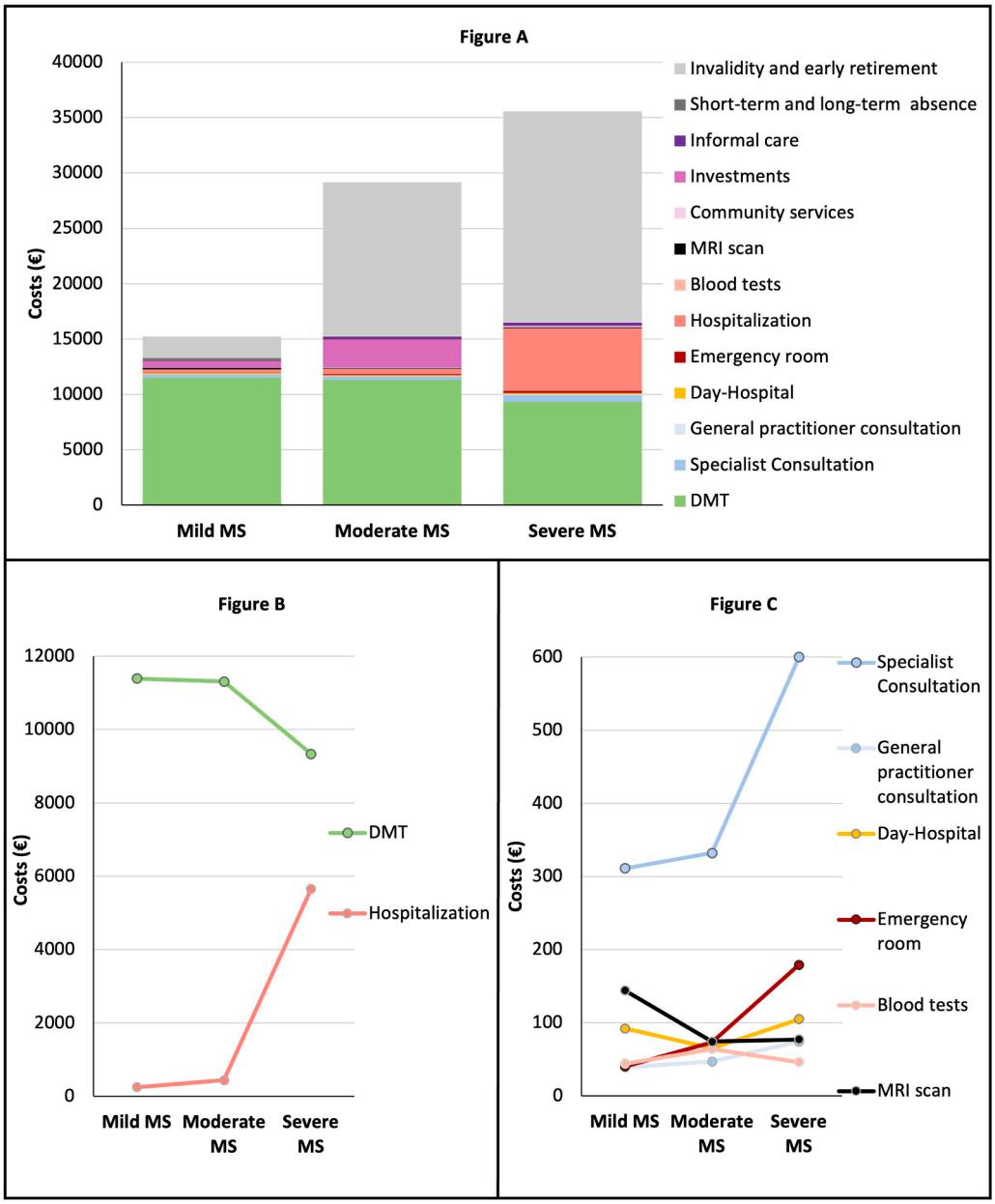

Fig. 3. Mean costs by MS severity. A: Distribution of total annual costs per patient in the overall population and by MS severity. B: Mean costs of DMT and hospitalization by MS severity category. C: Mean costs of other healthcare variables by MS severity category. Total costs increase with disease severity, but the allocation of resources shifts. As the disease progresses, costs associated with DMT and MRI scans decrease, while costs related to other healthcare variables, particularly hospitalization, significantly increase. Abbreviations: MS – Multiple sclerosis; DMT - disease modifying therapy.

and indirect costs, contextualized within both the Portuguese healthcare system and existing national and international evidence.

Sociodemographic characteristics were analyzed to contextualize the population and potential cost drivers. The high proportion of patients with higher education compared with the national average (21.2 %) (Portugal, 2021) is consistent with previous reports suggesting a slightly higher educational attainment among individuals with MS (Kavaliunas et al., 2021; Sa et al., 2017; Green et al., 2007; Pearson et al., 2017; Wiberg et al., 2019; Brenner et al., 2014; Tinghög et al., 2014). This proportion declined with increasing disease severity, likely reflecting age-related factors, although lower cognitive reserve could also play a role.

Marital status and lifestyle characteristics, including smoking prevalence, were broadly aligned with existing literature and highlight relevant factors that may influence disease progression, healthcare utilization, and productivity losses (Kavaliunas et al., 2021; Landfeldt et al., 2018; Pearson et al., 2017; Tinghög et al., 2014; Pfleger et al., 2010; Nunes, 2020; Rodgers et al., 2022; Ward and Goldman, 2022; Hawkes, 2007; Ramanujam et al., 2015; Barzegar et al., 2021).

Employment-related outcomes further illustrate the socioeconomic impact of MS. Although employment rates in our cohort were higher than those previously reported for Portuguese MS population (43 %), and the national average (55.3 %) (Sa et al., 2017; Portugal, 2021), unemployment increased with disability severity, and a substantial proportion of patients experienced job role changes or early retirement. Patients retired, on average, 16 years earlier than the statutory retirement age, underscoring the significant indirect costs associated with productivity loss and income reduction.

Direct healthcare costs represented a major component of the overall economic burden. The average annual direct healthcare cost per patient

Table 5
Total costs categorized by the occurrence of relapses.

Costs (euros)	No Relapses Mean (SD) $N = 132$	Relapses Mean (SD) $N = 27$	p value
Healthcare Costs	11,883 (4670)	15,160 (5605)	0.001
• **Specialist Consultation**	309 (193)	397 (279)	0.057
• **General Practitioner consultation**	39 (54)	54 (90)	0.7
• **Day-Hospital**	81 (109)	120 (80)	0.002
• **Emergency room**	43 (97)	83 (106)	0.02
• **Hospitalization**	300 (1592)	1170 (2179)	0.002
• **MRI scan**	119 (113)	185 (108)	0.003
• **Blood tests**	44 (36)	62 (57)	0.11
• **DMT**	10,936 (4218)	13,090 (4 365)	0.021
Services and informal care costs	107 (238)	50 (92)	0.7
• ***Community services***	5.8 (34.7)	9.6 (43.6)	0.4
• **Investments**	1071 (7923)	23 (56)	0.075
• ***Informal care***	101 (230)	40 (70)	0.5
TOTAL DIRECT COST	12,717 (9340)	15,233 (5611)	0.002
Short-term and long-term absence	172 (756)	363 (594)	0.003
Invalidity and early retirement	4475 (8108)	4234 (8072)	0.9
TOTAL INDIRECT COST	4647 (8047)	4597 (7895)	0.054
TOTAL COSTS	17,363 (12,785)	19,830 (10,854)	0.075

Abbreviations: MS – Multiple sclerosis; EDSS - expanded disability Status Scale; SD – standard deviation; DMT - disease modifying therapy.

was €12,406, increasing with disease severity. These estimates are consistent with previous Portuguese studies, while benefiting from linkage with hospital records and a larger, clinically well-characterized cohort. Compared with earlier reports, higher disease-modifying therapy (DMT) costs were observed, reflecting both greater treatment coverage and the increased use of moderate- and high-efficacy therapies, as well as the availability of newer agents.

When considering total costs, including direct and indirect components, expenditures rose markedly with disability severity. Our estimates closely align with previous national data and remain substantially lower than European averages, suggesting potential underinvestment in MS care in Portugal. (Sa et al., 2017; Pereira et al., 2004; Machado et al., 2010; Montóia et al., 2014) Relapses were associated with a significant increase in costs, driven primarily by DMT use and hospitalization, reinforcing the economic importance of effective relapse prevention strategies.

At a monthly level, average healthcare costs slightly exceeded the current Portuguese financing model for MS, indicating that existing reimbursement schemes may not fully reflect real-world care needs (ACSS 2023). Together, these findings highlight the substantial socioeconomic burden of MS and emphasize the need for adequate resource allocation, long-term planning, and investment in effective disease management strategies.

Several limitations should be acknowledged, including potential sampling bias related to the single-center design, exclusion of physiotherapy costs due to lack of standardization, and possible underestimation of indirect and intangible costs such as caregiver burden and quality-of-life impact. Despite these limitations, this study provides robust real-world evidence that contributes meaningfully to understanding the socioeconomic impact of MS in Portugal.

5. Conclusion

In conclusion, this study sheds light on the socioeconomic burden of multiple sclerosis, emphasizing its significant impact on patients, families, and healthcare systems. Costs associated with MS rise with disease severity, creating substantial financial challenges. The study also highlights disparities in employment, education, and access to care, underlining the need for tailored healthcare policies and support systems. By providing a comprehensive view of the social and economic challenges faced by MS patients, the findings stress the importance of effective resource allocation and improved disease management. Future efforts should prioritize access to high-efficacy treatments and interventions to enhance quality of life and societal participation.

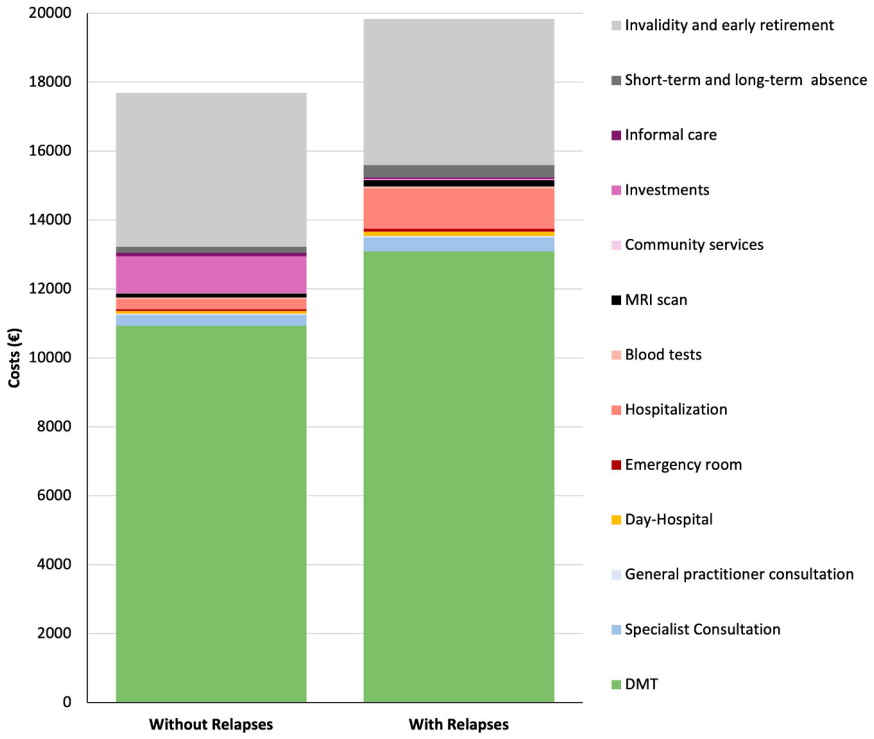

Fig. 4. The average 12-month costs associated with relapses were estimated by calculating the difference in costs between patients with relapses ($n = 27$) and those without relapses ($n = 132$). The cost of a relapse was estimated to be €2467, adding an average healthcare cost of €3277 per patient, with 86.3 % of this amount attributed to DMT. Abbreviations: DMT - disease modifying therapy.

Statements

Statement of ethics

This research was conducted following the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the Ethical Committee of Faculty of Medicine of the University of Coimbra (CE-010/2018) and the Regional Health Administration of Centro Portugal ethics committee (94/2018). The written informed consent was obtained from participants (or their caregiver) to participate in the study.

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Data availability statement

The research data used in this article are not publicly available on legal or ethical grounds.

CRediT authorship contribution statement

Inês Correia: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Carolina Cunha:** Investigation. **Catarina Bernardes:** Writing – review & editing, Investigation. **Gonçalo Carvalho:** Formal analysis. **Alex Xavier:** Formal analysis. **Carla Nunes:** Writing – review & editing, Investigation. **Carmo Macário:** Writing – review & editing, Investigation. **Lívia Sousa:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Sónia Batista:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

IC has received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Bristol Myers Squibb, Roche, Janssen.

CC, CB, GC and AX have no conflicts of interest to declare.

CN has received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Bristol Myers Squibb, Roche, Janssen.

CM has received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Bristol Myers Squibb, Roche, Janssen.

LS has received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Roche.

SB has received consulting fees from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Bristol Myers Squibb, Roche, Janssen.

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