Impact on healthcare resource utilization of multiple sclerosis in Spain

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Abstract

Background: Multiple sclerosis (MS) is a chronic disease with a high socioeconomic impact. The aim of this study was to assess healthcare resources utilization and costs in a sample of patients with MS.

Methods: A retrospective, cohort study was conducted using electronic medical records from 19 primary care centres in Asturias and Catalonia, Spain. Adult patients diagnosed with MS were distributed into two groups according to the Expanded Disability Status Scale (EDSS) score: 0–3.5 (no-moderate disability) and 4–9.5 (severe disability). Healthcare (direct cost) and non-healthcare costs (work productivity losses) were analysed. An analysis of covariance (ANCOVA) was used for correction, \( p < 0.05 \). A multiple regression model was performed to obtain the variables associated with costs.

Results: A total of 222 patients were analyzed; mean (SD) age: 45.5 (12.5) years, 64.4% female, and 62.2% presented a diagnosis of relapsing-remitting MS. Median EDSS score was 2.5, with 68.5% of the patients with no to moderate disability. The mean annual cost per MS patient was €25,103. For no-moderate and severe disability, the ANCOVA-adjusted mean annual cost was €23,157 and €29,242, respectively (\( p = 0.013 \)). Direct costs and MS disease-modifying therapy accounted for 39.4% and 31.7% of the total costs, respectively. The total costs were associated with number of relapses (\( \beta = 0.135, p = 0.001 \)), time since diagnosis (\( \beta = 0.281, p = 0.023 \)), and age (\( \beta = 0.198, p = 0.037 \)).

Conclusions: Multiple sclerosis imposes a substantial economic burden on the Spanish National Health System, patients and society as a whole. Costs significantly correlated with disease progression.

Keywords: Multiple sclerosis, Healthcare resource utilization, Costs, Electronic medical records

Background

Multiple sclerosis (MS) is a chronic, autoimmune disease characterised by inflammation of the central nervous system that leads to demyelination, axonal loss and progressive neuronal degeneration [1]. A prevalence of 125 cases/100,000 inhabitants was found in Spain affecting mainly young adults [2–5].

Multiple sclerosis progresses from episodic attacks followed by periods of remission (relapsing-remitting MS [RRMS]) to a more progressive state (secondary progressive MS [SPMS]) in approximately 80% of patients [1]. Primary progressive MS (PPMS) accounts for 10% of the overall population with MS and differs from RRMS and SPMS patients, in that progression consists of gradual worsening of neurologic disability from symptom onset [1]. Disease progression is linked to the accumulation of disability, which overall, is faster for patients with PPMS than for patients with RRMS [1]. Current MS disease-modifying therapies (DMTs) are used with the aim of reducing the number of relapses, their severity, and slowing the disability's progression [6].

The age of onset of MS is generally in the most financially productive time of the patients’ lives and consequently has a substantial economic burden on patients, their families, and society as a whole [7–10]. The European total annual cost of MS was €14.6 billion in 2010 (1.8% of the total annual economic cost of all brain disorders) [11]. A recent study involving 16,808 patients with MS in 16 European countries found that work capacity of MS patients declined from 82 to 8% with advancing disease, and utility declined from normal population values to less than zero [12]. Patients with PPMS present higher healthcare utilization than patients with SPMS and RRMS, due to different provider visits, emergency visits, and hospital admissions [13]. Disease-
modifying therapies are the main cost drivers for patients with mild disease severity, while for those with more advanced disability these are production losses and informal care [10, 12].

Mental and neurological disorders also have a substantial economic impact in Spain (equivalent to almost 8% of the country’s GDP) with a mean yearly per-patient cost of €30,050 for MS patients [14, 15]. However, information about the use of healthcare resources and associated costs among patients with MS in Spain is limited. The objective of this study was to assess the healthcare resources utilization of MS patients in Spain according to the degree of disability in order to provide detailed and updated information about the economic burden of the disease.

Methods
Study design
This study was a secondary analysis of electronic health records from 19 primary care centres in two regions of Spain (Asturias and Catalonia). The investigational review board of the Fundació Unió Catalana d’Hospitals (Barcelona) approved the protocol.

Study population
Key inclusion criteria were: age ≥ 18 years, a diagnosis of MS (International Classification of Primary Care and International Statistical Classification of Diseases, ninth revision criteria), requiring medical care from 2010 to 2015, and being in the long-term prescriptions program with a follow-up of ≥2 records in the computer system [16, 17].

Disability assessment
The Expanded Disability Status Scale (EDSS) is a clinician-administered scale that is widely used in both clinical trials and routine clinical practice to assess the clinical severity and the functional impairment of MS [18]. The score is based on measures of impairment in eight functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder function, visual function, cognition, and ‘other’. Each functional system is scored on a scale of 0 (no disability) to 5 or 6 (severe disability). The overall EDSS score ranges from 0 to 10 with higher scores indicating increased levels of disability.

Demographic and clinical variables
The following demographic and clinical variables were collected: age, gender, type of MS (RRMS, PPMS, SPMS and clinically isolated syndrome [CIS]), time since diagnosis, comorbidity and pharmacological treatments using the Anatomical Therapeutic Chemical Classification System (ATC) [19]. The number of chronic diseases, the Charlson Comorbidity Index, and Case-mix Index obtained from the Adjusted Clinical Groups (ACG) were used to summarize general comorbidity [20, 21].

Healthcare resources and costs
Direct healthcare costs were those related to healthcare activity (medical visits, hospitalisation days, emergency visits, diagnostic or therapeutic procedures and medication) and indirect costs related to work productivity loss (days off work due to sick leave). The cost was expressed as mean cost per patient (annual mean). Healthcare resources (€, year 2014) are shown in Table 1 and are expressed as mean cost per patient (cost/unit). The unit costs were obtained directly from the study centres with the exception of medication costs and work productivity loss. Prescriptions (acute, chronic, or upon request) were quantified according to the recommended retail price per package at the time of prescription (Bot Plus database) [22]. The days absent from work were collected from a specific computer program managed by primary care physicians and quantified according to the official minimum wage salary (source: Instituto Nacional de Estadística-INE, Spanish National Statistics Institute) [23]. A sub-analysis of resource was performed in patients stratified by type of MS (RRMS vs. PPMS) using the above calculations.

Statistical analysis
Demographic, clinical and economic variables were collected for the overall sample of valid patients and for stratified subgroups according to the EDSS score: no
disability - moderate disability (0.0–3.5) and severe dis-
ability (4.0–9.5). A descriptive analysis was presented for
all variables of interest with mean values, standard devi-
ation (SD) and 95% confidence intervals (CIs). Normal
data distribution was verified using a Kolmogorov-
Smirnov test. Costs were compared by analysis of
 covariance (ANCOVA) of age, gender, RUBs, Charlson
Comorbidity Index, and time since MS diagnosis
(generalized linear model). The bivariate analysis included
ANOVA, the chi-squared test, Pearson’s linear correla-
tion, and comparison of means. A multiple linear regression
model was used to evaluate the variables associated to the
costs (stepwise method) including age, gender, RUBs,
Charlson Comorbidity Index, time since MS diagnosis, and
EDSS score. The Statistical Package for the Social Sciences-
Windows (SPSSWIN) version 19 was used. A
\( p \)-value
< 0.05 was considered to be statistically significant.

Results
A total of 222 patients were included (Figure 1). The
mean (SD) age was 45.5 (12.5) years and 64.4% were
female. Prevalence of MS was 71 cases/100,000 inhab-
itants. Relapsing-remitting MS was the most common
clinical form (62.2% of the patients). The median
EDSS score was 2.5 (range: 1.0–8.5). The impact of
comorbidity was significantly greater in the severe
disability group vs. the no to moderate disability
group: mean number of comorbidities (6.0 vs. 4.5;
\( p = 0.001 \)), Charlson Index (1.0 vs. 0.7; \( p = 0.005 \)), and
RUBs (3.2 vs. 2.9; \( p = 0.003 \)). Demographic and clin-
ic characteristics of the patients are shown in
Table 2. Intramuscular interferon beta-1a (30.6%),
subcutaneous interferon beta-1a (23.9%) and glatira-
mer acetate (18%) were the most common disease-
modifying treatments administered.

Healthcare resource use
Table 3 shows the mean annual use of healthcare
resources by each disability group. Patients in the severe
disability group, presented a significantly higher number
of primary care medical visits (12.3 vs. 8.5; \( p < 0.001 \)),
specialised medical visits (3.0 vs. 2.3; \( p = 0.008 \)), emer-
gency room visits (2.0 vs. 1.2; \( p < 0.001 \)), and hospitalisa-
tion days (5.6 vs. 1.3 days; \( p < 0.001 \)) compared to
patients in the no-moderate disability group. Mean (SD)
work productivity losses were also significantly higher
for the severe disability group vs. to the no-moderate
disability group: 258.1 (162.0) vs. 160.9 (173.4) days,
\( p < 0.001 \), respectively.

Patients with PPMS showed a significantly higher
frequency of additional tests use (other than labora-
tory and radiology tests), days of hospitalisations
(both \( p \leq 0.001 \)), radiological tests use (\( p = 0.001 \)),
and specialised medical visits (\( p = 0.012 \)) compared to
RRMS patients (Table 4).

Direct healthcare costs and indirect costs
Table 5 specifies the direct healthcare costs and indirect
costs (unadjusted and adjusted values) by disability group.
From the total costs, 34.7% were related to primary care
and 4.8% to specialised care. Disease-modifying therapies
accounted for 31.7% of the total cost.

The total cost for the 222 study patients was 5.6 mil-
lion euros, 39.4% of which were direct healthcare costs.
The total annual mean cost (direct and indirect) per MS
patient was €25,103. This mean cost was significantly
higher in the severe disability (vs. no-moderate disabil-
ity) group (€31,608 vs. €22,107 \( p < 0.001 \)), predominat-
ly due to a higher healthcare resource utilization, in par-
ticular primary care visits (12.3 vs. 8.5; \( p < 0.001 \)).
The total costs were €23,157 (mean, SD = 174.7) in the severe disability group, €29,242 (mean, SD = 25.467) in the no-moderate disability group, and €33,016 (mean, SD = 175.5) in the moderate disability group.

In the adjusted model (ANCOVA) this mean (95% CI) difference in total cost was maintained: severe disability €29,242 (€25,467, €33,016) vs. no-moderate disability €23,157 (€20,561, €25,753); a statistically significant difference of approximately €6085 was observed (p = 0.013). In the multiple regression model, the total costs were associated to the number of relapses (β = 0.135, 95% CI 10.2–105.1, p = 0.001), time since diagnosis (β = 0.281, 95% CI -272.2-11.8, p = 0.023) and age (β = 0.198, 95% CI 3.1–195.2, p = 0.037). The EDSS score was included in the model but was not significant. The model's coefficient of determination was 33.5%. There were no significant differences between the evaluated variables by geographical regions. It is worth noting that 50.5% of the patients in the whole sample were unemployed due to their disability.

Discussion

Multiple sclerosis is a chronic disabling disease that is associated with reduced quality of life and a high socioeconomic impact [7]. Physical disability at diagnosis is the main determinant of the economic burden, with 13% increased annual costs for each additional point from baseline EDSS [24]. In addition, the costs increase with more severe disability.

| Table 2 Demographic and clinical characteristics |
|-----------------------------------------------|
| EDSS 0–3.5 | EDSS 4.0–9.5 | Total | p-value |
| N = 152 | N = 70 | N = 222 |
| Geographic regions in Spain, % |
| Asturias | 30.9 | 22.9 | 28.4 | 0.587 |
| Catalonia | 69.1 | 77.1 | 71.6 | 0.827 |
| Age, years, mean (SD) | 42.5 (11.5) | 52.2 (12.2) | 45.5 (12.5) | <0.001 |
| Gender, female, N (%) | 68.4 | 65.7 | 64.4 | 0.292 |
| Time since diagnostic, years, mean (SD) | 10.5 (7.6) | 19.8 (10.2) | 13.4 (9.5) | <0.001 |
| MS type, % |
| RRMS | 74.3 | 35.7 | 62.2 | <0.001 |
| SPMS | 13.8 | 50.0 | 25.2 | <0.001 |
| PPMS | 7.2 | 14.3 | 9.5 | 0.009 |
| CIS | 4.6 | 0.0 | 3.2 | <0.001 |
| Relapses during follow-up |
| Number of relapses, mean (SD) | 0.4 (0.6) | 1.2 (1.0) | 0.7 (0.9) | <0.001 |
| Proportion of population, N (%) |
| ≥ 1 | 36.8 | 67.1 | 46.4 | <0.001 |
| 1 | 29.6 | 18.6 | 26.1 | 0.008 |
| 2 | 6.6 | 40.0 | 17.1 | <0.001 |
| 3 | 0.7 | 8.6 | 3.2 | 0.790 |
| Comorbidity, mean (SD) |
| Number of comorbidities | 4.5 (2.7) | 6.0 (3.3) | 5.0 (3.0) | 0.001 |
| Charlson Index | 0.7 (0.6) | 1.0 (0.7) | 0.8 (0.6) | 0.005 |
| RUBs, mean | 2.9 (0.8) | 3.2 (0.7) | 3.0 (0.8) | 0.003 |
| Proportion of population, N (%) |
| 1 (healthy or very low morbidity) | 3.3 | 0.0 | 2.3 | <0.001 |
| 2 (low morbidity) | 25.7 | 14.3 | 22.1 | 0.038 |
| 3 (moderate morbidity) | 52.0 | 54.3 | 52.7 | 0.873 |
| 4 (high morbidity) | 18.4 | 28.6 | 21.6 | 0.041 |
| 5 (very high morbidity) | 0.7 | 2.9 | 1.4 | 0.031 |

CIS clinically isolated syndrome, EDSS expanded disability status scale, MS multiple sclerosis, PPMS primary progressive MS, RRMS relapsing remitting MS, RUBs resource utilization bands, SD standard deviation, SPMS secondary progressive MS.

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Discussion

Multiple sclerosis is a chronic disabling disease that is associated with reduced quality of life and a high socioeconomic impact [7]. Physical disability at diagnosis is the main determinant of the economic burden, with 13% increased annual costs for each additional point from baseline EDSS [24]. In addition, the costs increase with more severe disability.

| Table 3 Healthcare resource use and costs |
|-------------------------------------------|
| EDSS 0–3.5 | EDSS 4.0–9.5 | Total | p-value |
| N = 152 | N = 70 | N = 222 |
| Annual number per patient, mean (SD) |
| Medical visits, primary care | 8.5 (5.7) | 12.3 (5.7) | 9.7 (6.0) | <0.001 |
| Medical visits, specialists | 2.3 (1.5) | 3.0 (2.0) | 2.5 (1.7) | 0.008 |
| Laboratory tests | 2.8 (2.6) | 3.7 (2.7) | 3.1 (2.7) | 0.010 |
| Radiology tests | 1.9 (2.5) | 3.2 (2.6) | 2.3 (2.6) | <0.001 |
| Additional tests | 1.6 (2.3) | 3.4 (3.8) | 2.2 (3.0) | <0.001 |
| Hospitalisation days | 1.3 (3.8) | 5.6 (6.7) | 2.7 (5.3) | <0.001 |
| ER visits | 1.2 (1.3) | 2.0 (1.5) | 1.5 (1.4) | <0.001 |
| Work productivity losses, days (173.4) | 160.9 | 258.1 (162.0) | 191.6 | <0.001 |

| Table 4 Healthcare resource use and costs according to MS type |
|-----------------------------------------------|
| RRMS | PPMS | Total | p-value |
| N = 152 | N = 70 | N = 222 |
| Annual number per patient, mean (SD) |
| Medical visits, primary care | 8.9 (5.9) | 10.0 (7.1) | 9.1 (6.0) | 0.426 |
| Medical visits, specialists | 2.3 (1.6) | 3.3 (1.7) | 2.4 (1.7) | 0.012 |
| Laboratory tests | 2.9 (2.8) | 3.3 (1.8) | 3.0 (2.7) | 0.589 |
| Radiology tests | 1.6 (2.0) | 3.3 (2.2) | 1.8 (2.1) | 0.001 |
| Additional tests | 1.7 (2.6) | 4.6 (4.1) | 2.1 (3.0) | <0.001 |
| Hospitalisation days | 1.4 (4.0) | 5.4 (6.3) | 1.9 (4.6) | <0.001 |
| Hospital emergencies | 1.3 (1.3) | 1.7 (1.8) | 1.4 (1.4) | 0.237 |
| Work productivity losses, days (174.1) | 177 | 123.3 | 169.9 | 0.190 |

MS multiple sclerosis, PPMS primary progressive MS, RRMS relapsing remitting MS, SD standard deviation.
severe disability, especially when patients lose their upper limb function and independence (EDDS score > 7.0) [25].

The therapeutic landscape of treatment has changed dramatically over the last years. An increasing number of new drugs have recently shown encouraging results for the management of RRMS due to their proven higher efficacies compared to first-generation DMTs [6]. However, despite the availability of more treatment options, costs for all DMTs have increased substantially [10]. In addition, the early disease onset of MS has a significant impact on the patient’s most productive working years, leading to huge potential societal costs associated with this productivity loss [10]. Patients are less likely to be employed, are more likely to require time off work and to retire early compared to people without MS [7, 9, 12].

The impact on the costs of managing patients with MS is increasingly an area of interest [26–29]. However, comparing costs between countries with different socioeconomic, cultural, epidemiological background, and different systems for organizing and funding healthcare is very difficult [12, 30].

This study shows an overall annual mean cost per MS patient of €25,103. This mean cost was significantly higher in patients with severe disability compared than those with no-moderate disability (€29,242 and €23,157, respectively; \( p = 0.013 \)). Total cost was associated to the number of relapses, time since diagnosis, and age (\( p = 0.001, 0.023, \) and 0.037, respectively). Indirect costs and MS therapy accounted for 61% and 31.7% of the total costs, respectively.

In Spain, the available data for cost of MS is limited [12, 31–34]. These findings concur with prior studies. In a cost-of-illness analysis based on information from 1848 patients, Kobelt et al. found that the total mean costs per patient were driven by the distribution of the disease severity levels [30]. Workforce participation decreased from approximately 70% in the early disease stages to less than 5% in the very late stages. Productivity losses increased more than eightfold in patients with an EDSS score of 0–1 vs. 8–9. In another study with a sample of 200 MS patients in Barcelona, Casado et al. found that the main drivers for direct costs were DMTs...
in low disability stages and caregiver costs in severe disability stages [32]. Overall, direct healthcare costs accounted for 60% of total cost; within these direct costs DMTs accounted for 78% in the early disability stages to 11% in the later disability stages. The correlation of disability with the increasing economic burden of MS was also shown in the TRIBUNE study [34]. The mean cost per patient per year was €20,659 for patients with mild disease severity, while patients with moderate MS incurred more than double that cost (€43,948). DMTs were the most expensive cost component for patients with mild and moderate disability (58% and 32%, respectively) [34].

Missing values and differences on diagnostic codification are usual limitations related to studies with population databases [35]. McDonald 2010 criteria were not used in the study because our healthcare database collected diagnosis following only IPC-2 and ICD-9 classifications. In addition, concomitant medications were not evaluated. This study did not include any non-healthcare direct costs, classified as “out-of-pocket” costs paid by the patient/family, as they were not recorded in the database. The only direct costs considered were those relating to the public health system and the area of influence of the patient. Another limitation was the absence of informal caregivers to calculate informal costs. Sick leave (temporary or permanent) may in turn be a limited indicator of indirect costs as premature death and informal costs were not considered. In addition, standard cost for sick leave should have been applied, rather than the specific costs depending on patients’ income. Despite these limitations, these results reflect the economic impact of MS and how these vary between different disability levels.

Conclusions
Patients with MS show high healthcare resource utilization and large work productivity losses that cumulatively impose a substantial economic burden on the healthcare system and society as a whole. This burden was enhanced upon disease progression.

Therefore, a more proactive management strategy, including earlier use of high-efficacy DMTs and close monitoring of the clinical and radiological response to treatment, is recommended to slow or halt the progression of physical and cognitive impairments in patients with MS [36, 37]. No evidence of disease activity is emerging as a new standard MS outcome and may be associated with improved long-term disability.

Additional research focusing on direct healthcare and indirect costs as well as standardised methodologies to calculate costs are necessary to determine the association between the disease evolution and economic burden.
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