

**Direct medical costs of Spinal Muscular Atrophy in the region of Catalonia:
a population-based analysis**

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ABSTRACT

Background and objective: Spinal muscular atrophy (SMA) is a rare disorder, estimated to affect 1 per 10,000 live births. Patients affected with SMA often require intensive, chronic healthcare that represents great social and economic costs. This study aimed to evaluate the direct medical cost of SMA from the National Health System perspective in Catalonia and provide regional data for the development of optimal disease management protocols and resource allocation decisions at the regional level.

Methods: A retrospective population-based study was designed based on admission records from primary care centres, hospitals and specialised care settings (inpatient and outpatient care), emergency services and extended care facilities obtained from a regional governmental claims database.

Results: A total of 396 patients met inclusion criteria. Annual direct medical costs summed €58,606 per patient, taking into account the use of healthcare resources at all levels of care, excluding the cost of prescription medication. Specialised care represented 83% of the expenses that were mostly associated with the respiratory manifestations of SMA. In the year 2016, 71.26% of patients with SMA had 4 or more systems affected by a chronic condition versus the 23.50% in the general population, which had an impact in healthcare usage.

Conclusions: Inpatient extended care and the increased presence of multimorbid chronic conditions in these patients must be taken into account in order to develop multidisciplinary treatment protocols that reflect the complexity of this disease.

Forthcoming resource allocation decisions should reflect the intensive use of specialised care registered in these patients.

KEY POINTS

- Spinal Muscular Atrophy represents an annual direct medical cost of €58,606 per patient, in the region of Catalonia.
- Most of the costs were associated with the respiratory manifestations of Spinal Muscular Atrophy.
- More than 70% of the patients had 4 or more systems affected by a chronic condition.

KEYWORDS

Spinal muscular atrophy; disease management; multimorbidity; direct medical cost; claims database analysis; Spain.

1. Introduction

Chronic and genetic conditions such as spinal muscular atrophy (SMA) pose a challenge for families and the healthcare system in terms of economic costs [1]. In the US around 78% of health spending was estimated to be destined to treat patients with chronic conditions, a sum that grows exponentially as the number of chronic diseases per patient increases [2]. In Spain, a similar percentage is estimated, considering that these conditions are responsible for 80% and 60% of primary and specialised care consultations, respectively [3].

SMA is a rare disorder, estimated to affect 1 per 10,000 live births when considering all SMA types together [4]. However, the different degrees of motor function impediment derived from the degeneration of the alpha motor neurons of the spinal cord define extremely high healthcare costs to be assumed by patients, families and Healthcare Systems [5, 6]. Previous evaluations in Spain were based in questionnaires completed by caregivers, in which their socio-demographic characteristics and use of healthcare and non-healthcare resources were measured [7]. Such studies remark the socioeconomic costs of the disease, yet, regional data including a detailed evaluation of direct medical costs is still in need in the country. The chronicity associated with the disease and its multisystemic symptomatology require complex protocols that may increase treatment costs greatly [8]. Thus, the economic burden associated with SMA is estimated to be significant within the healthcare system due to patients need for extended care, long-term ventilation or nutritional support [9, 10]. Additionally, the number of multimorbidities in these patients is relatively high, including scoliosis, joint contractures, fatigue, and other

orthopaedic problems [11, 12], while healthcare systems are rarely prepared to handle multimorbidity in favour of individual diseases, with patients visiting a large number of different medical specialist every year [13, 14]. Cross-sectional studies have shown that a high multimorbidity number relates to poorer quality of life and a more intensive use of healthcare resources than in those without multimorbidity, which ultimately correlates with higher medical costs [15]. Contrarily, systems with successful integrated multimorbidity care are typically found in countries in which primary care takes a central role [16].

The National Healthcare System in Spain is predominantly publicly funded, with a strong primary care system, focused on improving health system coordination and addressing chronic conditions [17]. Health competences are transferred to the Autonomous Communities, whereas the National Healthcare System remains responsible for coordination and certain nationwide policies [18]. In the Spanish region of Catalonia, the regional government has developed a specialised programme that gathers details associated with patient admission records, going back to the year 2007. This programme of data analysis for research and innovation in health (PADRIS) aims to provide a tool for the evaluation of disease management, assessing not only healthcare use, but also, patients' characteristics in terms of multimorbidity [19]. This way, the regional government, aims to adapt the healthcare system to the population needs via the development of new protocols that reflect disease complexity, with a special focus on multidisciplinary care. In addition, the PADRIS programme aims to assist the regional Health Department that requires data acquired at the regional level for reimbursement

and resource allocation decisions. This real-world evidence provides the necessary data for health policy decisions in public health and the revision of the established protocols and guidelines [20].

In this context, the objective of this study was to estimate the direct medical costs that derive from SMA in the region of Catalonia by means of the PADRIS database, as well as to assess the presence of multimorbid conditions among these patients.

2. Methods

2.1 Data extraction

Anonymised admission records corresponding to patients diagnosed with SMA types I, II, III, IV and progressive SMA in the region of Catalonia (7.5 million inhabitants) between Jan 1 2014 and Dec 31 2017 were extracted from the PADRIS database under the supervision of the Health Evaluation and Quality Agency of Catalonia (AQuAS). Within the database, data was codified via the 9th revision of the International Statistical Classification of Diseases and Related Health Problems, Clinical Modification (ICD9-CM) [21]. Thus, to identify patients with SMA, the following ICD9-CM codes were used: 335.0, SMA-I or Werdnig-Hoffmann; 335.19, SMA in the adult (SMA-IV) and other, including SMA-II; 335.11, SMA-III or Kugelberg-Welander; 335.21, pure progressive SMA specified as such.

This study did not involve human participants, data was previously anonymised and there was no access to identifying information, for these reasons patient consent was not required in accordance with the Declaration of Helsinki and Spanish legislation (Law

14/2007, 3 July, on biomedical research, Spain). The University of Barcelona's Bioethics Commission approved research plan before data extraction.

2.2 Study variables

The files included admission data from primary care centres, hospitals and specialised care settings (inpatient, outpatient care and any physiotherapy sessions taking place therein), emergency services and extended care facilities, together with information of pharmaceutical consumption and laboratory analyses.

Separately, the database provided the classification of patients into multimorbidity groups, given automatically according to the number of systems they have affected by chronic conditions, using a morbidity measurement developed by the Catalan Health Institute (ICS). This measurement of morbidity uses Adjusted Morbidity Groups (GMA) as an alternative to the Clinical Risk Group (CRG) and classifies patients into 7 groups: healthy population, pregnancy, acute pathology, chronic disease in one system, chronic disease in two or three systems, chronic disease in four or more systems and neoplasia; each one of this groups (excluding the healthy population) is divided in 5 levels of complexity that is determined by their use of resources, risk of hospitalisation and mortality [22]. Therefore, in this method, higher GMA levels correlate with a more intensive use of healthcare resources and, thus, major medical costs [22]. Comorbidity indicators were extracted for the year 2016.

2.3 Data analysis

The patient population was categorised into SMA types by analysing the first admission registered per patient due to SMA in the study period. The complete admission data was

used for the remaining analyses. The direct medical costs of SMA between 2014 and 2017 were calculated based on the regional admission and medical procedures tariffs list determined by the Catalan government for the year 2013, the list of reference within the study period [23, 24].

The distinct centres were considered independently. In all cases, a first portion of direct medical costs was approximated based on the mean cost per admission determined by the Catalan government, which considers the expenses associated to personnel, nutrition (diet) and an average cost of general medical equipment [23]. The costs associated to specific procedures and healthcare (inpatient and outpatient) required by patients with SMA, treatment (examination, medication and surgery) and specialised equipment were calculated separately, taking into account that a patient with SMA might require more complex or specialised care, by multiplying the cost per procedure or per diagnosis as determined by the diagnosis related group (GRD) by the total number of procedures or diagnoses registered [23]. In addition, the following parameters were fixed in the analysis: the cost of specialised inpatient admissions was based on the average cost per day in hospitalisations of 6 or more days; the costs incurred by extended care facilities were given considering patients requiring level B support (out of three levels; medium complexity, pathology and dependency) [23, 24].

Data presentation is mainly descriptive. Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA).

3. Results

In total, 26,888 admission files were obtained from the distinct healthcare settings, which corresponded to 396 patients admitted with SMA in the region of Catalonia (7.5 million inhabitants) between the years 2014 and 2017. The patient population was composed by 170 (42.9%) patients with progressive SMA, 114 (28.7%) patients with SMA-III, 39 (9.8%) patients with SMA-II or SMA-IV, 22 (5.5%) patients with SMA-I and 51 (13.0%) patients unclassified. All of the patients were attended in primary and specialised care centres and emergency rooms at some point of the study period, while only 286 of the patients were attended in extended care facilities between 2014 and 2016. The majority of admissions, 22,936 (85.30%), were registered in primary care centres, 830 admissions (3.09%) were registered in specialised care centres, emergency services registered 2,836 admissions (10.55%) and extended care facilities 286 admissions (1.06%), with no trends observed during the study period (Table 1). When inpatient, specialised care admissions registered a mean length of stay of 8 days. The number of admissions corresponding to male patients was slightly above the 50% in all settings.

Table 1 Admissions included in the analysis and profile of the patients admitted per healthcare setting.

Setting	Admission number	% of males	Age (SD)
Total data	26,888	52.56	57.31 (25.22)
Primary care centres	22,936	52.30	57.34 (24.31)
Specialised care	830	57.35	55.50 (42.58)
Emergency Room admissions	2,836	53.39	56.49 (25.97)
Extended care facilities	286	51.05	68.17 (17.39)

The average direct annual medical cost associated with SMA in the region of Catalonia was €22,838,916, which corresponded to €58,606 per patient. Hospitalisation costs represented 73% of the expenses and were principally justified due to patients' extended need for mechanical ventilation (71.64%); physiotherapy was also accounted for in this section (Table 2). Costs originated in emergency rooms were principally derived from admissions due to acute and chronic respiratory failure, obstructive chronic bronchitis; essential hypertension and chronic kidney disease.

Table 2 Mean annual cost per patient per healthcare setting and principal procedures and conditions associated.

Care setting (unit cost, €)	Total cost	Cost per patient	% of total costs
Primary care	€1,697,933	€4,288	7.32
<i>Scheduled (€41)</i>	€412,337	€1,041	1.78
<i>Urgent (€62)</i>	€798,498	€2,016	3.44
<i>Nurse assistance in care centre (€29)</i>	€303,166	€766	1.31
<i>Nurse assistance at home (€46)</i>	€66,332	€168	0.29
<i>Cost of specified medical procedures</i>	€117,600	€297	0.51
General medical examination (€134)	€114,704	€290	0.49
Other procedures (<0.4% of total costs)	€2,896	€7	0.01
Specialised care	€18,756,974	€47,366	80.82
<i>Inpatient admissions(€2,545)</i>	€1,104,573	€2,995	4.76
<i>Outpatient admissions(€104)</i>	€41,184	€96	0.18
<i>Cost of specified procedures</i>	€17,611,217	€44,473	75.88
Mechanical ventilation (€29,945)	€16,625,664	€41,984	71.64
Internal/external fixation of bone (€3,038)	€413,820	€1,045	1.78
Injection of therapeutic substance (€231)	€253,440	€640	1.09
Physiotherapy (€1,142)	€239,580	€605	1.03
Other procedures (<0.4% of total costs)	€78,713	€199	0.34

Emergency services	€1,393,305	€3,518	6.00
<i>Emergency admissions (€130)</i>	€368,680	€931	1.59
<i>Cost per diagnosis related group</i>	€1,024,625	€2,587	4.41
Acute/chronic respiratory failure (€4,959)	€185,724	€469	0.80
Obstructive chronic bronchitis (€2,761)	€155,628	€393	0.67
Essential hypertension (€2,892)	€145,332	€367	0.63
Chronic kidney disease (€4,576)	€108,108	€273	0.47
Other diagnoses (<0.4% of total costs)	€429,833	€1,503	2.56
Extended care	€1,371,744	€3,464	5.91
<i>Cost per admission - level B support (€50)</i>	€14.363	€50	0.09
<i>Cost per diagnosis related group</i>	€1,357,381	€3,428	5.82
Essential hypertension (€2,892)	€248,712	€870	1.48
Acute/chronic respiratory failure (€4,959)	€158,688	€555	0.95
Chronic bronchitis (€2,761)	€124,245	€434	0.74
Diabetes mellitus (€2,690)	€118,360	€414	0.71
Chronic kidney disease (€4,576)	€109,824	€384	0.66
Heart failure (€4,673)	€102,806	€359	0.61
Anaemia (€3,148)	€94,440	€330	0.56
Other diagnoses (<0.4% of total costs)	€19,266	€67	0.11
Annual cost per patient	€22,838,916	€58,606	-

Laboratory tests in these patients did not represent significant sanitary expenses since analyses revealed a predominance of routine blood tests. Over the study period, 92,073 tests were registered, involving 337 patients and corresponding principally to complete blood count studies, measures of glucose, creatinine, cholesterol, potassium, sodium and various antibodies. Similar outcomes were obtained from the analysis of pharmacy dispensation; external pharmacy use was related to inexpensive medication prescribed in event of gastroesophageal reflux disease, peptic ulcer, generalised pain, cholesterol and

hypertension, not computed in final cost calculations. Nonetheless, information was obtained on patients' contribution to pharmaceutical costs, which is, in Catalonia, determined by income, age and sickness. Most patients, the 64.89%, contribute to 10% of pharmaceutical costs, with a distinct monthly limit in accordance with their income, whereas 26.34% of the patients paid via out-of-pocket payments a portion between the 40 and 60% of pharmaceutical expenses (Table 3). A 6.68% of patients were exempted from contribution due to old age or long term unemployment.

Table 3 Patients' contribution to pharmaceutical costs.

Patients' contribution	Patient number	% of patients
10% contribution (monthly limit at € 8.23)	220	55.53
10% contribution (monthly limit at € 18.52)	37	9.35
40% contribution	71	17.94
50% contribution	31	7.82
60% contribution	2	0.57
Exempted	26	6.68
Unspecified	8	2.10

Additionally, multimorbidity was assessed based on the GMA values for the year 2016. The data obtained corresponded to 348 patients (Table 4). According to this classification, the year 2016, 71.26% of patients diagnosed with SMA had 4 or more systems affected by a chronic condition, while this percentage was 23.50% in the general population (Figure 1). Instead, the general population contained a higher portion of individuals with 1 to 3 systems affected by chronic conditions.

Table 4 Number of patients per GMA group.

GMA group	Level of complexity					
Morbidity group	1	2	3	4	5	Total
1 system affected by a chronic condition	0 (0.00%)	7 (2.01%)	3 (0.86%)	3 (0.86%)	4 (1.15%)	17 (4.89%)
2 or 3 systems affected by a chronic condition	0 (0.00%)	11 (3.16%)	18 (5.17%)	14 (4.02%)	18 (5.17%)	61 (17.53%)
4 or more systems affected by a chronic condition	30 (8.62%)	59 (16.95%)	35 (10.06%)	61 (17.53%)	63 (18.10%)	248 (71.26%)
Patients with an active neoplasm	1 (0.29%)	4 (1.15%)	4 (1.15%)	5 (1.44%)	8 (2.30%)	22 (6.32%)

Figure 1 Percentage of patients in with SMA per multimorbidity groups vs. the general population (2016).

4. Discussion

The understanding of healthcare usage patterns will be crucial to establish protocols that take into account the needs of chronically ill patients, especially patients affected by more than one chronic condition. In addition, the revision of protocols and guidelines generally requires real-world evidence [20]. This study aimed to evaluate in detail the direct medical costs that derive from SMA in the region of Catalonia, while assessing the presence of multimorbid conditions in these patients and how it correlates with disease burden, vital in a region that relies in regionally acquired data for reimbursement and resource allocation plans [25].

Multimorbidity is called to be one of the determining challenges for healthcare management in the coming generations [26]. It has been proven that, as the number of diagnosed chronic conditions increase, healthcare expenses grow exponentially, as it does the number of admissions per patient [2, 27]. Herein, 71.26% of patients included in the

study had 4 or more systems affected by a chronic condition in 2016, whereas in the general population this group was 23.50% the same year [28]. A previous analysis in the general population showed that an increased complexity correlated with two to eleven times more ER admissions, and up to an eleven fold increase in pharmaceutical costs [22]. Similar outcomes can be assumed in patients diagnosed with SMA, hence the importance of complexity and multimorbidity in upcoming protocol revision and resource allocation.

In this study, costs resulting from hospitalisations were responsible for the majority of expenses, although only 830 admissions were registered, and were mostly due to complications derived from respiratory difficulties. The role of specialised care in resource expenditure is considerable; as a consequence, the goal of healthcare providers is to increase its efficiency while promoting the use of primary care. Some evidence suggests that broadening the care offered in primary care centres can reduce medical costs; yet, definitive data is hardly obtainable since a more specialised primary care may lead to early detection of conditions that require unavoidable hospitalisation [29, 30]. The opinion of clinicians and experts should be considered together with this data in order to promote health measures and for protocol modification.

The overall cost of SMA care has been estimated in multiple occasions; yet, huge discrepancies exist between data obtained from different regions and datasets. In Spain, a study from 2014 based on questionnaires completed by the caregivers of 88 patients estimated an annual medical cost of SMA of €10,882 per patient, increasing to the €33,721 when adding the cost of social services, non-healthcare formal costs, non-healthcare informal costs, family costs and others [7]. Similarly, in Germany, the direct

medical cost of SMA was established at €14,342 per patient in 2016, giving great weight to hospital inpatient care [31].

These estimations are significantly lower to the cost predicted in the present study, where the annual healthcare costs associated with patients with SMA was estimated to reach the €58,606 per patient. These discrepancies may be tightly associated with the methodology. Herein, specialised care and, in particular, mechanical ventilation and other procedures related to respiratory failure were estimated separately and accounted for most of the expenses. Comparably, in 2018, the cost of a single hospitalisation of patients with SMA-I in the United States was around the €45,000, billing mostly for nutritional and ventilator support, attributable to the complexity and duration of the care provided [10]. Also in the United States, estimations based on the US military healthcare system data, approximated a cost of €42,300 per year on direct medical costs for patients with SMA [32].

In contrast, costs estimated in the general population are considerably lower. The direct public healthcare cost per person in Spain was approximately €1,594 the year 2017, with 63.2% of total costs dedicated to specialised care [33].

Finally, data shows (in Table 3) that the healthcare system covers the majority of pharmaceutical costs. For 64.89% of patients, a minimum of 90% of costs are covered, having to contribute solely to 10% of the pharmaceutical costs. Current expenses are not significant, although patients' contributions may become relevant as new treatments arise and are released into the market [34]. One of the novel treatments for SMA is Nusinersen, a modified antisense oligonucleotide to treat SMA caused by mutations in chromosome 5q [35]. The approval of nusinersen in Spain was posterior to this study and its use will

presumably increase the overall medical costs covered by the Spanish National Healthcare System [36].

A series of limitations influence the results of this study. The ICD9-CM codification used in the database impedes the analysis per SMA type given the lack of specific codes for SMA-II and SMA-IV. The use of a fixed cost per admission plus a variable portion corresponding to medical procedures may lead to an overestimation of the costs associated to hospital bed, nutrition and personnel. On the other hand, rehabilitation taking place in external private centres was not included.

This study offers an evaluation of direct medical costs of SMA in Catalonia aiming to assist regional resource allocation decisions. Nonetheless, complementary research analysing informal care costs, indirect medical costs and nonmedical costs will be required to quantify the total burden of this condition.

5. Conclusions

SMA represents a significant burden for the Health Care System, €58,606 per patient, primarily associated with hospitalisations and the care of patients with respiratory failure. Patients require extended inpatient care, which determines an intensive use of resources and can be associated with the high presence of multimorbid conditions; 71.26% of the patients had 4 or more systems affected by a chronic condition. Healthcare systems need to adapt to patients' needs as the prevalence of multimorbidity increases, and promote multidisciplinary care.

6. Compliance with Ethical Standards

6.1 Disclosure of potential conflicts of interest

The author declares that no conflict of interest exists.

6.2 Compliance with Ethical Standards

Project approved by the University of Barcelona's Bioethics Commission. Data was anonymised prior to extraction in accordance with the Declaration of Helsinki and Spanish legislation (Law 14/2007, 3 July, on biomedical research, Spain). Patient consent was not required for this study.

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