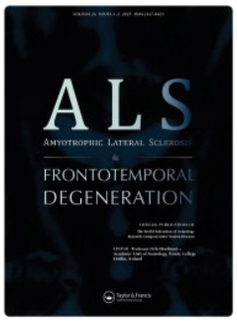

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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**RESEARCH ARTICLE**

# Characterization, epidemiology, and factors associated with evolution and survival in patients with amyotrophic lateral sclerosis in southeastern Spain, 2008–2021: a population-based study

YAIZA GARCÍA-RAMÍREZ[1], JUANA-MARÍA CAYUELA-FUENTES[2], MARÍA-PILAR MIRA-ESCOLANO[2], LUIS-ALBERTO MACEDA-ROLDÁN[2], EVA MIKULASOVA[2], CRISTINA OLIVA-LÓPEZ[2], ANTONIA SÁNCHEZ-ESCÁMEZ[2], PILAR CILLER-MONTOYA[2] & JOAQUÍN A. PALOMAR-RODRÍGUEZ[2]

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**Abstract**

*Objective*: To describe the epidemiology, characteristics, and factors associated with the evolution and survival in patients with amyotrophic lateral sclerosis (ALS) in a region of southeastern Spain. *Methods*: An observational study was carried out in people with a diagnosis of ALS in the period 2008–2021 who were registered in the Information System of Rare Diseases of the Region of Murcia (SIER). We calculated crude and standardized incidence rate (SIR) using European Standard Population of 2013 and point prevalence. The Kaplan–Meier method and the log-rank test were used to estimate and compare survival curves. *Results*: We identified 374 cases. The mean age at diagnosis was 66.5 ± 11.7 and 50.3% persons were spinal onset. Mean time from the onset of symptoms to diagnosis was 0.9 ± 1.0 years. The global SIR was 1.95/100,000 person-years (95%CI: 1.77–2.12), which was higher in men (ratio 1.34), and the point prevalence in 2021 was 4.57 per 100,000 (95% CI: 4.46–4.68). There were 297 deaths with a mean age of 69.8 ± 10.8. The median survival from clinical onset was 2 years (95%CI: 1.0–3.0). Factors associated with lower survival were bulbar onset ($p < 0.001$), older age at the onset of symptoms ($p < 0.001$), and the absence of riluzole treatment ($p = 0.003$). *Conclusions*: This study is one of few to evaluate the epidemiological, characteristics, and prognostic factors of ALS in Spain, with findings similar to previous population studies. The use of population-based registries offers reliable information on the magnitude, or evolution in these patients.

**Keywords:** *Amyotrophic lateral sclerosis, epidemiology, survival, population-based registry*

## Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects the upper and lower motor neurons of the central nervous system (1,2). This motor neuron impairment leads to the appearance of motor symptoms, including progressive bulbar, respiratory, and limb weakness, and in some cases cognitive impairment or frontotemporal dementia (2–5).

ALS is considered the third most frequent neurodegenerative disease after dementia and Parkinson's disease and the most common motor neuron disease in adults (1,6). The incidence of ALS varies, with rates between 0.8 and 3.8/100,000 person-years worldwide and between 2.0 and 3.0/100,000 in Europe, with a possible increasing trend in recent years and a greater frequency in men than in women (ratio 1.1–2.0) (1–5,7–19). Recent studies have found prevalence rates of approximately 3.4 and 8.4 cases/100,000 inhabitants (1–4,8,12,19,20).

In Spain, several studies have addressed the epidemiology of this disease, with the reported incidence rates ranging from 1.4 to 2.7 cases/100,000 person-years and a prevalence from 3.5 to 7.4/100,000(8–12). However, most of these studies were not carried out in the recent years, with few publications providing a recent view of the disease.

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Approximately 90% of ALS cases occur sporadically, whereas the remaining 5–10% are familial, with mutations in the *C9orf72*, *SOD1*, *TARDBP*, and *FUS* genes being the most frequently implicated (5,15,21,22).

In terms of initial manifestations of the disease, ALS patients may present with limb weakness (spinal onset), or dysarthria/dysphagia (bulbar onset). Spinal onset is present in between 60% and 80% of ALS patients (1,4,18), with a greater frequency of bulbar onset in women or patients of advanced age (1,8). Similarly, recent studies have noted that other onset, such as mixed (spinal and bulbar) or those in which the initial manifestations are respiratory symptoms, constitutes between 10% and 20% of all cases (1,7,23).

The survival of ALS patients varies, although death usually occurs approximately 2–5 years after the onset of symptoms, with an average survival of 20–50 months, and only approximately 5–10% of affected individuals survive 10 or more years (3,8,18,21,24). Moreover, earlier age at the onset of symptoms and diagnosis, the spinal onset, a higher initial score on the ALS Functional Scale-Revised (ALSFRS-R), or higher body mass index (BMI) have been associated with longer survival. In contrast, the older age, bulbar onset, cognitive impairment or depression, and worse nutritional status are associated with shorter survival (24–30).

Several authors have described the clinical–epidemiological features and factors related to the survival of patients with ALS, although few studies have been conducted based on the Spanish population. In addition, data from specific hospital clinical units have been evaluated in most of these studies, and none of them has been carried out in our geographical area.

Therefore, the objective of this study was to determine the incidence and prevalence of ALS patients, as well as their main characteristics, and to analyze the factors associated with the evolution and survival of these people using the information from registry of the rare disease in the Region of Murcia (RM), located in southeastern Spain.

## Methods

### *Study population*

An observational study of patients with a confirmed or probable diagnosis of ALS according to the criteria of El Escorial (31) and registered in the Rare Diseases Information System (SIER) of the RM from January 2008 to December 2021 was carried out (32). Nonresidents of the region and patients whose diagnosis was inconclusive or who had another motor neuron disease were excluded from the study.

Individual informed consent of the study population was not needed, as the SIER is subject to personal data protection regulations and registered with the Spanish Data Protection Agency (33).

### *Rare diseases information System (SIER)*

The SIER is a population-based registry of the RM, an Autonomous Community located in southeastern Spain, with a population of 1,531,878 inhabitants as of 1 January 2022, which constitutes 3.22% of the Spanish population (34). For the incorporation of people with a possible rare disease, a list of codes selected from the International Classification of Diseases (ICD) is used. For this study, for years up until 2015, the code 335.20 (ICD9-CM) was used, and for the years 2016–2021, the code G12.21 (ICD10-ES). The registry currently uses more than 50 sources of information to incorporate patients with some rare diseases. Those sources that have contributed cases of ALS are shown in Figure 1 and Table 1.

Once the cases are incorporated, they undergo a validation process, confirming the diagnosis through a review of the electronic medical records.

### *Data collection*

The data collected from each patient included the following:

**Basic data of the patient.** The data include sex, country of birth, date of birth, death of the patient (yes/no), and date of death.

**Family history.** Family history of the disease and transmitting parent: Positive family history was considered to be those in which the patient's medical history included a family member with a diagnosis of ALS. The associated genetic mutation was collected in patients with genetic study.

**Characteristics and symptoms of onset.** Characteristics include the year of diagnosis, date of onset of symptoms, and initial presentation of the disease (bulbar, spinal, bulbar-spinal, or respiratory). The times from the onset of symptoms to diagnosis (years) and from the onset of symptoms to death (years) were also recorded.

The initial clinical manifestations collected were: muscle weakness (cervical, upper limbs, lower limbs, or both), dysarthria, dysphagia, dyspnea, altered gait and clumsiness, muscle atrophy (upper limbs, lower limbs, or all limbs), muscle cramps, loss of dexterity, fasciculations (lingual, upper limbs, lower limbs, mixed), spasticity, and emotional lability (35).

**Evolution of the disease.** Information on treatment with riluzole, family support, palliative care, and the last wills of the patient was obtained. Finally, data were collected about recognition of disability (degree $\geq$33%) and/or dependence (degrees 1, 2, or 3 according to moderate, severe,

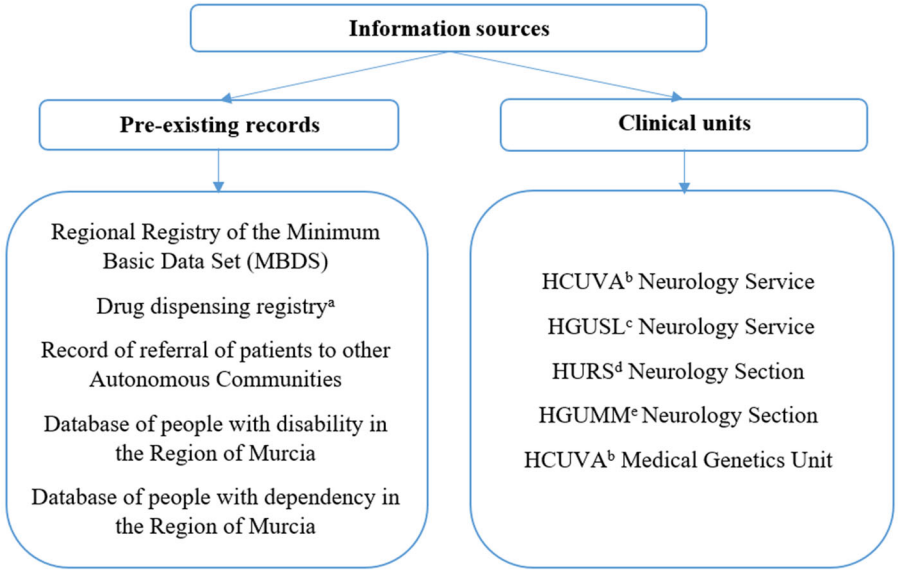


Figure 1. Information sources that contribute ALS patients to the SIER*.
*Each patient can be incorporated by more than one different source of information
[a]Includes Orphan drug dispensing registry of the Pharmaceutical Management Service and medications with special monitoring registry
[b]HCUVA: Virgen de la Arrixaca Universitary Clinic Hospital
[c]HGUSL: Santa Lucía General Universitary Hospital
[d]HURS: Reina Sofía Universitary Hospital
[e]HGUMM: Morales Meseguer General Universitary Hospital

Table 1. Number and percentage of ALS patients incorporated according to SIER information source.

| Information sources | Number of patients* | % patients |
|---|---|---|
| Regional Registry of the Minimum Basic Data Set (MBDS) | 331 | 88.50% |
| Drug dispensing registry[a] | 273 | 72.99% |
| Database of people with dependency and/or disability in the Region of Murcia | 179 | 47.86% |
| Neurology service or section[b] | 162 | 43.32% |
| Record of referral of patients to other autonomous communities | 28 | 7.49% |
| HCUVA Medical Genetics Unit | 9 | 2.41% |
| Total patients* | 374 | |

*Each patient can be incorporated by more than one different source of information.
[a]Includes orphan drug dispensing registry of the Pharmaceutical Management Service and medications with special monitoring registry.
[b]Includes the Neurology Service of Virgen de la Arrixaca Universitary Clinic Hospital (HCUVA), Neurology Service of Santa Lucía General Universitary Hospital (HGUSL), Neurology Section of Reina Sofía Universitary Hospital (HURS), and Neurology Section of Morales Meseguer General Universitary Hospital (HGUMM).

or great dependence) due to ALS assigned by the corresponding official evaluation services until 31 December 2021 (36,37).

### *Statistical analysis*

Crude and adjusted by age group, sex, and year rates were calculated. The adjusted incidence rates were calculated with the direct standardization method using European Standard Population of 2013 (38), and the temporal trends were analyzed with Joinpoint Regression Program, Version 5.0.2. May 2023 (Statistical Research and Applications Branch, National Cancer Institute) (https://surveillance.cancer.gov/help/joinpoint).

Demographic, genetic, and clinical characteristics of people with ALS were summarized using descriptive statistics. In addition, different hypothesis contrast tests were used according to the type of variables and the normality of their data distribution.

Survival was calculated from age at the onset of symptoms to age at death (end event) or through 31 December 2021 or loss to follow-up (censoring). The time scale to the event was measured in years. Patients with missing or unknown data were not included in the analyses. The Kaplan–Meier method and the log-rank test were used to estimate and compare survival curves.

All tests were two-tailed, and the level of statistical significance was set at $<0.05$. Statistical

analyses were performed with the IBM SPSS 25.0 statistical package (IBM Corporation, Armonk, New York, USA).

## Results

### *Incidence and prevalence*

There were 781 cases of ALS registered in the SIER, 508 classified as confirmed or probable cases, 374 of which were incidents from 2008 to 2021 (Figure 2).

The standardized incidence rate (SIR) was 1.95/100,000 person-years (95% confidence interval [CI]:1.77–2.12) higher in men than in women, with a ratio of 1.34. An increase in incidence was observed with age, with a maximum data between 75 and 84 years (SIR: 7.59; 95%CI: 5.98–9.19), followed by an overall decrease. However, in men the highest incidence was in the 65–74 year-old group (SIR:8.23; 95%CI: 6.30–10.16) (Table 2 and Figure 3).

Throughout the study, incidence rates ranged from 2.07/100,000 person-years in 2008 (95% CI: 1.33–2.82) to 2.77/100,000 in 2021 (95%CI: 1.93–3.60), the last year being when the highest incidence was recorded. However, the trend analysis did not reveal significant changes during this period ($p = 0.2$) (Figures 4 and 5).

The number of prevalent cases as of 31 December 2021 was 70 (the rate of 4.57 cases/100,000 inhabitants; 95%CI: 4.46–4.68), higher in men (5.73; 95%CI: 5.56–5.90) than in women (3.40; 95%CI: 3.27–3.53) (Table 3).

### *Demographic, clinical, and diagnostic features*

Of the total population analyzed, 54.8% were men, and 90.1% were born in Spain. The mean age at diagnosis was 66.5 ± 11.7 years (range 25.3–90.2 years), lower in men (65.4 ± 11.4) than in women (67.9 ± 12.0) ($p = 0.04$) (Table 4).

In 28 (7.5%) patients, there was evidence of a family history of the disease. Among those affected for whom information was available on the genetic mutation involved, 55.5% were associated with the *C9orf72* gene, 22.2% with the *FUS* gene, and the remaining 22.2% with other genes.

According to the site of onset, spinal ALS was the predominant in 50.3% of the patients (0.88 cases/100,000; 95%CI: 0.75–1.00), followed by bulbar ALS in 36.6% (0.64 cases/100,000; 95% CI: 0.53–0.74) (Tables 2 and 4). The other less frequent sites of onset were mixed (bulbar and spinal) in 4.0% and respiratory in 0.8%. In the remaining 8.3% of cases, this information was not available.

The most common site of onset in men was the spinal (57.6% vs. 26.8% bulbar), whereas in

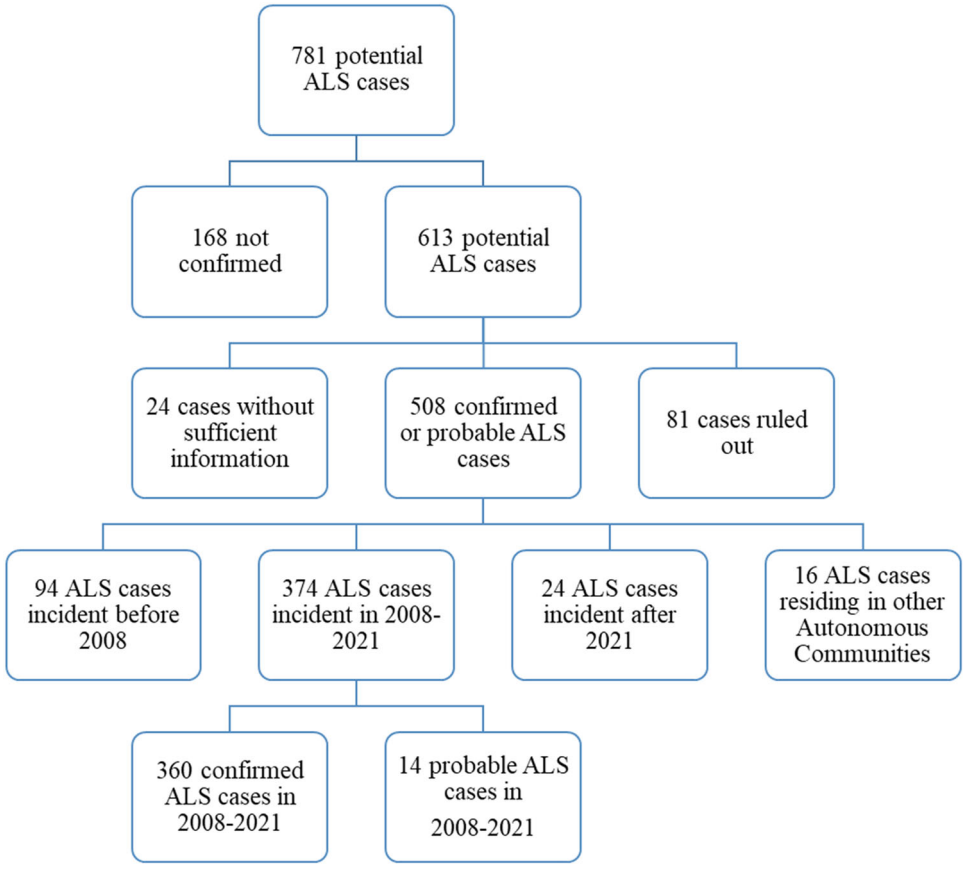


Figure 2. Flowchart of ALS cases incorporated to Rare Diseases Information System (SIER).

Table 2. Crude, and standardized sex- and age-specific incidence rates of ALS (2008–2021).

| | Incidence rate (IC95%*) | | |
|---|---|---|---|
| | Women | Men | Total |
| Cases | 169 | 205 | 374 |
| Person-years | 10,702,580 | 10,743,712 | 21,446,292 |
| Crude IR | 1.58 (1.34–1.82) | 1.91 (1.65–2.17) | 1.74 (1.57–1.92) |
| Standarized IR[a] | 1.68 (1.44–1.91) | 2.25 (1.99–2.51) | 1.95 (1.77–2.12) |
| Age-specific IR | | | |
| ≤44 | 0.14 (0.04–0.24) | 0.18 (0.07–0.29) | 0.16 (0.09–0.23) |
| 45–54 | 1.20 (0.67–1.72) | 1.47 (0.91–2.04) | 1.34 (0.95–1.73) |
| 55–64 | 2.39 (1.57–3.20) | 4.05 (2.98–5.12) | 3.21 (2.54–3.88) |
| 65–74 | 5.92 (4.37–7.46) | 8.23 (6.30–10.16) | 7.01 (5.79–8.24) |
| 75–84 | 7.43 (5.33–9.53) | 7.80 (5.32–10.27) | 7.59 (5.98–9.19) |
| ≥85 | 1.18 (0.02–2.35) | 2.67 (0.33–5.01) | 1.71 (0.59–2.83) |
| ALS phenotype IR | | | |
| Bulbar | 0.77 (0.60–0.93) | 0.51 (0.38–0.65) | 0.64 (0.53–0.74) |
| Spinal | 0.65 (0.50–0.81) | 1.10 (0.90–1.30) | 0.88 (0.75–1.00) |

*IC= 95% confidence interval; IR: incidence rate; [a]Incidence per 100,000 person-years adjusted to the 2013 European Standard Population.

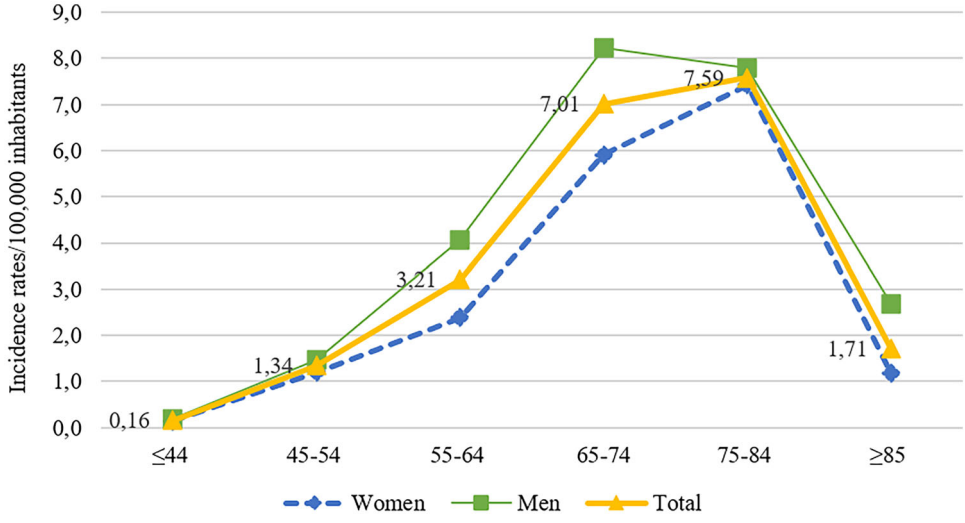


Figure 3. ALS incidence rates according to sex and age group (2008–2021).

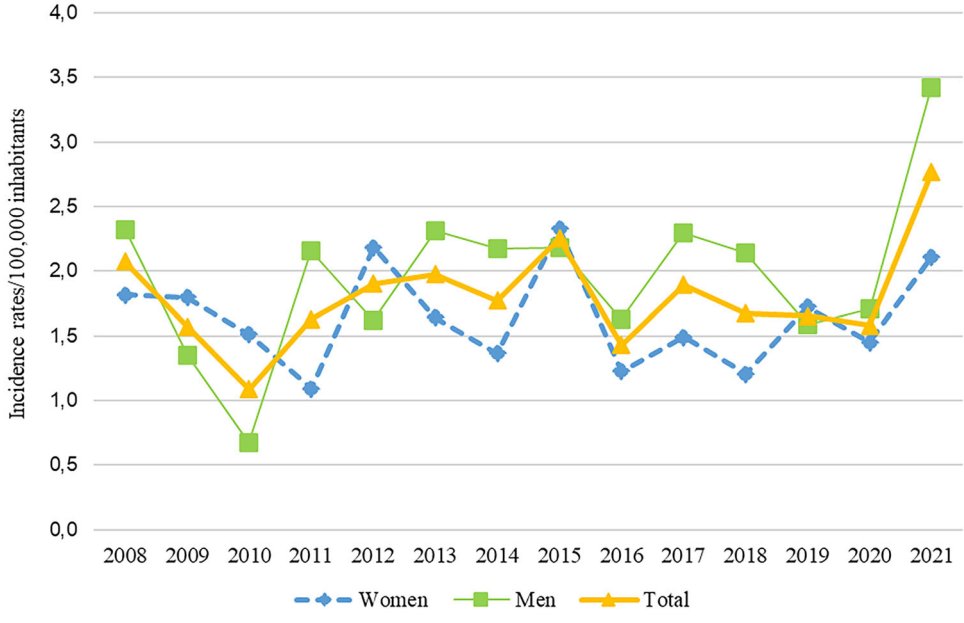


Figure 4. Incidence rates of ALS according to sex and year of diagnosis (2008–2021).

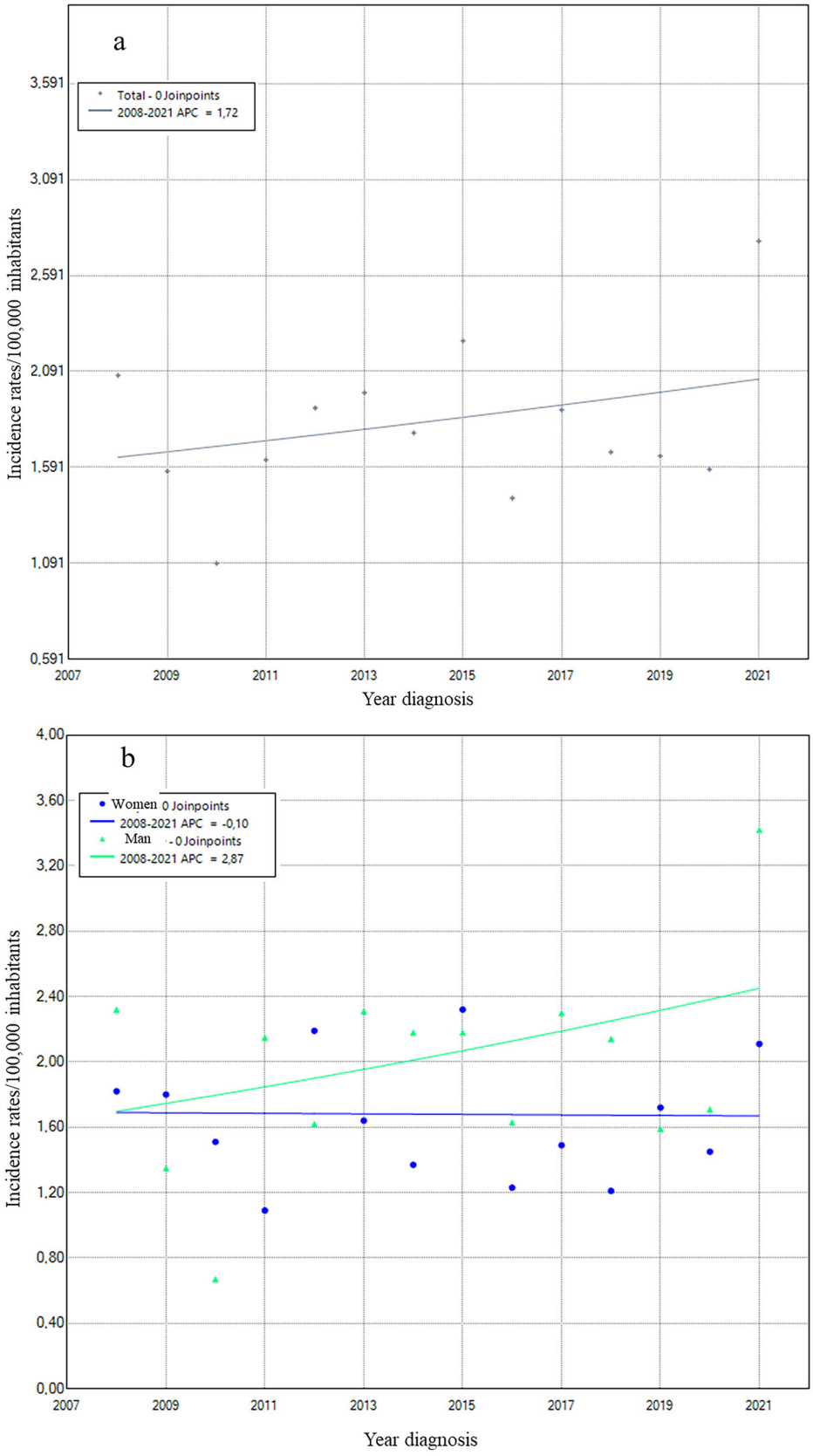


Figure 5. Trends in ALS incidence* (2008–2021): global (a) and by sex (b).
(*) Incidence rates adjusted to the 2013 European Standard Population/100,000 inhabitants

women was the bulbar (48.5% vs. 41.4% spinal), with significant differences ($p = 0.03$) (Table 4). In analyses by age group, the spinal onset predominated until 74 years of age, after which the bulbar onset had the highest incidence (Figure 6).

Table 3. Prevalence and clinical–epidemiological characteristics of ALS patients on 31 December 2021.

| | Women *n* (%) | Men *n* (%) | Total *n* (%) |
|---|---|---|---|
| Cases | 26 (37.1) | 44 (62.9) | 70 (100.0) |
| Prevalence (IC95%*) | 3.40 (3.27–3.53) | 5.73 (5.56–5.90) | 4.57 (4.46–4.68) |
| Age (years) at diagnosis | | | |
| ≤44 | 2 (7.7) | 5 (11.4) | 7 (10.0) |
| 45–54 | 5 (19.2) | 9 (20.5) | 14 (20.0) |
| 55–64 | 7 (26.9) | 10 (22.7) | 17 (24.3) |
| 65–74 | 7 (26.9) | 17 (38.6) | 24 (34.7) |
| 75–84 | 5 (19.2) | 2 (4.5) | 7 (10.0) |
| ≥85 | 0 (0.0) | 1 (2.3) | 1 (1.4) |
| Mean ± SD | 63.5 ± 12.6 | 60.3 ± 11.0 | 61.5 ± 11.6 |
| Median (25–75) | 64.7 (53.8–74.4) | 61.6 (51.5–67.9) | 63.1 (52.8–69.8) |
| Range (min.–max.) | 37.3 – 81.6 | 36.5 – 85.2 | 36.5 – 85.2 |
| Native country Spain | 22 (84.6) | 33 (75.0) | 55 (78.6) |
| Site of onset disease | | | |
| Bulbar | 11 (42.3) | 7 (15.9) | 18 (25.7) |
| Spinal | 13 (50.0) | 32 (72.7) | 45 (64.3) |
| Bulbar and spinal | 1 (3.8) | 2 (4.5) | 3 (4.3) |
| Respiratory | 0 (0.0) | 1 (2.3) | 1 (1.4) |
| Unknow | 1 (3.8) | 2 (4.5) | 3 (4.3) |
| Family history of ALS | | | |
| Maternal | 2 (7.7) | 5 (11.4) | 7 (10.0) |
| Paternal | 2 (7.7) | 1 (2.3) | 3 (4.3) |
| Other | 1 (3.8) | 1 (2.3) | 2 (2.9) |
| Unknown | 0 (0.0) | 2 (4.5) | 2 (2.9) |
| No family history | 21 (80.8) | 35 (79.5) | 56 (80.0) |
| Genetic mutation | | | |
| Negative | 15 (57.7) | 27 (61.4) | 42 (60.0) |
| *C9orf72* NM_018325.5(C9orf72):>60 GGGGCC repeats | 2 (7.7) | 1 (2.3) | 3 (4.3) |
| *FUS* NM_004960.4(FUS):c.4G > A; (p.Ala2Thr) | 0 (0.0) | 1 (2.3) | 1 (1.4) |
| Unknown | 9 (34.6) | 15 (34.1) | 24 (34.3) |

SD = Standard deviation; 25–75 = 25th–75th percentile; IC= 95% confidence interval.

The mean time from the onset of symptoms to diagnosis was less than 1 year (0.9 ± 1.0 years), with no significant differences between the sexes ($p = 0.5$) (Table 4). However, when analyzed according to the site of onset, the diagnostic delay was shorter for the bulbar ALS (85.4% vs.78.6% for the spinal in the first 2 years), although this difference was not significant ($p = 0.9$) (Figure 7).

Overall, the most frequent clinical manifestations at the onset of disease were muscle weakness (71.1%), followed by fasciculations (66.0%), muscle atrophy (61.2%), and altered gait/clumsiness (53.0%). In turn, patients affected by bulbar ALS presented more dysarthria and dysphagia as an onset symptom (more than 80% in both cases), whereas those classified as having spinal ALS presented mostly muscle weakness, atrophy, fasciculations, and altered gait or clumsiness ($p < 0.001$) (Table 5).

### *Evolution of the disease and factors associated with survival*

In 90.9% of all patients, there was evidence of treatment with riluzole, and 48.2% of all cases had recognized disability and/or dependence due to the disease (15.5% disability, 11.0% dependence, and 21.7% both). The mean time from the ALS diagnosis to the recognition of disability was 13.5 months, and the mean time to dependence was 17.2 months.

In addition, 51.6% of patients had received palliative care, 75.7% had family support, and 39.3% had last wills in their medical records (Table 4). Of these, 84.4% refused to receive supportive measures but did accept sedation, whereas 15.6% wanted any measure that would prolong life.

During the study period, 297 people died (79.4% of the total), 53.2% of which were men, and the mean age at death was 69.8 ± 10.8 years (70.9 ± 10.9 in women and 68.8 ± 10.6 in men), without significant differences ($p = 0.09$) (Table 6).

For the survival analysis, 22 cases with missing or unknown data were excluded. The mean number of years from the onset of symptoms to death was 2.6, and the median was 2 years (95%CI: 1.0–3.0). Furthermore, 85.5% patients survived more than 1 year after diagnosis, 11.8% more than 5 years, and 1.0% more than 10 years.

Kaplan–Meier curves showed that the median survival was lower in patients with bulbar ALS (2 vs. 3 years; $p < 0.001$), >75 years at the onset of symptoms (2 vs.3 years; $p < 0.001$), and those

Table 4. Clinical and epidemiological characteristics of incident ALS cases, stratified by sex (2008–2021).

| | Women *n* (%) | Men *n* (%) | Total *n* (%) |
|---|---|---|---|
| Cases | 169 (45.2) | 205 (54.8) | 374 (100.0) |
| Age (years) at diagnosis | | | |
| ≤44 | 8 (4.7) | 11 (5.4) | 19 (5.1) |
| 45–54 | 20 (11.8) | 26 (12.7) | 46 (12.3) |
| 55–64 | 33 (19.5) | 55 (26.8) | 88 (23.5) |
| 65–74 | 56 (33.1) | 70 (34.1) | 126 (33.7) |
| 75–84 | 48 (28.4) | 38 (18.5) | 86 (23.0) |
| ≥85 | 4 (2.4) | 5 (2.4) | 9 (2.4) |
| Mean ± SD | 67.9 ± 12.0 | 65.4 ± 11.4 | 66.5 ± 11.7 |
| Median (25–75) | 70.5 (60.1–76.9) | 66.0 (57.9–73.7) | 67.7 (58.8–75.2) |
| Range (min.–max.) | 25.3–90.2 | 25.8–90.1 | 25.3–90.2 |
| Native country Spain | 155 (91.7) | 182 (88.8) | 337 (90.1) |
| Site of onset disease | | | |
| Bulbar | 82 (48.5) | 55 (26.8) | 137 (36.6) |
| Spinal | 70 (41.4) | 118 (57.6) | 188 (50.3) |
| Bulbar and spinal | 6 (3.6) | 9 (4.4) | 15 (4.0) |
| Respiratory | 0 (0.0) | 3 (1.5) | 3 (0.8) |
| Unknown | 11 (6.5) | 20 (9.8) | 31 (8.3) |
| Family history of ALS | | | |
| Maternal | 4 (2.4) | 6 (2.9) | 10 (2.7) |
| Paternal | 2 (1.2) | 1 (0.5) | 3 (0.8) |
| Other | 9 (5.3) | 6 (2.9) | 15 (4.0) |
| Unknown | 44 (26.0) | 56 (27.3) | 100 (26.7) |
| No family history | 110 (65.1) | 136 (66.3) | 246 (65.8) |
| Genetic mutation | | | |
| Negative | 33 (19.5) | 52 (25.4) | 85 (22.7) |
| *SOD1* NM_000454.5(SOD1):c*G > C | 0 (0.0) | 1 (0.5) | 1 (0.3) |
| *C9orf72* NM_018325.5(C9orf72):>60 GGGGCC repeats | 4 (2.4) | 1 (0.5) | 5 (1.3) |
| *FUS* NM_004960.4(FUS):c.4G > A; (p.Ala2Thr); NM_004960.4(FUS):c.1394-2del | 0 (0.0) | 2 (1.0) | 2 (0.5) |
| *OPTN* NM_001008212.2(OPTN):c.883-9G > A | 0 (0.0) | 1 (0.5) | 1 (0.3) |
| Unknown | 132 (78.1) | 148 (72.2) | 280 (74.9) |
| Time (years) from onset to diagnosis | | | |
| Mean ± SD | 1.0 ± 1.1 | 0.9 ± 1.0 | 0.9 ± 1.0 |
| Median (25–75) | 1.0 (0.0–1.0) | 1.0 (0.0–1.0) | 1.0 (0.0–1.0) |
| Riluzole treatment | 153 (90.5) | 187 (91.2) | 340 (90.9) |
| Last wills | 62 (36.7) | 85 (41.5) | 147 (39.3) |
| Palliative care | 89 (52.7) | 104 (50.7) | 193 (51.6) |

SD = Standard deviation; 25–75 = 25th–75th percentile.

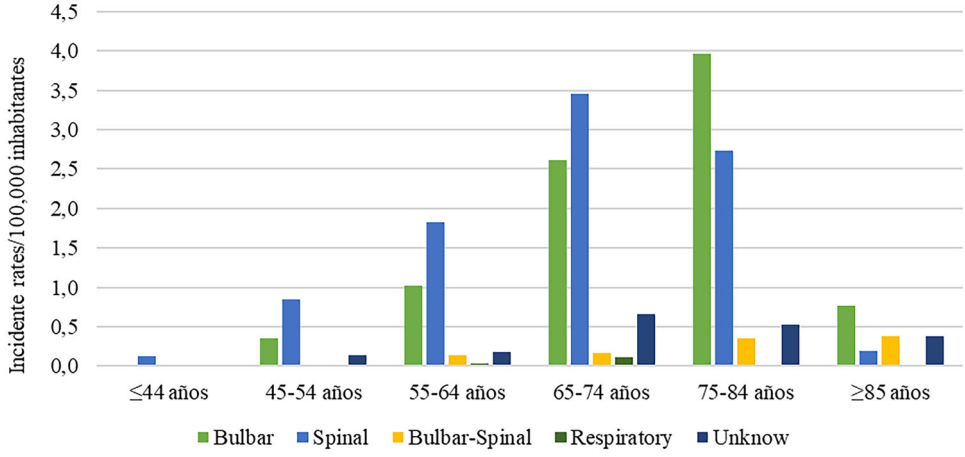


Figure 6. ALS incidence rates by age group at diagnosis and site of onset disease (2008–2021).

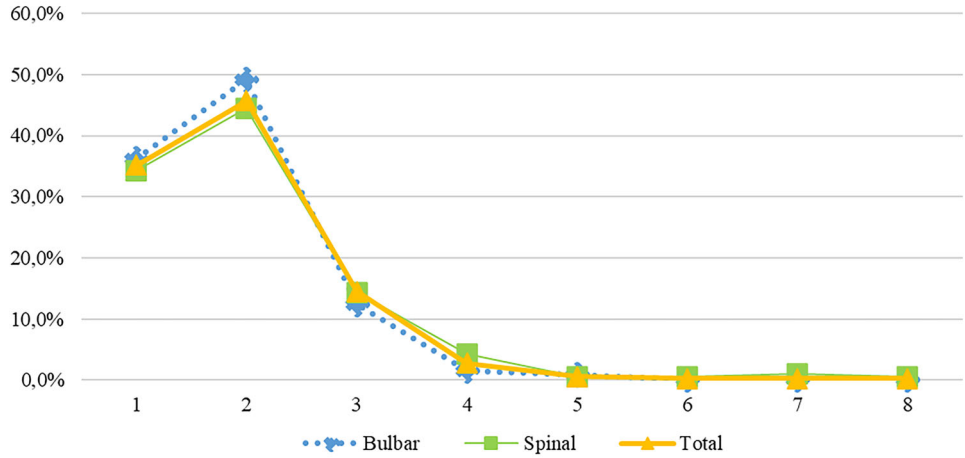


Figure 7. Time in years from symptoms onset to diagnosis of ALS according to location of onset disease and sex (%) (2008–2021).

Table 5. Initial clinical manifestations of ALS patients according to the onset of the disease (2008–2021).

| *n* (%) | Bulbar | Spinal | Bulbar and spinal | Respiratory | Unknown | Total |
|---|---|---|---|---|---|---|
| Total cases | 137 (36.6) | 188 (50.3) | 15 (4.0) | 3 (0.8) | 31 (8.3) | 374 (100.0) |
| Muscle weakness | 63 (46.0) | 178 (94.7) | 12 (80.0) | 3 (100.0) | 10 (32.3) | 266 (71.1) |
| Fasciculations | 90 (65.7) | 138 (73.4) | 10 (66.7) | 2 (66.7) | 7 (22.6) | 247 (66.0) |
| Muscle atrophy | 72 (52.6) | 141 (75.0) | 9 (60.0) | 2 (66.7) | 5 (16.1) | 229 (61.2) |
| Altered gait/clumsiness | 45 (32.8) | 135 (71.8) | 10 (66.7) | 1 (33.3) | 7 (22.6) | 198 (53.0) |
| Dysarthria | 121 (88.3) | 36 (19.1) | 11 (73.3) | 0 (0.0) | 5 (16.1) | 173 (46.3) |
| Dysphagia | 110 (80.3) | 28 (14.9) | 12 (80.0) | 1 (33.3) | 6 (19.4) | 157 (42.0) |
| Reduction of dexterity | 28 (20.4) | 101 (53.7) | 9 (60.0) | 1 (33.3) | 4 (12.9) | 143 (38.2) |
| Emotional lability | 47 (34.3) | 45 (23.9) | 4 (26.7) | 1 (33.3) | 3 (9.7) | 100 (26.7) |
| Muscle cramps | 18 (13.1) | 73 (38.8) | 2 (13.3) | 1 (33.3) | 1 (3.2) | 95 (25.4) |
| Spasticity | 26 (19.0) | 48 (25.5) | 2 (13.3) | 0 (0.0) | 4 (12.9) | 80 (21.4) |
| Dyspnea | 41 (29.9) | 24 (12.8) | 5 (33.3) | 2 (66.7) | 4 (12.9) | 76 (20.3) |

Table 6. Characteristics of death patients with ALS, stratified by sex (2009–2021).

| | Women | Men | Total |
|---|---|---|---|
| Cases (*n*, %) | 139 (46.8) | 158 (53.2) | 297 (100.0) |
| Age (years) at death ($n = 297$) | | | |
| Mean ± SD | 70.9 ± 10.9 | 68.8 ± 10.6 | 69.8 ± 10.8 |
| Median (25–75) | 73.2 (65.0–79.7) | 69.7 (62.0–76.1) | 71.4 (62.7–77.7) |
| Survival (years) from onset of symptoms ($n = 275$) | | | |
| Mean ± SD | 2.6 ± 2.0 | 2.5 ± 1.9 | 2.6 ± 2.0 |
| Median (25–75) | 2.0 (1.0–3.0) | 2.0 (1.0–3.0) | 2.0 (1.0–3.0) |

SD = Standard deviation; 25–75 = 25th–75th percentile.

without treatment with riluzole (1 vs. 3 years; $p = 0.003$) (Figure 8).

## Discussion

This is the first study to report the epidemiological and clinical characteristics of ALS patients in the RM, and one of few to analyze this information and the factors associated with ALS survival from a population-based registry in Spain.

The SIR for the study period is 1.95/100,000 person-years, and the prevalence in 2021 is 4.57/100,000 inhabitants, which is within the range estimated in international and national studies (2,4,8,12,17,20,22). It should be noted that around 10% of the patients studied were not from Spain, of which 40.5% came from northern European countries and 59.5% from countries in which a lower frequency of ALS than in Spain has been described (19,39). In addition, we report higher incidence rates in men than in women, with a ratio of 1.34, which is in line with that described by other authors (1,3,4,16,40).

There are no significant trend changes throughout the study period, and the incidence increases with age, with the maximum peak occurring in the 75–84-year age group, which coincides with other reports (7,8,40). Notably, although some studies have found a possible increase in the incidence of ALS in recent years, the results are disparate (2,7,13,14,16,41).

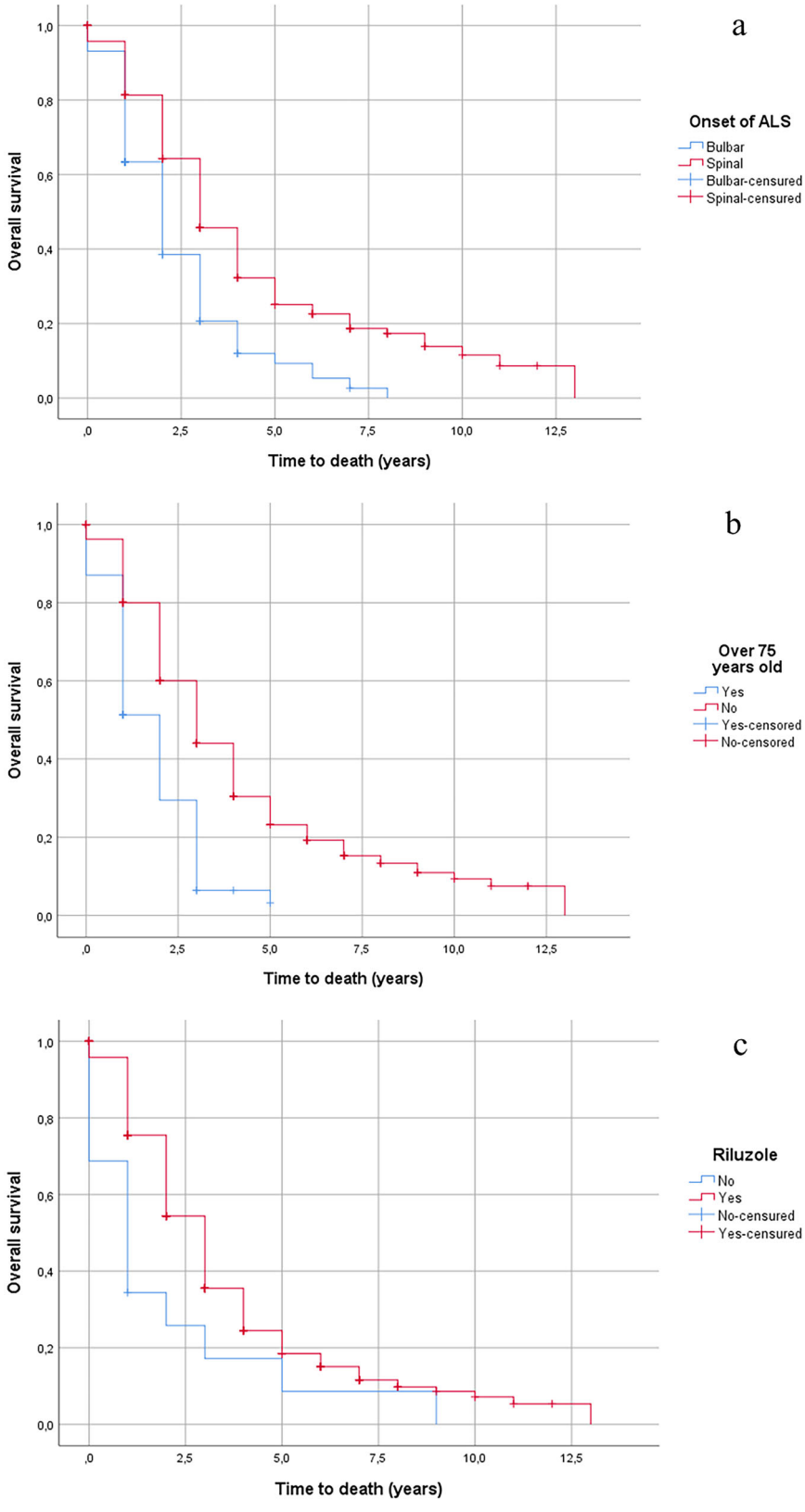


Figure 8. Kaplan–Meier survival curves of patients with ALS according to the site of disease onset (a), age at the onset of symptoms (b) and treatment with riluzole (c).

The mean age at diagnosis of our population is 66.5 years, which is consistent with the recent studies that found data between 54 and 69 years (1,3,7,18). International studies have also found a higher mean age at diagnosis in women (1,42), which is similar to what is observed in our study (67.9 vs.65.4) ($p = 0.04$).

Familial forms of ALS constituted 7.5% of the cases analyzed, which are in line with the reported percentages, which are between 6.2% and

7.6%(8,40,43–45). Furthermore, in our study we found a similar age of onset of the disease of familiar ALS compared to those cases without family history or sporadic cases ($p = 0.7$). However, other authors reported an earlier age of onset, which could be due, at least in part, to factors such as closer surveillance of the symptoms of the disease among relatives of those diagnosed (46).

On the other hand, mutations in the *C9orf72*, *FUS*, or *SOD1* genes are the most frequently involved, which is consistent with the previous reports (5,16,21,27,28,45).

The findings regarding the predominant site of onset agree with those of most previous studies, with the spinal ALS being the most common (1,8,17,40). Similarly, the bulbar onset appears more frequently in women and in older age groups, as also have described by Leighton et al. (7) and Jericó et al. (8).

The time from the onset of symptoms to diagnosis, although variable according to the series, is estimated by many authors to be between 9 and 24 months, which coincides with our finding of 0.9 years and is very close to other international and national studies in which it has been estimated at approximately 10–12 months (3,4,8,28). Similarly, patients with bulbar onset are diagnosed earlier than those with spinal onset (2,8), which were also observed in our study, although the difference was not statistically significant.

Although ALS is characterized by rapid progression and limitations, only 48.2% of the patients had an official recognition of disability and/or dependency. However, the disease duration of the patients was not the same, so it is possible that several patients were evaluated after the end of the study. Still, when only the deceased patients were analyzed, 49.5% did not have an official recognition of disability and/or dependency at the time of death.

Regarding the deceased, the average number of years from the onset of symptoms to death was 2.6 years, similar to that reported in other studies, in which an average time between 26 and 50 months was found (2,3,8,26,47). In addition, 11.8% of patients survived for more than 5 years, which is similar to other studies that estimate it at less than 13%(8). However, the percentage obtained from patients with slow forms of the disease or a survival of 10 years or more was 1.0%, which is below the 5–10% reported by other authors (26,47–49). The wide heterogeneity in the selection criteria in the different studies may explain this difference, since some of these studies included possible and suspected cases, as well as other motor neuron diseases, and this may favor a longer survival.

Finally, those factors that were related to a lower survival in our population are the bulbar onset, older age at the onset of symptoms of the disease, and the absence of treatment with riluzole. This finding reinforces what has been described by previous research indicating that patients who are older at the onset of symptoms or with bulbar onset of disease have a worse prognosis compared to those who are with younger at onset of symptoms or the spinal-onset ALS (2–4,8,18,25,27,29,47). With respect to treatment with riluzole, previous population-based studies have found an improvement in survival in the first years of the disease in patients treated with riluzole (49–51), indicating that earlier treatment after the onset of symptoms seems to be associated with longer survival (52).

We did not find differences in terms of familial cases or sex, despite a higher frequency of the bulbar onset in women (7,26,53). However, with a few exceptions, most studies have reported no effect of sex on ALS survival (8,24,25,49,54,55). We also did not find significant results by countries of origin, contrary to other sources in which differences according to ethnicity have been described (26).

Regarding the limitations of our study, although the size of the population studied was relatively small, which would be relevant for a type II error, statistically significant results were found.

In addition, although a wide set of variables were analyzed, other such as BMI, the presence of different comorbidities, cognitive disability, and/or depression, were not addressed in this study. These variables can be included in future studies to evaluate their impact on survival.

Notably, despite the missing data regarding the onset of symptoms and time to death, the number of people without this information was low, and there were no significant differences regarding the characteristics of the patients, such as sex or form of onset of symptoms of the disease among those with or without this information, so information bias is unlikely.

## Conclusion

This study is one of few to evaluate the epidemiological and clinical features and prognostic factors of ALS in Spain, with findings similar to previous population studies. This analysis of data from a population-based registry over a long study period provides up-to-date, representative, and comprehensive information on patients with ALS, allowing us to know the incidence of the disease and its evolution and survival in this population, which is useful for planning the necessary resources of those affected and their families (56,57). Despite this, to support the results obtained, it would be interesting to carry out future studies that address the aspects discussed and use the same methodology in a broader population.

## Author contributions

YGR, JCF, and MPME designed and initiated the study. JCF was responsible for collecting clinical and genetic manifestations data. JCF, MPME, LAMR, EM, COL, ASE, and PCM and JAPR coordinated the purification of the information and managed the SIER. YGR, JCF, and MPME analyzed the data and wrote the draft of the manuscript. All authors commented on and approved the final manuscript.

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## Declaration of interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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