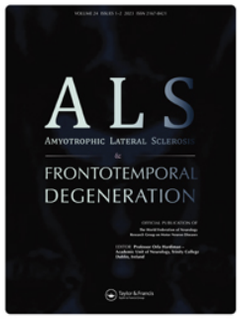

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RESEARCH ARTICLE

Clinical and demographical characteristics in a cohort of MND patients treated with riluzole. Differences between tablets and oral suspension

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Abstract

Objective: To describe the clinical and demographic characteristics of patients with MND treated with riluzole by comparing two dosage forms (oral suspension and tablets), as well as the impact on survival in patients with and without dysphagia according to the form of dosage.

Methods: Retrospective and prospective cohort of patients diagnosed with MND at the multidisciplinary functional unit of Motor Neuron Disease in our center in the period between 1 of January 2011 and 31 of December 2020 ($n = 742$). A descriptive analysis (univariate and bivariate) was carried out and survival curves were estimated.

Results: During the follow-up period, 402 males (54.18%) and 340 females (45.82%) were diagnosed with MND. Of these patients, 632 (97.23%) were being treated with 100mg riluzole: 282 (54.55%) patients took this in tablet form and 235 (45.45%) oral suspension. Riluzole in tablet form is taken more frequently by men than women, in younger age ranges, and mostly without dysphagia (78.31%). Also, it is the predominant dosage form for classic spinal ALS and respiratory phenotypes. Dosages via oral suspension are taken by patients in the older age ranges (over 64.8 years), mostly with dysphagia (53.67%) and more frequently with bulbar phenotypes such as classic bulbar ALS and PBP. Because of this, patients using oral suspension (most of them with dysphagia) had a poorer survival rate (at 90% CI) than patients using tablets (most of them without dysphagia).

Conclusions: The most appropriate dosage form should be given according to the patient's needs at each stage of the disease and, furthermore, oral suspension could improve adherence to treatment because it avoids having to change from one form (tablet) to the other (suspension) when swallowing disorders appear.

Keywords: *Amyotrophic lateral sclerosis (ALS), motor neuron disease, dysphagia, riluzole*

Introduction

Amyotrophic lateral sclerosis (ALS) is the most prevalent motor neuron disease (MND) clinical phenotype, and it is commonly used indistinctly to refer to any MND. However, within the spectrum of MND we can find "complete forms" with upper and lower motor neuron involvement (classic ALS), and "incomplete forms" with only upper or lower motor neurons involved (1). Classic ALS is the most prevalent phenotype, making up 96.7% of the cases in our region (2). The clinical heterogeneity of the ALS can be explained, among other factors, by the variability in the presence of upper and lower motor neuron signs.

The factors independently related to a longer survival (3,4) are age (< 55 years), site of onset (spinal more than bulbar) (5–7) and riluzole treatment (8–10). Also frontotemporal dementia (11) or respiratory onset (12) are factors related to a poor prognosis.

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Bulbar involvement leads to oropharyngeal dysphagia (OD), and this is described in 35–80% of MND patients (13–15). Dysphagia has a direct impact on the patient's quality of life (16,17) and leads to a state of malnutrition and dehydration due to ineffective swallowing, as well as the respiratory challenge caused by the lack of safety while swallowing (18,19). A gastrostomy tube placement must be considered (20) in up to 63.7% of ALS patients (21). Previous to this, a texture modification of solid and liquid meals should be considered to minimize the risk of choking, and different drug formulations also need to be modified (22,23) to ensure treatment adherence (24).

In Europe, riluzole is the only approved drug for modifying the course of ALS, and should be offered to reduce disease progression (20); that said, the most appropriate stage of disease progression for initiating riluzole treatment (25) and the duration of said treatment (26) have not yet been fully established (27). Riluzole is currently available as a tablet or in oral suspension, two bioequivalent forms (28). Starting treatment with riluzole oral suspension avoids dosage form changes during disease progression and ensures adherence to treatment (29), including those patients with a gastrostomy feeding tube (30).

From a Cochrane literature review (31), it was reported that a daily dose of 100 mg of riluzole is reasonably safe and probably extends median survival by about two to three months in patients with ALS. A recent review publication (2020) suggested that survival may be increased by six to nineteen months in patients treated with riluzole (32). In addition, two other medical treatments are related to extending survival: noninvasive ventilation (NIV), to facilitate breathing, and gastrostomy tube placement for optimal feeding (33).

The main objective of our work was to describe the clinical and demographic characteristics of patients with MND treated with riluzole by comparing those taking it in oral suspension to those taking tablets. In addition, we looked at the impact on survival in patients in our cohort with and without dysphagia according to how (oral suspension vs tablets) the riluzole treatment was being administered.

Material and methods

Study design

The study was conducted based on a retrospective and prospective cohort of patients diagnosed with MND at the multidisciplinary functional unit of Motor Neuron Disease (UFMN) in our center from the 1st of January 2011 through to the 31st of December 2020 ($n = 742$). All patients were diagnosed with ALS (classic limb or bulbar according to the El Escorial diagnostic criteria (34)), or with other MND phenotypes included in the revised-2015 El Escorial diagnostic criteria (35) such as primary lateral sclerosis (PLS)(36), progressive muscular atrophy (PMA), progressive bulbar palsy (PBP), or flail leg or flail arm syndromes (37). Respiratory phenotypes (38) were also included but as a separate group.

Patients were referred to our hospital from other less specialized medical centers. Informed consent to be included in the unit's database for clinical research purposes was signed on the first visit. Those patients who had agreed to participate were then included as cohorts in our study.

Variables collected

Basic clinical and demographic data were collected, along with data about treatments. Patients were assessed by a dietician and a neurophysiologist, both members of the UFMN in our center.

Statistical analysis

A comprehensive descriptive analysis was carried out, both univariate and bivariate, with mean/median and standard deviation/interquartile range (IQR) for continuous or discrete variables, and proportions for qualitative variables. The bivariate analysis was performed stratifying by the variables of interest.

Simple inference was carried out using both parametric and non-parametric tests. We used the Chi-square test for the difference of proportions and the Student's *t*-test to compare two means, and ANOVA to compare more than two means. As non-parametric tests, we chose Fisher's exact test (correction of the chi-square test when the expected frequencies were less than 5) for the difference of proportions; Mann-Whitney *U* and Wilcoxon U to compare two means (independent and paired samples, respectively); and Kruskal-Wallis to compare more than two means when the frequency distribution of the response variables is not symmetrical.

To understand disease progression, survival curves were estimated using the Kalbfleisch-Prentice method (39) (equivalent to Kaplan-Meier estimators) and compared using the log Rank test (40).

Results

Univariate descriptive analysis

During the follow-up period, 402 males (54.18%) and 340 females (45.82%) were diagnosed with MND (classified by phenotypes at disease onset—Table 1), with ages at diagnosis ranging from 25.25 years to 89.83 years (Table 1). Of the 742 patients, 501 (67.52%) died during the study

Table 1. Demographic and clinical characteristics of patient cohort.

Variable	
Gender *n* (%)	(*n* = 742)
Male	402 (54.18)
Female	340 (45.82)
Age at diagnosis (years)[a]	(*n* = 742)
Mean (*SD*)	63.81 (12.54)
Median (Q1–Q3)	65.04 (55.92–73.56)
Age at diagnosis	(*n* = 742)
[25.2,55.7)	181 (24.39)
[55.7,64.8)	183 (24.66)
[64.8,73.2)	186 (25.07)
[73.2,89.8]	192 (25.88)
Death, *n* (%)	(*n* = 742)
No	241 (32.48)
Yes	501 (67.52)
Phenotype at diagnosis, *n* (%)	(*n* = 736)
Classic limb ALS	347 (47.15)
Classic bulbar ALS	170 (23.1)
Respiratory ALS	25 (3.4)
PBP	34 (4.62)
PMA	56 (7.61)
PLS	18 (2.45)
Flail arm	15 (2.04)
Flail leg	17 (2.31)
Others	54 (7.34)
Riluzole treatment, *n* (%)	(*n* = 650)
No	18 (2.77)
Yes	632 (97.23)
First riluzole prescription dosage form, *n* (%)	(*n* = 517)
Tablets	282 (54.55)
Oral suspension	235 (45.45)
Switch in riluzole dosage form, *n* (%)	(*n* = 517)
Tablets (no changes)	212 (41.01)
Oral suspension (no changes)	212 (41.01)
From tablets to oral suspension	70 (13.54)
From oral suspension to tablets	23 (4.45)
Diagnostic delay (months)[a]	(*n* = 742)
Mean (*SD*)	15.57 (18.14)
Median (Q1–Q3)	11.26 (7.18–18.02)
ALSFRS-R score, first registration[a]	(*n* = 354)
Mean (*SD*)	32.661 (11.18)
Median (Q1–Q3)	36 (27–41)
ALSFRS-R score, last registration[a]	(*n* = 354)
Mean (*SD*)	23.941 (11.40)
Median (Q1–Q3)	24 (15–33)
ALSFRS-R score, increase score[a]	(*n* = 354)
Mean (*SD*)	−8.72 (11.48)
Median (Q1–Q3)	−7 (−16–0)
Cognitive impairment, *n* (%)	(*n* = 268)
No	84 (31.34)
Yes	184 (68.66)
Cognitive impairment assessment, *n* (%)	(*n* = 260)
Normal	91 (35)
ALSci	73 (28.08)
ALSbi	12 (4.62)
ALScibi	25 (9.62)
FTD	23 (8.85)
Alzheimer's dementia	4 (1.54)
Others	32 (12.31)
Dysphagia at diagnosis, *n* (%)	(*n* = 498)
No	292 (58.63)
Yes, liquid dysphagia	94 (18.88)
Yes, solid food dysphagia	28 (5.62)
Yes, liquid & solid dysphagia	84 (16.87)
Gastrostomy feeding tube placement, *n* (%)	(*n* = 503)
No	373 (74.16)
Yes	130 (25.84)
Noninvasive ventilation (NIV), *n* (%)	(*n* = 412)
No	245 (59.47)
Yes	167 (40.53)

(*Continued*)

Table 1. (*Continued*).

ALS: amyotrophic lateral sclerosis; PBP: progressive bulbar palsy; PMA: progressive muscular atrophy; PLS: primary lateral sclerosis. ALSci: cognitive impairment; ALSbi: behavioral impairment; ALScibi: cognitive and behavioral impairment; FTD: frontotemporal dementia. (Q1–Q3) = IQR: interquartile range. *SD*: standard deviation.

follow-up period. The mean diagnostic delay time of the studied cohort was 15.57 months (*SD* = 18.14) (median = 11.26 months, IQR = 10.84 months), ranging from 0 months to 287.64 months (23.97 years) (Table 1).

Of these patients, 632 (97.23%) were undergoing 100 mg riluzole treatment. We only have "first riluzole prescription" data for 517 (81.8%) of them, observing that 282 (54.55%) patients had tablets and 235 (45.45%) oral suspension (Table 1). If we look at the "switch in riluzole dosage form" of these 517 patients during the period from the "first riluzole prescription" until "death or completion of the study," 212 (41.01%) took riluzole tablets and 212 (41.01%) took riluzole in oral suspension without any switching over the course of the disease. Otherwise, 70 patients (13.54%) started with riluzole tablets and switched to oral suspension, and 23 (4.45%) started with riluzole oral suspension and switched to oral tablets (Table 1).

It is important to note that 130 (25.84%) of our patients had a gastrostomy tube placement. Otherwise, 167 patients (40.53%) were on noninvasive ventilation (NIV) (Table 1). No data was collected about tracheostomy. Regarding dysphagia assessment at diagnosis, 292 patients (58.63%) had no dysphagia, 94 (18.88%) had swallowing problems with liquid food, 28 (5.62%) with solid food and 84 (16.87%) had swallowing problems with liquid and solid foods (Table 1).

Regarding cognitive impairment, 184 patients (68.66%) had cognitive impairment throughout the follow-up period while 84 (31.34%) did not. Of these 268 patients, we have cognitive examination for 260 of them (35% normal, 28.08% ALSci, 4.62% ALSbi, 9.62% ALScibi, 8.85% frontotemporal dementia, 1.54% Alzheimer dementia and 12.31% others) (Table 1). The remaining eight were classified as cognitively impaired without performing cognitive assessment.

The mean score on the ALSFRS-R functional rating scale (*n* = 354) was 32.67 (*SD* = 11.18) at the first assessment and 23.94 (*SD* = 11.40) at the

last assessment, with an average decrease of 8.72 points ($SD = 11.48$) (Table 1).

Bivariate descriptive analysis

As reported above, all the results about demographic and clinical characteristics were stratified by the variables of interest:

First riluzole prescription dosage form (tablets vs oral suspension). Riluzole in tablet form is taken more frequently by men than women, at younger age ranges, and mostly without dysphagia (78.31%), with the predominant phenotypes being classic spinal ALS and respiratory form. Otherwise, oral suspension is taken by patients in the older age ranges (over 64.8 years), mostly with dysphagia (53.67%) and more frequently with bulbar phenotypes such as classic bulbar ALS and PBP (Table 2).

Switch in riluzole dosage form: from or/to tablets—oral suspension. According to the variable "switch in riluzole dosage form," we found that there were statistically significant differences (at 95% confidence interval -CI-) with respect to sex, age group, phenotype at diagnosis, gastrostomy placement, cognitive study, and age at diagnosis. The clinical status (assessed by the ALSFRS-R scale) had statistically significant differences (at 95% CI) concerning first ALSFRS-R assessment and last ALSFRS-R assessment, although these differences were not statistically significant when comparing the increase in ALSFRS-R score between the first and last assessments (Table 3).

Dysphagia at diagnosis: no dysphagia, swallowing problems with liquids, swallowing problems with solids, swallowing problems with liquids and solids. According to the variable "dysphagia at diagnosis," we found that there were statistically significant differences (at 95% CI) with respect to gender, age at diagnosis, phenotype at diagnosis, first riluzole dosage prescription, diagnosis delay, cognitive impairment, gastrostomy placement and first ALSFRS-R assessment; and at 90% CI with respect to last ALSFRS-R assessment, and difference between the last and first ALSFRS-R assessment (Table 4).

Survival analysis

Total survival curves and survival curves stratified by different variables of interest (first riluzole prescription, phenotype at diagnosis, dysphagia at diagnosis, and type of dysphagia) were estimated, as well as the main descriptive statistics.

Regarding the survival analysis, when we analyzed survival time (time from MND diagnosis to death and/or end of the study - 31 December 2020), we found that there were statistically significant differences (at 95% CI) with respect to different categories of the variables "first riluzole prescription," including a better survival probability when starting treatment with riluzole tablets (Figure 1). However, these differences disappeared when we separately analyzed each of the phenotypes at diagnosis. In this case, only a faster decrease of the slope was observed and was statistically different for those patients taking riluzole oral suspension affected by a respiratory ALS form or with a PMA phenotype (Figure 2). These results may be explained by the fact that patients with phenotypes involving greater severity and rapid disease progression, i.e., classic bulbar ALS and PBP, are more likely to be treated with oral suspension rather than tablets from the beginning (or switched rapidly to oral suspension), and, on the contrary, the slower progression phenotypes remained more frequently in the tablet-taking group. When we assessed patients with or without dysphagia separately (regardless of the initial phenotype of the disease), we found that there were also statistically significant differences between "first riluzole prescription" categories: patients with oral suspension (most of them with dysphagia) had poorer survival than patients with tablets (most of them without dysphagia), although these differences were only significant at 90% CI (Figure 3). Our hypothesis to explain these results is that riluzole in oral suspension was given more frequently to those patients who were more severely ill. In relation to this, when we analyzed the survival time for the different categories of the variable "dysphagia at diagnosis," we noticed that patients with the poorest survival rates were those who had dysphagia to liquids and solids, followed by those with dysphagia to solids, then dysphagia to liquids and, finally, those with no dysphagia. These differences were statistically significant ($p < 0.001$) (Figure 4).

Discussion and conclusions

Our study has found similar results in terms of clinical and demographic characteristics previously described in the literature (1,3,37,38). Survival of the population studied is influenced by gender, age, phenotype and the presence or absence of dysphagia (41). As described above, in our sample (and as reported in the literature) the most prevalent MND phenotype is classic ALS with spinal involvement (47.15%), followed by the bulbar phenotypes (bulbar ALS and PBP), followed by more sporadic forms such as flail arm and flail leg phenotypes. The least prevalent is the respiratory form (3.4%), as compared to the 1.1% reported by Chiò et al. (3). In terms of age and gender, without stratifying by phenotype, the mean age at diagnosis of the disease was 63.81 (±12.54) years,

Table 2. Clinical and demographic characteristics of patients stratified by first riluzole prescription dosage form.

	First riluzole dosage form prescription		
Variable	Tablets	Oral suspension	*p*-Value
Gender *n* (%)	(*n* = 282)	(*n* = 235)	
Male	170 (60.28)	110 (46.81)	0.0022
Female	112 (39.72)	125 (53.19)	
Age at diagnosis (years)[a]	(*n* = 282)	(*n* = 235)	
Mean (*SD*)	61.915 (12.60)	65.821 (11.25)	0.0002192
Median (Q1–Q3)	63.625 (53.17–72.19)	67.167 (58.33–74.33)	
Age at diagnosis	(*n* = 282)	(*n* = 235)	
[25.2,55.7)	84 (29.79)	46 (19.57)	0.0268
[55.7,64.8)	69 (24.47)	53 (22.55)	
[64.8,73.2)	66 (23.4)	69 (29.36)	
[73.2,89.8]	63 (22.34)	67 (28.51)	
Death, *n* (%)	(*n* = 282)	(*n* = 235)	
No	82 (29.08)	90 (38.3)	0.0267
Yes	200 (70.92)	145 (61.7)	
Phenotype at diagnosis, *n* (%)	(*n* = 279)	(*n* = 234)	
Classic limb ALS	156 (55.91)	92 (39.32)	0.000
Classic bulbar ALS	39 (13.98)	71 (30.34)	
Respiratory ALS	16 (5.73)	5 (2.14)	
PBP	3 (1.08)	23 (9.83)	
PMA	23 (8.24)	14 (5.98)	
PLS	5 (1.79)	6 (2.56)	
Flail arm	7 (2.51)	3 (1.28)	
Flail leg	12 (4.3)	4 (1.71)	
Others	18 (6.45)	16 (6.84)	
Riluzole treatment, *n* (%)	(*n* = 282)	(*n* = 235)	
No	0 (0)	1 (0.43)	0.273
Yes	282 (100)	234 (99.57)	
Switch in riluzole dosage form, *n* (%)	(*n* = 282)	(*n* = 235)	
Tablets (no changes)	212 (75.18)	0 (0)	0.000
Oral suspension (no changes)	0 (0)	212 (90.21)	
From tablets to oral suspension	70 (24.82)	0 (0)	
From oral suspension to tablets	0 (0)	23 (9.79)	
Diagnostic delay (months)[a]	(*n* = 282)	(*n* = 235)	
Mean (*SD*)	15.407 (20.08)	14.490 (13.87)	0.554
Median (Q1–Q3)	11.211 (7.26–11.90)	10.948 (6.87–15.75)	
ALSFRS-R score, first registration[a]	(*n* = 118)	(*n* = 164)	
Mean (*SD*)	33.559 (10.347)	33.518 (10.991)	0.975
Median (Q1–Q3)	37 (27.25–42)	36 (28–42)	
ALSFRS-R score, last registration[a]	(*n* = 118)	(*n* = 164)	
Mean (*SD*)	25.076 (11.546)	23.03 (10.744)	0.127
Median (Q1–Q3)	24 (15.25–35)	23 (15–30)	
ALSFRS-R score, increase score[a]	(*n* = 118)	(*n* = 164)	
Mean (*SD*)	−8.483 (11.044)	−10.488 (11.949)	0.153
Median (Q1–Q3)	−7 (−12.75– −1)	−9 (−19.25–0)	
Cognitive impairment, *n* (%)	(*n* = 184)	(*n* = 84)	
No	49 (38.89)	20 (23.81)	0.0227
Yes	77 (61.11)	64 (76.19)	
Cognitive impairment assessment, *n* (%)	(*n* = 125)	(*n* = 81)	
Normal	54 (43.2)	22 (27.16)	0.0932
ALSci	36 (28.8)	27 (33.33)	
ALSbi	4 (3.2)	2 (2.47)	
ALScibi	12 (9.6)	7 (8.64)	
FTD	6 (4.8)	13 (16.05)	
Alzheimer's dementia	1 (0.8)	1 (1.23)	
Others	12 (9.6)	9 (11.11)	
Dysphagia at diagnosis, *n* (%)	(*n* = 166)	(*n* = 218)	
No	130 (78.31)	101 (46.33)	0.000
Yes, liquid dysphagia	23 (13.86)	47 (21.56)	
Yes, solid food dysphagia	6 (3.61)	19 (8.72)	
Yes, liquid & solid dysphagia	7 (4.22)	51 (23.39)	
Gastrostomy feeding tube placement, *n* (%)	(*n* = 167)	(*n* = 219)	
No	131 (78.44)	150 (68.49)	0.0295
Yes	36 (21.56)	69 (31.51)	

(*Continued*)

Table 2. (*Continued*).

Variable	First riluzole dosage form prescription		*p*-Value
	Tablets	Oral suspension	
Noninvasive ventilation (NIV), *n* (%)	(*n* = 139)	(*n* = 176)	
No	71 (51.08)	101 (57.39)	0.316
Yes	68 (48.92)	75 (42.61)	

ALS: amyotrophic lateral sclerosis; PBP: progressive bulbar palsy; PMA: progressive muscular atrophy; PLS: primary lateral sclerosis. ALSci: cognitive impairment; ALSbi: behavioral impairment; ALScibi: cognitive and behavioral impairment; FTD: frontotemporal dementia. (Q1–Q3) = IQR: interquartile range. *SD:* standard deviation.

Table 3. Clinical and demographic characteristics of patients stratified by switch in riluzole dosage form.

Variable	Switch in dosage form				*p* Value
	Tablets (no changes)	Oral suspension (no changes)	From tablets to oral suspension	From oral suspension to tablets	
Riluzole treatment, *n* (%)	(*n* = 212)	(*n* = 212)	(*n* = 70)	(*n* = 23)	
Gender *n* (%)	(*n* = 212)	(*n* = 212)	(*n* = 70)	(*n* = 23)	
Male	138 (65.09)	97 (45.75)	32 (45.71)	13 (56.52)	0.000381
Female	74 (34.91)	115 (54.25)	38 (54.29)	10 (43.48)	
Age at diagnosis (years)[a]	(*n* = 212)	(*n* = 212)	(*n* = 70)	(*n* = 23)	
Mean (*SD*)	61.74 (13.06)	65.90 (11.19)	62.44 (11.16)	65.109 (11.93)	0.004883
Median (Q1–Q3)	62.67 (52.13–72.58)	67.13 (58.48–74.33)	64.25 (56.69–70.23)	67.25 (54.42–73.33)	
Age at diagnosis	(*n* = 212)	(*n* = 212)	(*n* = 70)	(*n* = 23)	
[25.2,55.7)	67 (31.6)	39 (18.4)	17 (24.29)	7 (30.43)	0.0249
[55.7,64.8)	50 (23.58)	51 (24.06)	19 (27.14)	2 (8.7)	
[64.8,73.2)	43 (20.28)	61 (28.77)	23 (32.86)	8 (34.78)	
[73.2,89.8]	52 (24.53)	61 (28.77)	11 (15.71)	6 (26.09)	
Death, *n* (%)	(*n* = 212)	(*n* = 212)	(*n* = 70)	(*n* = 23)	
No	74 (34.91)	79 (37.26)	8 (11.43)	11 (47.83)	0.000271
Yes	138 (65.09)	133 (62.74)	62 (88.57)	12 (52.17)	
Phenotype at diagnosis, *n* (%)	(*n* = 209)	(*n* = 211)	(*n* = 70)	(*n* = 23)	
Classic limb ALS	116 (55.5)	83 (39.34)	40 (57.14)	9 (39.13)	0.000
Classic bulbar ALS	27 (12.92)	66 (31.28)	12 (17.14)	5 (21.74)	
Respiratory ALS	9 (4.31)	5 (2.37)	7 (10)	0 (0)	
PBP	0 (0)	21 (9.95)	3 (4.29)	2 (8.7)	
PMA	21 (10.05)	12 (5.69)	2 (2.86)	2 (8.7)	
PLS	5 (2.39)	5 (2.37)	0 (0)	1 (4.35)	
Flail arm	5 (2.39)	3 (1.42)	2 (2.86)	0 (0)	
Flail leg	11 (5.26)	2 (0.95)	1 (1.43)	2 (8.7)	
Others	15 (7.18)	14 (6.64)	3 (4.29)	2 (8.7)	
No	0 (0)	1 (0.47)	0 (0)	0 (0)	0.696
Yes	212 (100)	211 (99.53)	70 (100)	23 (100)	
First riluzole prescription dosage form, *n* (%)	(*n* = 212)	(*n* = 212)	(*n* = 70)	(*n* = 23)	
Tablets	212 (100)	0 (0)	70 (100)	0 (0)	0.000
Oral suspension	0 (0)	212 (100)	0 (0)	23 (100)	
Diagnostic delay (months)[a]	(*n* = 212)	(*n* = 212)	(*n* = 70)	(*n* = 23)	
Mean (*SD*)	16.147 (22.386)	13.893 (12.015)	13.164 (10.095)	19.995 (25.049)	0.222
Median (Q1–Q3)	11.688 (7.96–18.22)	10.833 (6.76–15.05)	10.964 (6.97–15.76)	12.86 (10.06–18.95)	
ALSFRS-R score, first registration[a]	(*n* = 97)	(*n* = 146)	(*n* = 21)	(*n* = 18)	
Mean (*SD*)	34.814 (9.659)	33.308 (10.958)	27.762 (11.64)	35.222 (11.43)	0.0451
Median (Q1–Q3)	38 (28–42)	35 (28–42)	29 (21–37)	38.5 (32.75–42.5)	
ALSFRS-R score, last registration[a]	(*n* = 97)	(*n* = 146)	(*n* = 21)	(*n* = 18)	
Mean (*SD*)	26.99 (11.02)	22.973 (10.537)	16.238 (9.853)	23.5 (12.632)	0.000275
Median (Q1–Q3)	26 (19–37)	23 (15–30)	14 (10–22)	21.5 (15–34.5)	
ALSFRS-R score, increase score[a]	(*n* = 97)	(*n* = 146)	(*n* = 21)	(*n* = 18)	
Mean (*SD*)	−7.825 (11.01)	−10.336 (12.162)	−11.524 (10.948)	−11.722 (10.272)	0.259

(*Continued*)

Table 3. (*Continued*).

Variable	Switch in dosage form				
Riluzole treatment, *n* (%)	Tablets (no changes) (*n* = 212)	Oral suspension (no changes) (*n* = 212)	From tablets to oral suspension (*n* = 70)	From oral suspension to tablets (*n* = 23)	*p* Value
Median (Q1–Q3)	−5 (−12–0)	−9 (−19–0)	−8 (−15– −4)	−7.5 (−19.75– −4.25)	
Cognitive impairment, *n* (%)	(*n* = 90)	(*n* = 77)	(*n* = 36)	(*n* = 7)	
No	34 (37.78)	18 (23.38)	15 (41.67)	2 (28.57)	0.142
Yes	56 (62.22)	59 (76.62)	21 (58.33)	5 (71.43)	
Cognitive impairment assessment, *n* (%)	(*n* = 89)	(*n* = 74)	(*n* = 36)	(*n* = 7)	
Normal	38 (42.7)	20 (27.03)	16 (44.44)	2 (28.57)	0.0282
ALSci	23 (25.84)	24 (32.43)	13 (36.11)	3 (42.86)	
ALSbi	2 (2.25)	2 (2.7)	2 (5.56)	0 (0)	
ALScibi	9 (10.11)	7 (9.46)	3 (8.33)	0 (0)	
FTD	5 (5.62)	12 (16.22)	1 (2.78)	1 (14.29)	
Alzheimer's dementia	1 (1.12)	0 (0)	0 (0)	1 (14.29)	
Others	11 (12.36)	9 (12.16)	1 (2.78)	0 (0)	
Dysphagia at diagnosis, *n* (%)	(*n* = 130)	(*n* = 197)	(*n* = 36)	(*n* = 21)	
No	108 (83.08)	85 (43.15)	22 (61.11)	16 (76.19)	0.000
Yes, liquid dysphagia	10 (7.69)	45 (22.84)	13 (36.11)	2 (9.52)	
Yes, solid food dysphagia	6 (4.62)	18 (9.14)	0 (0)	1 (4.76)	
Yes, liquid & solid dysphagia	6 (4.62)	49 (24.87)	1 (2.78)	2 (9.52)	
Gastrostomy feeding tube placement, *n* (%)	(*n* = 131)	(*n* = 198)	(*n* = 36)	(*n* = 21)	
No	117 (89.31)	131 (66.16)	14 (38.89)	19 (90.48)	0.000
Yes	14 (10.69)	67 (33.84)	22 (61.11)	2 (9.52)	
Noninvasive ventilation (NIV), *n* (%)	(*n* = 111)	(*n* = 156)	(*n* = 28)	(*n* = 20)	
No	59 (53.15)	87 (55.77)	12 (42.86)	14 (70)	0.302
Yes	52 (46.85)	69 (44.23)	16 (57.14)	6 (30)	

ALS: amyotrophic lateral sclerosis; PBP: progressive bulbar palsy; PMA: progressive muscular atrophy; PLS: primary lateral sclerosis. ALSci: cognitive impairment; ALSbi: behavioral impairment; ALScibi: cognitive and behavioral impairment; FTD: frontotemporal dementia. (Q1–Q3) = IQR: interquartile range. *SD:* standard deviation.

with a slightly higher prevalence in men than in women (54.18 vs 45.82), thus resulting in a lower survival rate in older men. Otherwise, the presence or absence of dysphagia was a clinically relevant factor concerning survival; people with dysphagia died earlier. According to a recent review published in 2019 (42), another relevant factor in relation to survival is cognitive impairment. It is important to note that the time of the diagnosis of cognitive impairment was not described by the authors. Thus, there may be patients at different stages of disease evolution at the time of their cognitive impairment diagnosis, with different clinical conditions not being comparable between them. In our study, the time of assessment of cognitive impairment was not recorded either, but we have recorded that 65% of patients with a cognitive-behavioral assessment had some type of cognitive impairment (Table 1).

The clinical management or treatment approaches described in the literature (20,43) for extending survival are widely implemented in our center. In Spain, our center is one of the pioneers with regards to early placement of NIV (12), and which is why 40.53% of the patients had NIV. In the literature, a range from 30% (44) to 56.99% NIV rate (45) is described. As for feeding tube placement, in our population 25.84% of patients had a gastrostomy placement, while the literature reports around 30% (46) to 63.7% (21). Treatment with riluzole is extensive (97.23%) and the main reason for discontinuing treatment is the occurrence of one or more of the side effects listed in the summary of product characteristics (SPC). Although not collected in our study, in our clinical practice we have observed a similar proportion of side effects as described in the literature by Introna et al. (24).

Table 4. Clinical and demographic characteristics of patients stratified by dysphagia.

Variable	No dysphagia	Liquid dysphagia	Solid food dysphagia	Liquid and solid dysphagia	*p* Value
Gender *n* (%)	(*n* = 292)	(*n* = 94)	(*n* = 28)	(*n* = 84)	
Male	176 (60.27)	37 (39.36)	12 (42.86)	31 (36.9)	0.000
Female	116 (39.73)	57 (60.64)	16 (57.14)	53 (63.1)	
Age at diagnosis (years)[a]	(*n* = 292)	(*n* = 94)	(*n* = 28)	(*n* = 84)	
Mean (*SD*)	61.203 (12.161)	63.109 (11.18)	64.756 (14.41)	71.108 (10.98)	0.000
Median (Q1–Q3)	63.208 (52.23–70.92)	62.25 (56.15–71.81)	69.833 (54.19–73.83)	73.208 (62.90–79.54)	
Age at diagnosis	(*n* = 292)	(*n* = 94)	(*n* = 28)	(*n* = 84)	
[25.2,55.7)	88 (30.14)	21 (22.34)	8 (28.57)	9 (10.71)	0.000
[55.7,64.8)	75 (25.68)	33 (35.11)	2 (7.14)	14 (16.67)	
[64.8,73.2)	76 (26.03)	20 (21.28)	10 (35.71)	19 (22.62)	
[73.2,89.8]	53 (18.15)	20 (21.28)	8 (28.57)	42 (50)	
Death, *n* (%)	(*n* = 292)	(*n* = 94)	(*n* = 28)	(*n* = 84)	
No	149 (51.03)	36 (38.3)	9 (32.14)	26 (30.95)	0.00232
Yes	143 (48.97)	58 (61.7)	19 (67.86)	58 (69.05)	
Phenotype at diagnosis, *n* (%)	(*n* = 289)	(*n* = 94)	(*n* = 27)	(*n* = 83)	
Classic limb ALS	147 (50.87)	30 (31.91)	9 (33.33)	13 (15.66)	0.000
Classic bulbar ALS	18 (6.23)	39 (41.49)	15 (55.56)	48 (57.83)	
Respiratory ALS	10 (3.46)	2 (2.13)	0 (0)	2 (2.41)	
PBP	6 (2.08)	10 (10.64)	1 (3.7)	13 (15.66)	
PMA	41 (14.19)	1 (1.06)	1 (3.7)	1 (1.2)	
PLS	12 (4.15)	4 (4.26)	0 (0)	0 (0)	
Flail arm	6 (2.08)	1 (1.06)	0 (0)	0 (0)	
Flail leg	17 (5.88)	0 (0)	0 (0)	0 (0)	
Others	32 (11.07)	7 (7.45)	1 (3.7)	6 (7.23)	
Riluzole treatment, *n* (%)	(*n* = 271)	(*n* = 83)	(*n* = 28)	(*n* = 72)	
No	4 (1.48)	1 (1.2)	1 (3.57)	4 (5.56)	0.168
Yes	267 (98.52)	82 (98.8)	27 (96.43)	68 (94.44)	
First riluzole prescription dosage form, *n* (%)	(*n* = 231)	(*n* = 70)	(*n* = 25)	(*n* = 58)	
Tablets	130 (56.28)	23 (32.86)	6 (24)	7 (12.07)	0.000
Oral suspension	101 (43.72)	47 (67.14)	19 (76)	51 (87.93)	
Switch in riluzole dosage form, *n* (%)	(*n* = 231)	(*n* = 70)	(*n* = 25)	(*n* = 58)	
Tablets (no changes)	108 (46.75)	10 (14.29)	6 (24)	6 (10.34)	0.000
Oral suspension (no changes)	85 (36.8)	45 (64.29)	18 (72)	49 (84.48)	
From tablets to oral suspension	22 (9.52)	13 (18.57)	0 (0)	1 (1.72)	
From oral suspension to tablets	16 (6.93)	2 (2.86)	1 (4)	2 (3.45)	
Diagnostic delay (months)[a]	(*n* = 292)	(*n* = 94)	(*n* = 28)	(*n* = 84)	
Mean (*SD*)	17.752 (18.65)	13.090 (11.86)	25.262 (54.23)	14.380 (13.34)	0.02768
Median (Q1–Q3)	12.74 (8.58–21.41)	10.95 (6.98–15.61)	8.83 (6.03–15.54)	10.87 (7.46–17.65)	
ALSFRS-R score, first registration[a]	(*n* = 220)	(*n* = 65)	(*n* = 15)	(*n* = 51)	
Mean (*SD*)	33.841 (11.25)	31.538 (9.85)	32.333 (9.41)	28.882 (12.33)	0.0297
Median (Q1–Q3)	38 (29–42)	32 (25–40)	33 (25.5–39.5)	29 (22.5–38)	
ALSFRS-R score, last registration[a]	(*n* = 220)	(*n* = 65)	(*n* = 15)	(*n* = 51)	
Mean (*SD*)	24.627 (11.514)	21.062 (10.674)	26.933 (10.464)	23.02 (11.399)	0.0964
Median (Q1–Q3)	24 (16–34)	21 (12–30)	25 (18–32)	21 (15–31.5)	
ALSFRS-R score, increase score[a]	(*n* = 220)	(*n* = 65)	(*n* = 15)	(*n* = 51)	
Mean (*SD*)	−9.214 (11.46)	−10.477 (9.994)	−5.4 (8.096)	−5.863 (13.675)	0.097

(*Continued*)

Table 4. (*Continued*).

Variable	No dysphagia	Liquid dysphagia	Solid food dysphagia	Liquid and solid dysphagia	*p* Value
Median (Q1–Q3)	−7 (−17–0)	−8 (−18–0)	0 (−14–0)	−6 (−14.5–0)	
Cognitive impairment, *n* (%)	(*n* = 97)	(*n* = 33)	(*n* = 11)	(*n* = 26)	
No	34 (35.05)	11 (33.33)	0 (0)	3 (11.54)	0.0153
Yes	63 (64.95)	22 (66.67)	11 (100)	23 (88.46)	
Cognitive impairment assessment, *n* (%)	(*n* = 93)	(*n* = 33)	(*n* = 11)	(*n* = 23)	
Normal	35 (37.63)	13 (39.39)	1 (9.09)	3 (13.04)	0.323
ALSci	28 (30.11)	12 (36.36)	4 (36.36)	9 (39.13)	
ALSbi	2 (2.15)	1 (3.03)	0 (0)	1 (4.35)	
ALScibi	8 (8.6)	1 (3.03)	1 (9.09)	3 (13.04)	
FTD	5 (5.38)	4 (12.12)	3 (27.27)	5 (21.74)	
Alzheimer's dementia	2 (2.15)	0 (0)	0 (0)	0 (0)	
Others	13 (13.98)	2 (6.06)	2 (18.18)	2 (8.7)	
Gastrostomy feeding tube placement, *n* (%)	(*n* = 292)	(*n* = 93)	(*n* = 28)	(*n* = 84)	
No	252 (86.3)	52 (55.91)	18 (64.29)	45 (53.57)	0.000
Yes	40 (13.7)	41 (44.09)	10 (35.71)	39 (46.43)	
Noninvasive ventilation (NIV), *n* (%)	(*n* = 251)	(*n* = 77)	(*n* = 18)	(*n* = 58)	
No	142 (56.57)	48 (62.34)	11 (61.11)	38 (65.52)	0.569
Yes	109 (43.43)	29 (37.66)	7 (38.89)	20 (34.48)	

ALS: amyotrophic lateral sclerosis; PBP: progressive bulbar palsy; PMA: progressive muscular atrophy; PLS: primary lateral sclerosis. ALSci: cognitive impairment; ALSbi: behavioral impairment; ALScibi: cognitive and behavioral impairment; FTD: frontotemporal dementia. (Q1–Q3) = IQR: interquartile range. *SD*: standard deviation.

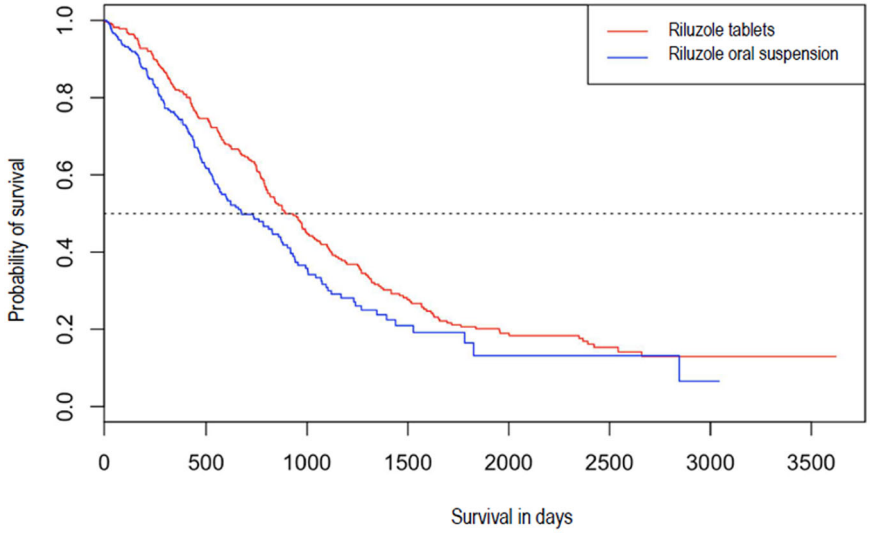

Figure 1. Kaplan–Meier survival analysis of patients treated with different riluzole dosage forms.

To the best of our knowledge, there is no published literature about demographic differences between patients treated with riluzole in tablet form or oral suspension. From our sample (*n* = 650 patients), 54.55% were treated with riluzole tablets and the remaining 45.45% with oral suspension. Disease progression, dysphagia and/or the need for gastrostomy tube placement are all situations that justify changing the dosage form of riluzole from tablets to oral suspension. Looking at these changes, we found that 13.54% of those who started with riluzole tablets had to switch to an oral suspension formulation at some point during our registration. Additionally, it is important to note that only 4.45% of the sample switched from oral suspension to tablets.

The reasons for medication switches were not collected for the study, but some possible causes

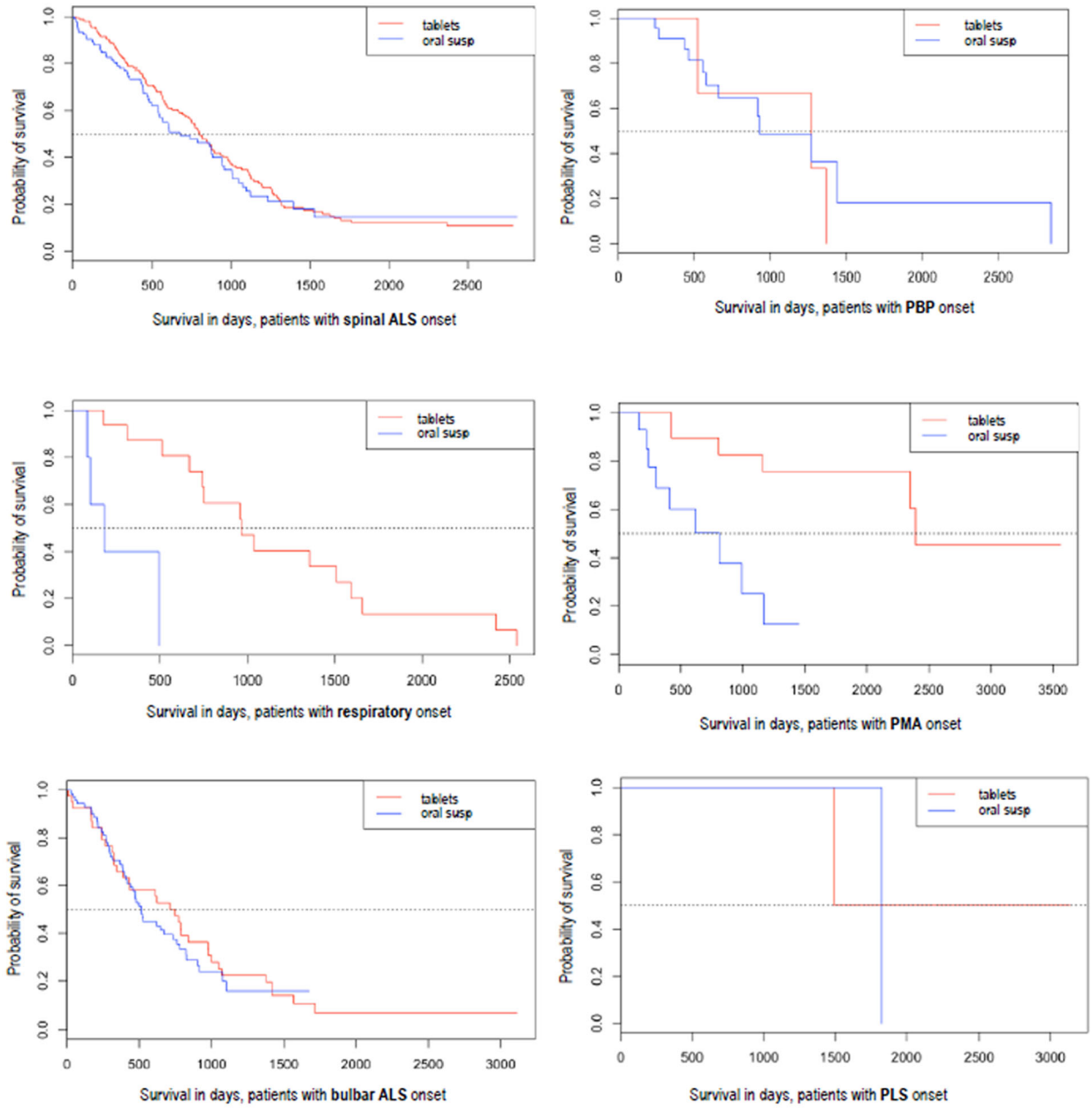

Figure 2. Kaplan–Meier survival analysis of patients treated with different riluzole dosage form regimes (tablets vs oral suspension) according to phenotype at diagnosis.

could be: (1) patients who do not have bulbar involvement but have loss of strength in the upper extremities which makes it difficult to handle the oral suspension bottle as the safety cap could be difficult for patients to manipulate, in cases with no dysphagia, a switch to tablets would be possible; (2) patients with no dysphagia but reporting some anesthetic effect when taking the oral suspension, as described in the technical data sheet. In our study population, there were minimal cases of dysphagia patients requesting a switch from suspension to tablets. This might be explained by the specific situations of those who have a serious aversion to liquid drug formulations. In their study, Belissa et al. (47) noted that oral palatability remains crucial in older populations, especially for women.

If we look at survival based on the form in which riluzole was taken, we notice that, apparently, patients treated with oral suspension had a poorer prognosis. This lower survival related to the oral suspension group can probably be explained by the fact that these patients were more severely ill and/or corresponded mainly to the classic bulbar ALS and PBP phenotypes, than those taking tablets and, therefore, cannot be attributed to the administration of oral suspension. Riluzole in oral suspension may be given to patients who have swallowing disorders, even if they are incipient, or as a precaution to avoid changes in medication

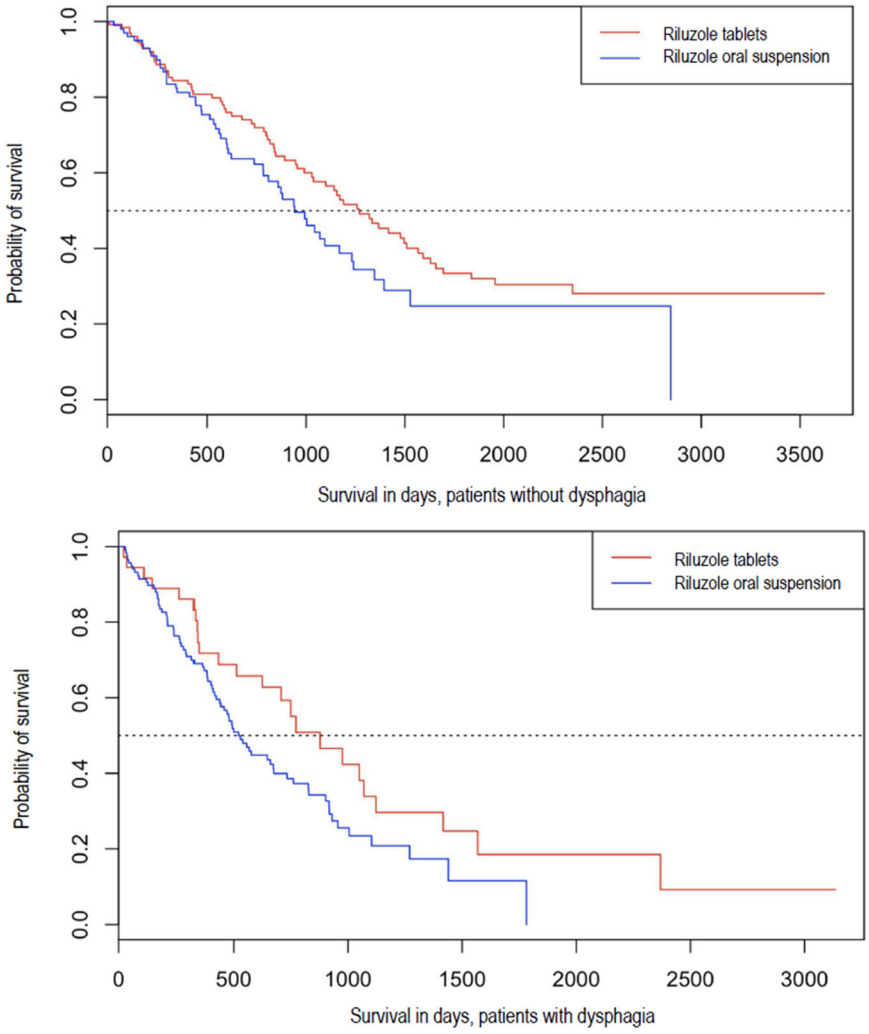

Figure 3. Kaplan–Meier survival analysis of patients treated with different riluzole dosage forms according to dysphagia.

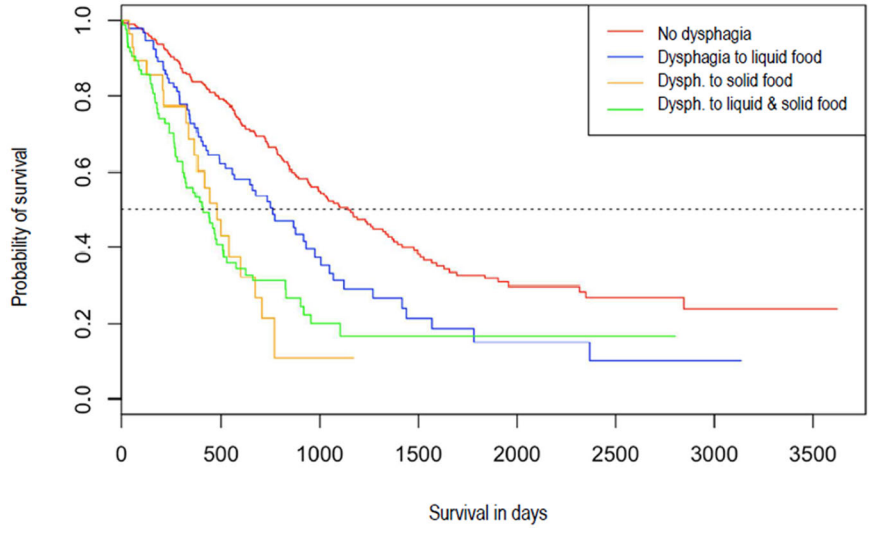

Figure 4. Kaplan–Meier survival analysis according to type of dysphagia.

forms over the course of the disease. Manipulation of a solid formulation in patients with dysphagia has been reported to result in loss of adherence to treatment, along with an increased risk to safety and efficacy due to changes in the pharmacokinetic and pharmacodynamic properties of the drug (28). A higher acceptability in the dysphagic population (in comparison with the non-dysphagic) for pharmaceutical forms easier to swallow than tablets and capsules has been reported (48).

Riluzole has been available in tablet form since FDA approval in 1995, and in oral suspension since 2014 in Spain, when, in our center we started to prescribe it for ALS patients with dysphagia. Later, as there was no change in economic terms (for further information see Annex 1), we also decided to prescribe oral suspension as the first choice to minimize treatment changes. A recently published European ALS expert opinion consensus document concluded that, *starting therapy with riluzole oral suspension rather than tablets could ensure better compliance, minimizing adherence losses and the psychological burden for patients and caregivers due to medication switches* (29).

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Declaration of interest

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