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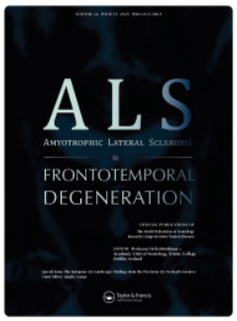

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RESEARCH ARTICLE

Real-world prognostic role of riluzole use in ALS: a multi-center study from PRECISION-ALS

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Abstract

Background: Amyotrophic Lateral Sclerosis (ALS) remains an incurable disease, with limited treatment options, and riluzole is the most widely available drug. We evaluated survival in a large cohort of patients with ALS, comparing those treated with riluzole to those who were not. *Methods*: Using data from the PRECISION-ALS database, we retrospectively analyzed patients with ALS who were treated with 100 mg of riluzole daily at the time of diagnosis. ALSFRS-R slope from onset to diagnosis (ΔFRS) was calculated. Based on the ΔFRS distribution, we defined fast progressors as patients having a ΔFRS $>$ 1.17, intermediate progressors as those with $1.17 > \Delta FRS > 0.31$ and slow progressors as those with a ΔFRS $<$ 0.31 points per month. We used Kaplan-Meier curves and Cox proportional hazards model to explore the association of riluzole use with patient survival since diagnosis. *Results*: Out of the 5842 patients with available riluzole data, 4847 (82.9%) received riluzole. The overall survival significantly differed between patients treated and not treated with riluzole (HR 0.70, 95%CI 0.69, 0.79), independently of sex, site of onset, age at onset and diagnostic delay. Patients treated with riluzole exhibited a 7 month longer median survival than those who did not receive riluzole (17.6 months, IQR 9.7, 29.9 vs 10.7 months, IQR

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4.3, 23.4; $p = 2 \times 10^{-16}$). The relationship between riluzole use and extended survival varied across ΔFRS strata, being only evident among fast progressors (HR = 0.50, 95% 0.40, 0.63). *Conclusions*: Treatment with riluzole is an independent prognostic factor in ALS. The extended survival related to riluzole use was only evident among fast-progressing patients.

Keywords: *Amyotrophic Lateral Sclerosis, riluzole, prognosis, survival, epidemiology*

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a relentless neurodegenerative disease primarily affecting motor neurons. It is characterized by the progressive inability to perform voluntary movements, ultimately resulting in respiratory failure and death, within 2 to 5 years from the onset of symptoms (1). Despite numerous clinical trials aimed at extending the survival of ALS patients, there is no effective disease modifying therapy, with the exception of those patients carrying a *SOD1* mutation (2).

Riluzole is a benzothiazole-derived compound that modulates glutamatergic neurotransmission, and alters neuronal excitability. Although there is evidence to suggest that ALS pathogenesis may relate in part to a calcium dependent excitotoxic mechanism, riluzole may also act on membrane sodium channels (3). In 1994, a randomized clinical trial showed that a dosage of 100 mg of riluzole daily extended ALS patient survival by 38% at 12 months, which corresponded to approximately 3 months (3). Subsequently, a larger clinical trial confirmed efficacy (4,5). Since then, riluzole has become the primary treatment for ALS worldwide. However, subsequent real-world experience has provided contrasting evidence on whether the effectiveness of riluzole varies during the disease course or among different subgroups of patients with ALS (6,7). Such information would be crucial for guiding treatment decisions of both patients and neurologists in clinical practice.

Here, we used an international multicenter cohort derived from some of the largest European ALS tertiary centers to compare survival between patients treated and not treated with riluzole, including analyses across different subgroups of ALS patients. As such, this paper provides the most detailed characterization of the relationship between riluzole use and survival across various patient characteristics in ALS.

Methods

Data for this study originated from the PRECISION-ALS Extant Study (8). In brief, nine European specialized ALS centers comprising the PRECISION Consortium provided data from prospective population-based, or extensive clinic-based Registers. On completion of GDPR compliant data sharing agreements, each center provided patient-level, de-identified data on demographic and disease characteristics obtained at diagnosis. All patients presenting with clinically possible, clinically probable-laboratory supported, clinically probable, or clinically definite, according to the revised El Escorial criteria (9), were eligible. Patients fulfilling the criteria for Primary Lateral Sclerosis, Progressive Muscular Atrophy or atypical ALS were excluded. Centers provided all consecutively diagnosed patients from the beginning of their registry until December 2022. Complete survival data (date of death or last follow-up) were obtained by checking the municipal population register at 3-monthly intervals. Datasets were harmonized and combined into a single database, together with an indicator variable for each cohort.

Information on the use of riluzole was collected. For the aim of this study, we categorized patients as taking riluzole if a patient was prescribed 100 mg of riluzole at the time of diagnosis. None of the patients included in this dataset received edaravone during their disease course.

Longitudinal follow-up data of the ALS Functional Rating Scale revised version (ALSFRS-R) collected during the disease course were gathered. The ALSFRS-R at diagnosis was considered as the nearest evaluation within 3 months from the time of diagnosis. The ALSFRS-R slope at diagnosis (ΔFRS) was calculated according to the following formula: (48 − ALSFRS-R at diagnosis)/months elapsing from onset to diagnosis. Patients were then categorized as fast, intermediate and slow progressors based on the 25th (0.31 points/month) and 75th (1.17 points/month) percentiles of the ΔFRS distribution from the overall PRECISION-ALS cohort (the distribution of ΔFRS values within each progression rate category is shown in Supplementary Figure 5). King's stages at diagnosis were derived using the ALSFRS-R evaluations at diagnosis (10).

All genetic testing was performed in accredited diagnostic laboratories across Europe. Data regarding the genotype of *SOD1*, *TARDBP, FUS* and *C9orf72* genes was collected for each patient.

Statistical analysis

Onset site was classified as bulbar, spinal or respiratory. Survival was defined as the earliest time from diagnosis to death, tracheostomy, last follow-up date or censoring date (i.e. the date of data transfer from each Center). Patients with an atypical survival of >10 years were excluded from the analysis.

Comparisons between means and proportions were evaluated using *t*-tests and chi-squared tests, respectively. In the case of a non-normal distribution, appropriate non-parametric tests were performed.

Survival curves were constructed using the Kaplan–Meier method and compared with the log-rank test. A proportional hazards Cox analysis was then performed to compare survival between patients treated with riluzole and those who were not, adjusting by sex (females as reference), site of onset (spinal onset as reference), age at onset (considered as a continuous variable), diagnostic delay (months from onset to diagnosis) and ΔFRS (categorized according to tertiles).

We also investigated whether the association between riluzole use and longer survival significantly varied based on some patients' demographic and clinical characteristics, and in particular across sex, onset site, *C9orf72* status, genetics status (considered as positive if any mutation in *SOD1*, *TARDBP*, *FUS* and *C9orf72* genes was detected) and ΔFRS. Consequently, various models were constructed, incorporating an interaction term between riluzole and each variable regarded as a potential effect modifier. The p-value from the interaction term was considered for statistical significance, while the riluzole Hazard Ratios (HRs) and the respective 95% confidence intervals (95%CI) across different strata of the considered variable were derived by modifying the reference category.

In order to not rely on the assumption of proportional hazards, a secondary analysis was also conducted summarizing survival as restricted mean survival time (RMST), with 95%CI. The restriction time for the overall cohort was set to 115 months, corresponding to the shorter of the two longest survival times in each group—specifically, the longest follow-up duration among untreated patients (11).

All statistical analyses were performed using R software version 4.2.2 (12). The RMST statistics was conducted using the R package survRM2.

Ethics

All procedures and methodologies were in accordance with the ethical guidelines and standards of the institutional and national ethics committees of each of the sites involved. Informed consent was obtained from all participants, ensuring their autonomy and understanding of the study's objectives. Ethical approvals were obtained from the local Institutional Review Board (IRB) at each participating site for use of the data in this study and for the central storage required to facilitate the cleaning and harmonization of the data. Personal data were transferred and stored securely to ensure that the privacy of these data was maintained, and relevant steps were taken to minimize any potential harm to participants.

Results

Based on our inclusion criteria, information regarding riluzole use was accessible from four sites (namely, ALS Centres located in Leuven, Tours, Dublin, and Turin), encompassing a total of 6688 patients. Of these 5842 individuals (87.4%) had sufficient data to perform the analyses (Supplementary Table 1). Patients with available riluzole information did not significantly differ from those for whom riluzole information was not available, with the exception of a slightly younger age at diagnosis (65.5, IQR 57.2, 72.6, vs 67.0, IQR 57.6, 74.5, $p < 0.001$; Supplementary Table 2).

Demographical and clinical characteristics of the 5842 patients considered for the analysis were similar to those reported from other registry-based studies (Table 1). Riluzole was prescribed to 4847 (82.9%) patients. Patients treated with riluzole were younger and experienced a shorter diagnostic delay compared to those who did not receive the treatment (Table 1). Notably, among patients receiving riluzole, 4142 (85.4%) died or underwent tracheostomy during the follow-up period, compared to 906 (91.1%) among those who were not treated with riluzole ($p = 0.000003$). Patients treated with riluzole exhibited a median survival of 7 months longer than patients not treated with riluzole (17.6 months, IQR 9.7, 29.9 vs 10.7 months, IQR 4.3, 23.4; $p = 2 \times 10^{-16}$). This significant difference persisted when considering patients who were alive at the time of last follow-up or censoring date (Table 1). The log-rank test confirmed the longer survival of patients treated with riluzole (Figure 1; $p < 2 \times 10^{-16}$), while the multivariable Cox analysis identified riluzole use as an independent positive prognostic factor, showing a HR of 0.71 (95%CI 0.66, 0.77, $p < 2 \times 10^{-16}$) (Supplementary Table 3). Patients were followed up for a maximum of 115.3 months among those not treated and 119.3 months among those who were treated. The RMST was 29.9 months (95%CI 29.0–30.7) for patients treated with riluzole and 23.7 months (95%CI 21.8–25.6) among those not treated (difference 6.2, 95%CI 4.1–8.3; $p < 0.0001$).

The overall survival among patients treated and not treated with riluzole did not significantly differ among males and females (the HRs were 0.69, 95%CI 0.61, 0.77 and 0.73, 95%CI 0.66, 0.81, respectively; $p = 0.38$) (Supplementary Table 3 and Figure 1; RMST results are reported in the Supplementary Table 7). However, the HR of riluzole use was significantly lower among patients with respiratory onset (HR 0.25, 95%CI 0.15, 0.42) compared to bulbar (HR 0.64, 95%CI 0.57, 0.73; $p = 0.0004$) and spinal onset patients (HR 0.78, 95%CI 0.71, 0.86; $p = 0.00002$) (Supplementary Table 3 and Figure 2). Such different association of riluzole use with survival between bulbar and spinal onset patients was statistically significant ($p = 0.02$). When considering only patients who died or underwent tracheostomy during the study period, bulbar and spinal onset patients demonstrated comparable survival with riluzole use (survival among bulbar-onset patients treated vs untreated was 15.3, IQR

Table 1. Demographical and clinical characteristics of ALS patients included in the study, overall and stratified by riluzole use.

		Riluzole use		
	Overall population ($n = 5842$)	No ($n = 995$)	Yes ($n = 4847$)	p-value
Sex, *M* (%)	3280 (56.2)	541 (54.4)	2739 (56.5)	0.227
Onset age, median (IQR)	65.5 (57.2–72.6)	68.1 (58.9–74.8)	65.0 (57.0–72.0)	**<0.001**
Missing (%)	116 (2)	36 (3.6)	80 (1.7)	
Onset site (%)				0.186
Bulbar	1993 (34.1)	364 (36.6)	1629 (33.6)	
Respiratory	118 (2.0)	18 (1.8)	100 (2.1)	
Spinal	3731 (63.9)	613 (61.6)	3118 (64.3)	
Diagnostic delay, median (IQR)	9.4 (6.0–14.8)	11.2 (6.1–18.4)	9.2 (6.0–14.2)	**<0.001**
Missing (%)	116 (2)	36 (3.6)	80 (1.7)	
C9ORF72 status, expanded (%)	347 (8.8)	39 (9.0)	308 (8.8)	0.957
Missing (%)	1918 (32.8)	563 (56.5)	1355 (27.9)	
SOD1 status, mutated (%)	64 (2.5)	8 (3.6)	56 (2.4)	0.380
Missing (%)	3304 (56.6)	775 (77.9)	2529 (52.2)	
TARDBP status, mutated (%)	37 (1.7)	0 (0.0)	37 (1.8)	0.086
Missing (%)	3616 (61.9)	781 (78.5)	2835 (58.5)	
FUS status, mutated (%)	12 (0.6)	0 (0.0)	12 (0.6)	0.504
Missing (%)	3685 (63.1)	781 (78.5)	2904 (59.9)	
Survival, median (IQR)	16.4 (8.4–28.7)	10.7 (4.3–23.4)	17.6 (9.7–29.9)	**<0.001**
Time to event, median (IQR)	17.9 (9.2–32.6)	11.9 (4.8–26.0)	19.1 (10.3–33.8)	**<0.001**

Survival refers to the time from diagnosis to death or tracheostomy (observed in 4954, 84.8%, of patients during the follow-up) while time to event refers to time from diagnosis to death, tracheostomy, last follow-up date or censoring date.
Bold refers to statistically significant results.

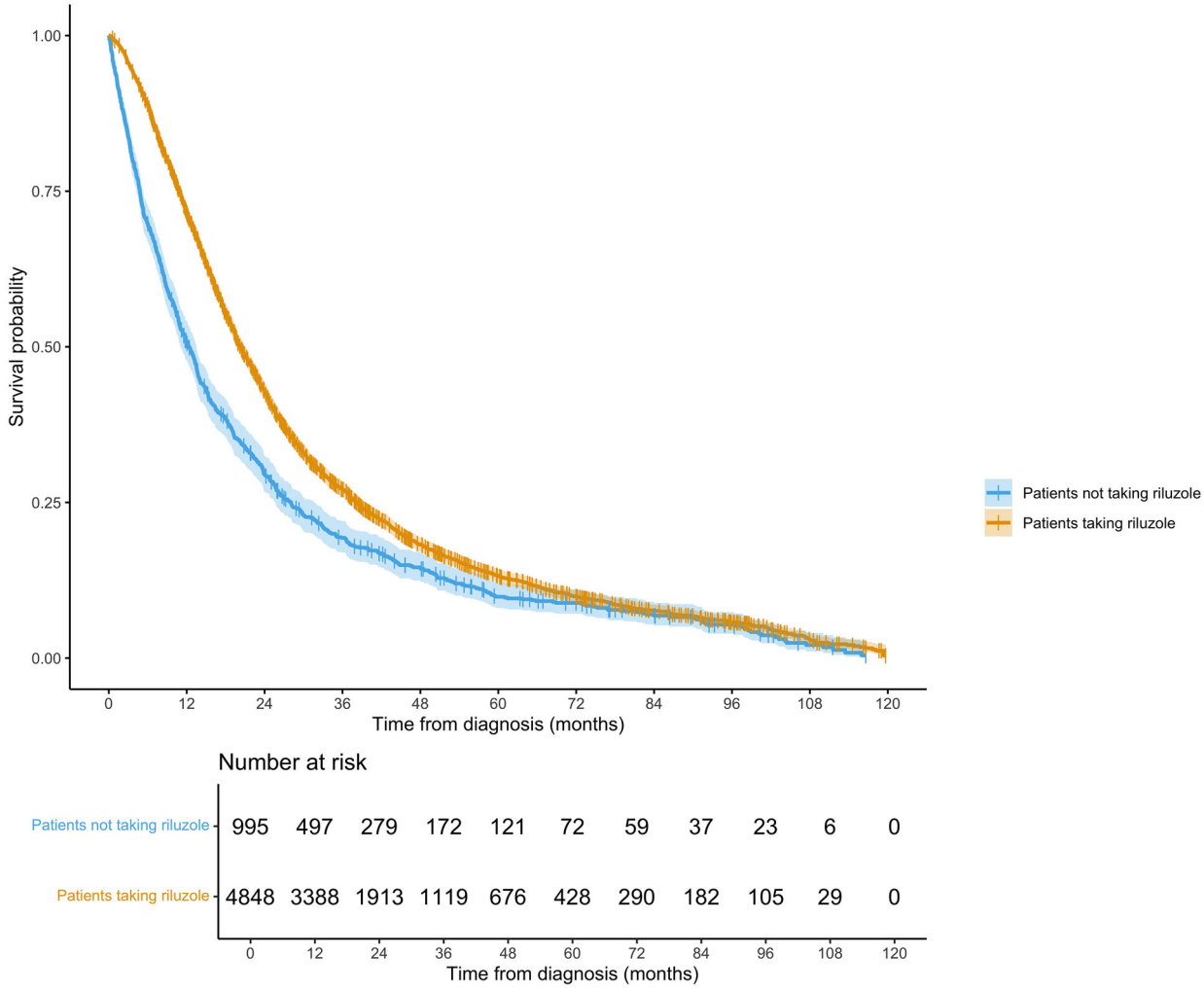

Figure 1. Kaplan–Meier curves of patients' survival from the time of diagnosis according to riluzole administration.

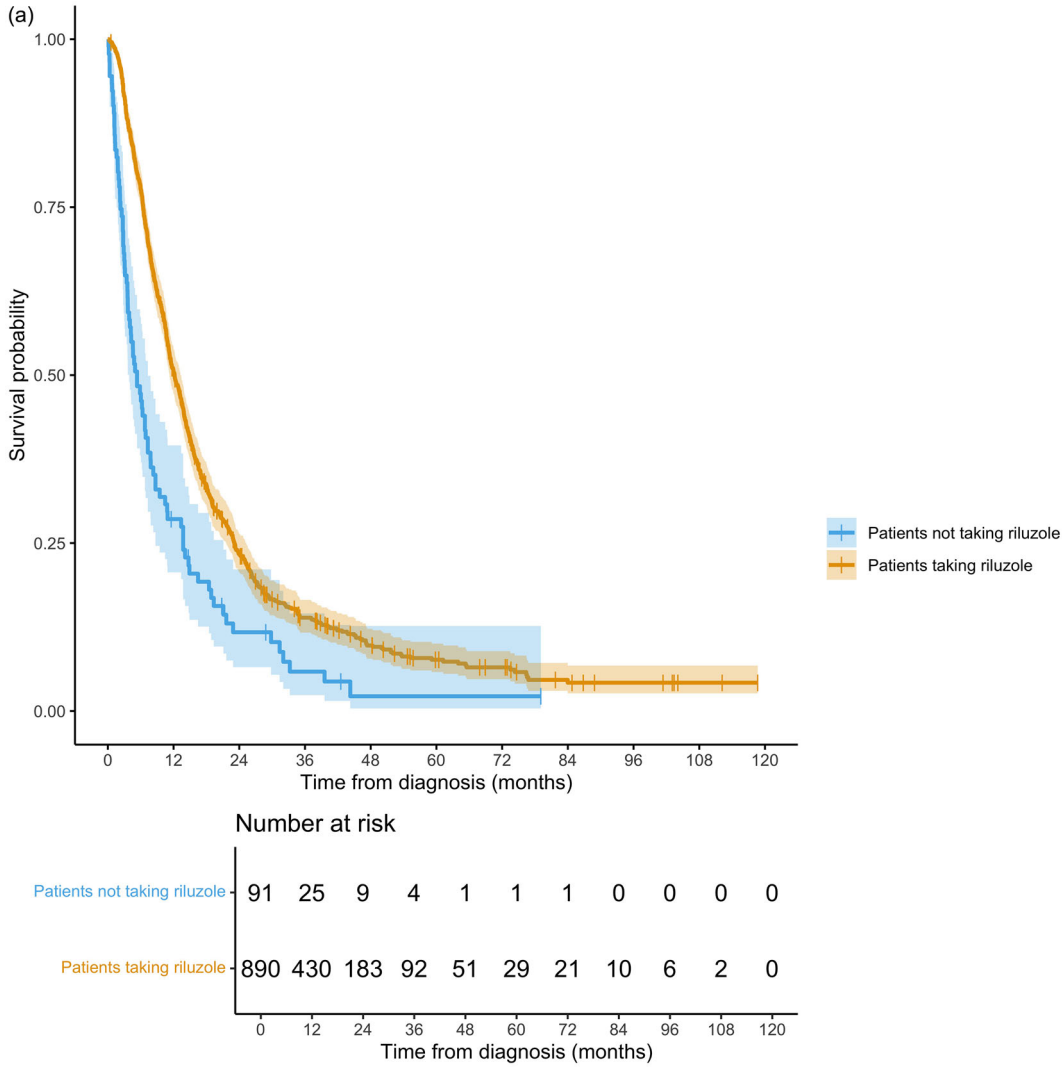

Figure 2. Kaplan–Meier curves of patients' survival from the time of diagnosis according to riluzole administration (blue = not taking riluzole, orange = taking riluzole) and stratified by rate of progression (fast (a), intermediate (b) and slow progressors (c) patients).

8.4–24.6, vs 8.8, IQR 3.9–17.4, $p < 2 \times 10^{-16}$; survival among spinal-onset patients treated vs untreated was 19.7, IQR 10.8–34.2, vs 12.9, IQR 4.8–26.7, $p < 2 \times 10^{-16}$) while patients treated displayed a significant longer survival in the respiratory onset group (survival among patients treated vs untreated was 12.1, IQR 5.7–22.1, vs 4.3, IQR 1.9–8.2, $p = 0.002$) (Supplementary Table 7).

Riluzole's prognostic role did not differ among *C9orf72* expanded versus non-expanded patients (HR = 1.03, 95%CI 0.72, 1.47 vs HR = 0.80, 95%CI 0.72, 0.90, respectively; $p = 0.21$) and among genetic-positive versus genetic-negative patients (HR = 1.11, 95%CI 0.79, 1.56 vs HR = 0.93, 95%CI 0.79, 1.10, respectively; $p = 0.85$) (Supplementary Figure 3). However, the RMST difference between treated and untreated patients was not statistically significant among *C9orf72*-positive and genetically positive patients, possibly because of the small sample size of these subgroups (Supplementary Table 7). ALSFRS-R at diagnosis was available for 3298 (56.5%) patients. Patients without ALSFRS-R data at diagnosis exhibited mild difference in their clinical characteristics. Notably, a greater proportion presented with a bulbar onset ($n = 947$, 37.2%, vs $n = 1046$, 31.7% among those with ALSFRS-R at diagnosis, $p = 0.00004$); additionally, this group displayed a higher percentage of patients who died or underwent tracheostomy during the follow-up period ($n = 2\,378$, 93.5%, vs $n = 2\,576$, 78.1%, $p < 2 \times 10^{-16}$) (Supplementary Table 4).

A Cox analysis was conducted within the group of patients where ALSFRS-R data was available, adding the ΔFRS to the set of covariates previously considered. The model confirmed the previous findings, confirming riluzole use as an independent prognostic factor whether considering ΔFRS as continuous (HR = 0.84, 95%CI 0.7, 0.96; $p = 0.055$) or categorical based on the aforementioned cut-offs (HR = 0.82, 95%CI 0.71, 0.94; $p = 0.004$). Interestingly, the prognostic role of riluzole use significantly differed across ΔFRS strata, being significant only in fast progressing patients (HR = 0.50, 95% 0.40–0.63) when compared to slow (HR =

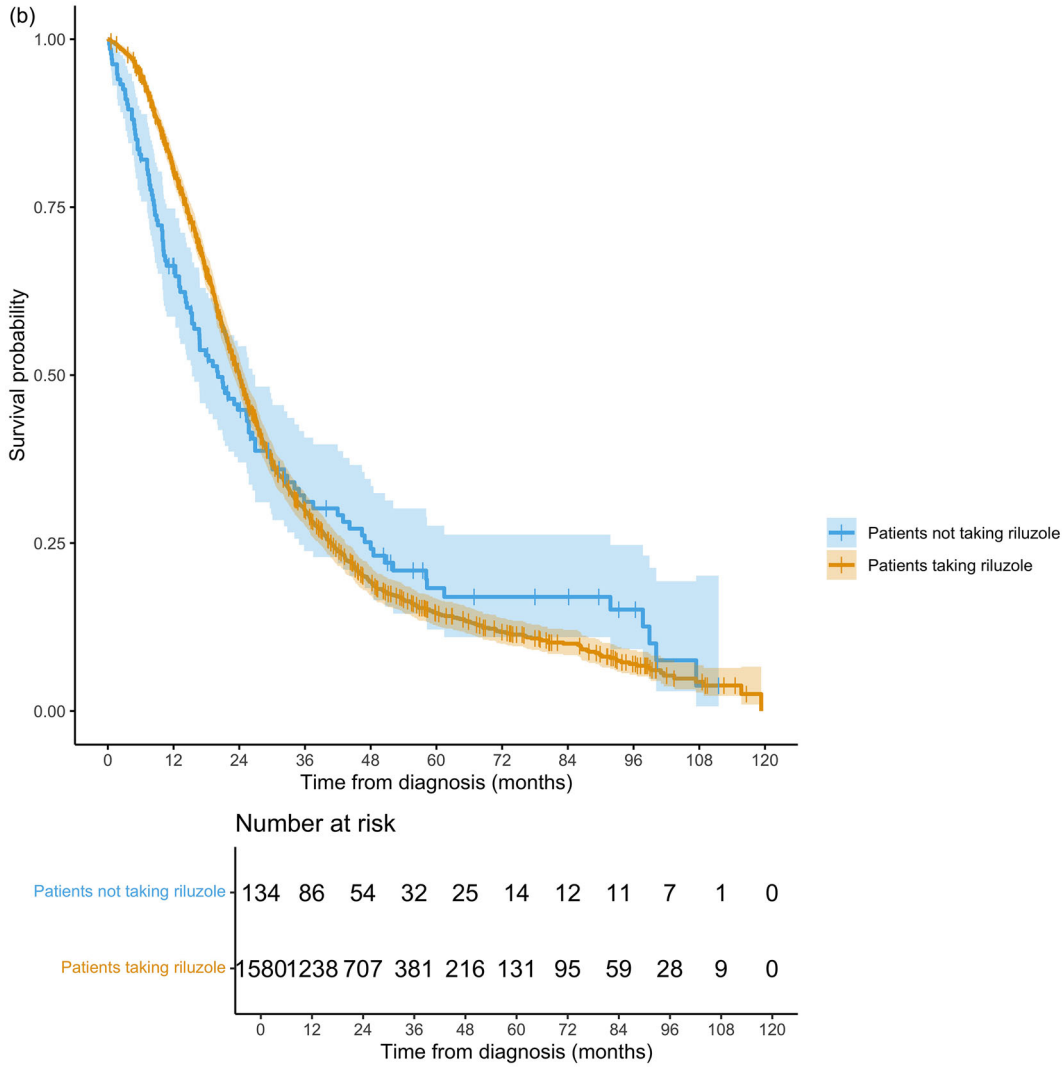

Figure 2. Continued.

1.11, 95%CI 0.79, 1.56; $p = 0.00018$) and intermediate progressors (HR 0.99, 95%CI 0.81, 1.21; $p = 0.000012$) (Figure 2 and Supplementary Table 5). Notably, the RMST analysis confirmed these findings (Supplementary Table 7).

This was also true when disease progression was defined based on the distribution of bulbar or respiratory subscores' preslopes, with the relationship between riluzole use and longer survival being evident only among bulbar fast progressors (HR = 0.61, 95%CI 0.49, 0.77) and respiratory fast progressors (HR = 0.49, 95%CI 0.38, 0.62).

To evaluate whether the varied relationship based on site of onset could be attributed to the distinct progression rates typically associated with these groups, we introduced the riluzole × site of onset interaction term into the model which included ΔFRS as a covariate. While the distinction between bulbar and spinal onset was no longer significant (HR = 0.72, 95%CI 0.56, 0.92, vs HR = 0.88, 95%CI 0.75, 1.04; $p = 0.19$), the difference between respiratory (HR = 0.40, 95%CI 0.16, 1.03) and spinal onset patients displayed borderline significance ($p = 0.057$).

Finally, no differences were found in the relationship between riluzole use and extended survival across King's stages measured at the time of diagnosis (Supplementary Table 6 and Figure 4).

Discussion

Using a large multicentre prospectively collected cohort from large European ALS Centres, our study confirmed that treatment with 100 mg of riluzole daily is an independent positive prognostic factor in ALS, with treated patients experiencing a median increased survival of approximately 7 months.

That first clinical trial of riluzole demonstrated that 100 mg of riluzole daily reduced the mortality by 38% at 12 months (and by 19% at 21 months), a finding later confirmed by a larger randomized clinical trial where the same dosage reduced mortality by 35% at 18 months (4). Notably, considering these two studies along with an additional study conducted on elderly patients with ALS (13), it was observed that the improvement in survival was of a similar magnitude to the improvement in functional decline, as measured by the Norris Scale (5). In

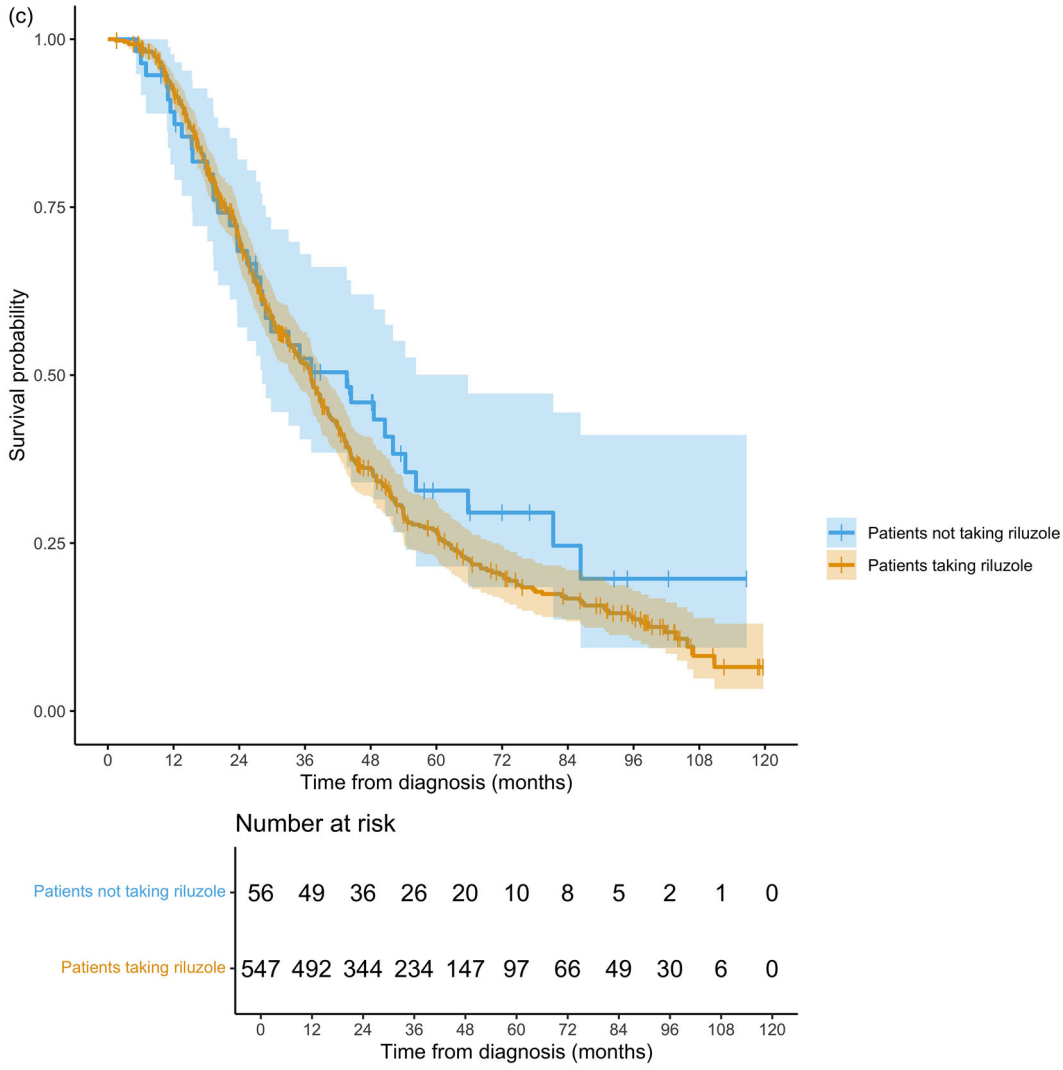

Figure 2. Continued.

1995, the FDA approved riluzole for the treatment of ALS (6). However, a lack of effect on muscle strength or respiratory function, observed in the second trial, led to questions of whether the effect could also be mediated by central mechanisms (13). It has also been suggested that riluzole may have a cardioprotective effect (14,15), mediated by reduced Na + intracellular flow, decreased oxidative stress, or induction of autophagy, although the exact mechanisms remain unclear.

The stringent inclusion and exclusion criteria commonly employed in clinical trials can raise concerns about the generalizability of results to the overall heterogeneous ALS population. Both trials terminated their follow-up at 12 and 18 months, leaving little knowledge of the long-term effects of riluzole use (16–18). Accordingly, observational studies have explored the effect of riluzole in real-world settings (6,7,16–23). These studies analyzed cohorts of variable size, ranging from 130 to 2600 individuals, and collectively confirmed the efficacy of riluzole. Notably, they showed that the relationship between riluzole use and a longer survival could be more marked than initially observed in the first randomized clinical trial, with survival advantages that span from 6 (17,20,21) to 11 months (22) for treated patients.

Our study is the first to analyse data from ALS tertiary centres and registries across Europe, showing a survival advantage of approximately 7 months on average among patients treated with riluzole, substantially longer than the 3 month advantage reported in the earlier trials.

Longer follow-up periods extending beyond those typically observed in clinical trials have revealed conflicting evidence regarding whether the efficacy of riluzole declines over the course of the disease, or at an advanced stage (24). Observational studies have shown that survival curves of patients treated versus those untreated often intersect around 18 months following the diagnosis (16,17,21). These results suggest that the efficacy of riluzole might diminish over time, being detectable only in the early stages of the disease (16). However, to determine whether this is related to disease progression, longitudinal data on clinical

stages should also be considered. Additionally, the lack of information regarding whether the decision not to administer riluzole is influenced by the rate of progression and survival further complicates the interpretation of these results. A single study utilized longitudinal data derived from the riluzole confirmatory clinical trial (4). After converting the clinical data obtained during the trial into King's stages, the authors analyzed the time spent in each stage for both treated and untreated patients. The post-hoc analysis revealed that patients treated with riluzole showed an extended duration of stage 4, suggesting an efficacy in later stages (24). Subsequently, another study, using data from the PRO-ACT database confirmed this finding (25). However, a different study found that riluzole demonstrated efficacy in both King's stages 1 and 4 (26).

In our study, patients treated with riluzole demonstrated a survival advantage throughout the entire 10-year follow-up. This difference was consistently observed across both sexes, in both *C9orf72* expanded and non-expanded patients, as well as in patients positive for mutations in any of the four major genes compared to those who were not. However, ΔFRS acted as a modifier of the relationship between riluzole use and longer survival. In particular, the riluzole prognostic role was more evident among patients classified as fast progressors at the time of diagnosis when compared to intermediate and slow progressors, with these differences being statistically significant. This result aligns with a previous study that also aimed to identify subgroups of ALS patients with varying treatment effects. Using data from the PRO-ACT database and applying partitioning algorithms (27), the authors found that forced vital capacity levels at trial entry predicted riluzole efficacy, with patients experiencing more severe impairment showing the greatest benefit (28).

However, this finding could potentially result from a statistical phenomenon, wherein the modest effect of the drug becomes evident only when applied to a more rapid disease progression. Also, the paradoxical phenomenon of better survival among untreated slow progressors may result from an atypical slow disease progression, leading physicians to refrain from initiating the treatment during the early stages of the disease. In contrast, fast progressors may not have received riluzole due to a perceived futility. Additionally, the use of the ΔFRS to summarize disease progression should be considered a limitation of the study, based on evidence indicating that disease progression may not follow a linear trajectory (29–32).

There has been debate regarding whether riluzole might be more effective, or exclusively effective, among bulbar-onset ALS patients. This hypothesis arises from the initial trial data (3) and subsequent observational studies (16). Our results suggest that, although the longer survival was evident in all patients treated with riluzole, it was notably more pronounced among those experiencing respiratory onset, and significantly more robust in bulbar onset when compared to spinal onset patients. However, the shift in significance observed when including the ΔFRS as a covariate suggests that these differences could be driven by the different progression rate of these patients and thus by the variable efficacy of riluzole across the ΔFRS categories.

This study is the largest study assessing the real-world riluzole prognostic role in ALS, with all data collected prospectively. Notably, patients were enrolled from the largest European ALS centres, ensuring a high standard of data quality. However, this study reflects a secondary use of the existing data, which is a limitation.

Our data on riluzole use was confined to the time of diagnosis. Therefore, we were unable to perform a time-dependent analysis considering the duration of riluzole administration, and accordingly, this study should be regarded as an "intention-to-treat" analysis.

Moreover, we lack information regarding the reasons why certain patients did not receive riluzole. If the reasons for non-administration indirectly relate to the outcome, it could introduce a potential selection bias. This could be the case of patients who might not have received riluzole during the early stages of the disease due to a very slow disease progression that delayed the diagnosis. Conversely, severe and early dysphagia might have prevented physicians from administering riluzole in the absence of an alternative method of administration. Also, if some patients chose not to be treated with riluzole, we cannot completely rule out the possibility of a selection bias towards people who tend to refuse other interventions (such as ventilation) or to a globally lower compliance throughout the disease course.

The main limitation, however, is represented by the observational design of the study, lacking randomization. Consequently, known and unknown prognostic factors that could act as confounders might not have been balanced between the groups of patients. This concern is particularly relevant to the differences in the relationship with longer survival observed across progression rates. As discussed above, these differences may stem from factors other than a true effect of riluzole, such as variations in prescribing practices. Consequently, this study does not establish the causal relationship between riluzole's effect and survival across different progression rates, leaving this as an open question for further investigation. Randomized clinical trials could possibly overcome this limitation by eliminating biases in prescribing practices while also

accommodating and taking into account alternative formulations for patients with swallowing difficulties. However, the challenges posed by the ethical limitations of using placebos, given riluzole's established efficacy, must be considered in the study design.

Notwithstanding, this study showed that patients treated with riluzole experienced a longer survival than those who were not treated, and is the first to detect that this extended survival could be also present in those carrying known disease causing gene variants. Moreover, the relationship between riluzole use and extended survival was greater among fast progressors. However, the absence of longitudinal data on disease staging and progression rates complicates our understanding of this phenomenon in relation to clinical changes, emphasizing the need for the prospective PRECISION ALS study, in which all aspects of the patient journey is collected in a harmonized manner across multiple European sites.

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Declaration of interest

Alejandro Caravaca Puchades reports, Cristina Terrafeta Pastor, Stefan Sennfält, Oskar Holmdahl, Sarah Opie-Martin, Frederik Hobin, Fouke Ombelet, Harry E. McDonough, Mohammed Mouzouri Robert McFarlane, Miriam Galvin, Mark Heverin, Nikita Lamaire, Éanna Mac Domhnaill, Rosario Vasta, Umberto Manera, Ruben van Eijk, Daphne Weemering, Jan Veldink, Leonard van den Berg: no competing interests to declare. Adriano Chiò serves on the editorial advisory board of Amyotrophic Lateral Sclerosis and Neurological Sciences. Adriano Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Biogen, Roche, Denali Pharma, Cytokinetics, Lilly, Ferrer, Zambon Biotech, and Amylyx Pharmaceuticals, has received a research grant from Biogen and serve on Drug Safety Monitoring Board for AB Science, Corcept, and Eli Lilly. He has received research support from the Italian Ministry of Health (Ricerca Finalizzata), Regione Piemonte (Ricerca Finalizzata), Italian Ministry of University and Research (PRIN projects), University of Turin, and the European Commission (Health Seventh Framework Programme, Horizon 2020 and Horizon Europe). Philip Van Damme reports advisory boards for Biogen, CSL Behring, Alexion Pharmaceuticals, Ferrer, QurAlis, Cytokinetics, Argenx, UCB, Muna Therapeutics, Alector, Augustine Therapeutics, VectorY, Zambon, Amylyx (paid to institution). He has received speaker fees from Biogen, Zambon and Amylyx (paid to institution). He is supported by the E. von Behring Chair for Neuromuscular and Neurodegenerative Disorders (from CSL Behring, paid to institution). Mònica Povedano Panadés reports consultancies/advisory boards for Amylyx Pharmaceuticals, Biogen, Ferrer, Grifols, Italfarmaco, Mitsubishi Tanabe Pharma and Roche. Caroline Ingre has consulted for Cytokinetics, Pfizer, BioArctic, Novartis, Tikomed, Ferrer, Amylyx, Prilenia and Mitsubishi. She is also a board member of Tobii Dynavox; all outside the submitted work. Ammar Al-Chalabi reports consultancies or advisory boards for Amylyx, Apellis, Biogen, Brainstorm, Clene Therapeutics, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, Quralis, Sano, Sanofi, and Wave Pharmaceuticals. Cristopher J. McDermott reports consultancies or advisory boards for Amylyx, Ferrer, Novartis, PTC therapeutics, Verge Therapeutics. Pamela J. Shaw reports consultancies or advisory boards for Biogen, Aclipse Therapeutics, Quell Therapeutics, BenevolentAI, QurAlis, Astex, GeniUS, Lilly, Novartis, Samsara, Eikinoklastes, Maat Pharma and AL-S Pharma and collaborates with and has received research funding from Quell Therapeutics, Aclipse Therapeutics, Pfizer SwanBio, and Takeda. Philippe Corcia reports consultancies or advisory boards for Amylyx, Biogen, Coave Therapeutics, Cytokinetics, Ferrer, Mitsubishi Tanabe,QurAlis, Vectory, Zambon. He is member of the Board of the Journal Amytrophic Lateral Sclerosis and the Frontotemporal Dementias and of the Revue Neurologique. Orla Hardiman reports consultancies/advisory boards for Biogen, Takeda, Ferrer, Novartis, Alchemab and Medici Nova. She

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Data availability statement

The data set used for the analysis in this paper was provided by PRECISION ALS. These data are stored, and access governed by the PRECISION ALS Consortium. Requests to access this data can be made through the Scientific Board of the PRECISION ALS Consortium.

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Amyotroph Lateral Scler Frontotemporal Degener. 2020; 21:509–18.
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