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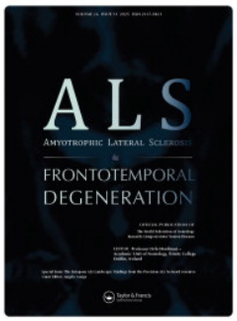

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Natural history of the revised ALS functional rating scale and its association with survival: the PRECISION-ALS Extant Study

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RESEARCH ARTICLE

Natural history of the revised ALS functional rating scale and its association with survival: the PRECISION-ALS Extant Study

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Abstract

Objective: To characterize the natural history of the revised ALS functional rating scale (ALSFRS-R) over a 24-month period following initial assessment, and to assess its associations with survival. *Methods*: Longitudinal ALSFRS-R measurements and survival data were obtained from seven population-based, European cohorts. Different models for the ALSFRS-R trajectory were evaluated, including tests for linearity and between-cohort differences. We employed a joint modeling framework to factor in mortality, thereby aiming to derive a more precise estimate of the population's rate of decline, while simultaneously delineating its relationship with survival. *Results*: In total, 7,030 patients were included who produced 31,746 ALSFRS-R measurements during a follow-up period of 10,285 person-years. There was substantial evidence for a non-linear time trend within all cohorts (all $p < 0.001$), with faster progression rates at the beginning of follow-up. The average rate over 24 months was 0.89 points per month; 95% of the patients had a rate between 0.04 and 1.96. Overall, two components of the ALSFRS-R trajectory were found to be associated with survival: (1) the actual value of the ALSFRS-R total score and (2) the rate of change at any given time (both $p < 0.001$). *Conclusions*: Functional loss in ALS follows a decelerating trajectory, where the current functional status and the rate of change have a direct impact on

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the patient' s probability of survival. Given the pivotal role of the ALSFRS-R in drug development, these results help to separate treatment benefit from the disease's natural trajectory and to estimate the impact on survival.

Keywords: *ALSFRS-R, joint model, survival, ALS*

Introduction

Evaluating efficacy has posed an enduring challenge for clinical trials in Amyotrophic Lateral Sclerosis (ALS) (1). This challenge arises from the extensive clinical heterogeneity (2), rendering it complex to pinpoint a singular endpoint that is applicable to all patients (3). Hence, assessing survival time has long been the gold standard, but requires prolonged placebo-controlled studies. Recognizing the need for more patient-centered trial designs (4), there has been a shift toward shorter clinical trials with a focus on intermediate outcomes (5). Consequently, functional decline, as measured by the revised ALS functional rating scale (ALSFRS-R) (6), has emerged as the primary endpoint in most pivotal clinical trials today (7,8).

This is unsurprising, given the advantages the ALSFRS-R has, namely: it is simple to administer, consistent across studies, and has strong associations with quality of life and survival (6,9–11). Despite these benefits, however, regulatory interactions have highlighted critical shortcomings that limit the usability of the ALSFRS-R in clinical trials (12,13). In addition to the uncertainty surrounding what constitutes a meaningful difference in ALSFRS-R scores (14,15), its trajectory of progression remains debatable, especially as this is influenced by mortality and symptomatic therapies (16). These factors complicate the interpretation of ALSFRS-R outcomes and the ability to accurately gauge the benefit of novel treatments.

Better estimation of the ALSFRS-R trajectory is, therefore, of considerable interest. The joint modeling framework has been proposed to overcome the limitations faced by conventional methods, providing more flexibility and factoring in mortality (17,18). Like other statistical strategies, however, joint models make assumptions, which could be imprecise and potentially lead to inaccurate conclusions (19). In this study, therefore, we characterize the natural history of the ALSFRS-R – when conjoined with mortality in a joint modeling framework – in multiple, population-based cohorts. Furthermore, we assess the association between the natural history of the ALSFRS-R and survival. These results provide a better rationale in modeling ALSFRS-R decline, allowing better separation of treatment benefit from the disease's natural trajectory, and refinement of the analysis of ALS clinical trials.

Methods

Individual patient data

Data for this study originated from the PRECISION-ALS Extant Study. In brief, nine European specialized ALS centers comprising the PRECISION Consortium provided data from prospective population-based, or extensive clinic-based registers. Each site collected data in accordance with the ENCALS ALS Core Clinical Dataset standard operating procedure, including training of evaluators for key clinical outcomes. On completion of General Data Protection Regulation (GDPR) compliant data sharing agreements, each center provided patient-level, de-identified data on demographic and disease characteristics obtained at diagnosis, together with longitudinal follow-up data of the ALSFRS-R. All patients present with either possible, probable (laboratory supported) or definite ALS, according to the revised El Escorial criteria, were eligible (20). 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 (online) municipal population register at 3-monthly intervals. Datasets were harmonized and combined into a single database, together with an indicator variable for cohort.

To make the data suitable for analysis, ALSFRS-R scores with unknown assessment dates were removed from the analysis (0.75%; 371 of 49,450). Among the remaining scores, there were 124 ALSFRS-R scores of zero (0.25%). As most of these scores appeared to be wrongful entries (e.g., subsequent scores increased by 20 points or more), zero scores were removed. Finally, measurement time was calculated for each patient individually and expressed as the number of months relative to their initial ALSFRS-R assessment. As the duration of virtually all clinical trials and longitudinal cohort studies in ALS is less than 24 months, and as the data after this time became increasingly sparse, we censored all ALSFRS-R assessments carried out 25.5 months after the initial assessment (i.e., assuming a 6-week window around a hypothetical final study assessment at month 24). A similar censoring rule was applied to the survival time; the data of patients who were alive, or who had an event 25.5 months after their initial ALSFRS-R assessment, were censored after 25.5 months.

Statistical analysis

Our primary objective was to characterize the population-level average rate of decline in ALSFRS-R total scores over a 24-month period following the initial ALSFRS-R assessment. Recognizing the presence of repeated measurements within

individuals, we employed mixed effects models to address the inherent dependencies in the ALSFRS-R data. It is important to note that an essential confounding factor is the impact of mortality, leading to informative censoring of ALSFRS-R scores, with higher death rates being observed among patients with lower scores (16). To address this issue, we employed a joint modeling framework to factor in mortality (21), aiming to derive a more precise estimate of the population's rate of decline.

In brief, the joint modeling framework consists of a longitudinal sub-model describing the ALSFRS-R trajectory over time, which is then incorporated as a "covariate" into a survival model that describes the probability of survival. By optimizing these models simultaneously – on *both* the ALSFRS-R and survival data – one adjusts the estimated ALSFRS-R trajectory for its association with mortality (referred to as "*mortality-adjusted progression*" or MAP) (22). This is different from an "ordinary" mixed model, which is optimized on the ALSFRS-R data only and thus disregards the survival information.

For the longitudinal sub-model, the most simplistic model consisted of a model with a fixed linear effect over time, and a random intercept and random slope for time per patient. This model requires two model estimates per patient and, on average, two observations per patient to be identifiable. Hence, we excluded cohorts from the analysis that averaged less than two observations per patient (Utrecht and King's, Figure S1). Subsequently, we extended the model by adding a quadratic term for time, both as random and fixed effect, thus assuming a non-linear course over time; the additional value of the quadratic term was evaluated with likelihood ratio tests.

For the survival model – following a Weibull distribution (23) – we tested the assumption that the latent (modeled) ALSFRS-R scores are indeed better associated with the hazard compared to the actual observed ALSFRS-R scores, supporting the use of a joint model over a time-varying-covariate model (see e-Methods) (24). In addition, we investigated different association structures between the best-fitting ALSFRS-R sub-model and the hazard for death (25), including the association with the current ALSFRS-R total score, the rate of change in ALSFRS-R, the cumulative value of the entire ALSFRS-R history, or a combination of these. The different models were compared using Akaike Information Criterion (AIC) and likelihood ratio tests. To evaluate the consistency of our results, we repeated all analysis steps in each cohort separately.

Finally, we explored whether certain cohorts or baseline characteristics were differentially associated with the rate of change in ALSFRS-R. Missing data in baseline characteristics varied between 0% and 47.4%; in total, 3,424 out of 7,030 records (48.7%) were incomplete. Missing data were addressed by creating multiple imputed datasets ($n = 25$), using predictive mean matching and bootstrapping, disregarding the first 100 iterations (burn-in). The imputation model contained all covariates, including vital status and survival time; survival time was incorporated as Nelson-Aalen estimator (26). For the interaction analyses, we added in the longitudinal sub-model a main term for the respective baseline covariate and its interaction with time, thereby assessing whether the rate of change in ALSFRS-R total score depended on the baseline covariate. This step was repeated in each imputed dataset, and results pooled using Rubin's rules (27). As sensitivity analysis, we repeated the analysis on the subset of complete cases (28). An exploratory analysis was conducted to evaluate differential progression rates in patients with a diagnostic workup for *C9orf72*, *SOD1*, *FUS* and *TARDBP*; patients without gene testing were excluded from the analysis. Confidence intervals around the longitudinal trajectories and model coefficients were obtained by parametric bootstrapping or the delta method (error propagation). All analyses were conducted in R (version 4.3.2) using the JM library (version 1.5-2, Rizopoulos D, 2022) (21).

Results

In total, we included 7,030 patients who produced 31,746 ALSFRS-R total scores, resulting in an average number of observations per patient of 4.5 (range 1 to 24). The total follow-up duration was 10,285 person-years with a mean follow-up time per patient of 1.46 years. During follow-up, 3,508 survival events occurred (49.9% of the patients); the 12- and 24-month probabilities of survival following initial assessment were 0.728 (95% CI 0.718 to 0.739) and 0.497 (95% CI 0.485 to 0.509), respectively. Patient characteristics are presented in Table 1, together with their missing data rates; additional cohort details are presented in Table S1(a,b).

Longitudinal ALSFRS-R trajectory

There was substantial evidence of a non-linear time trend at both the patient and population levels. The AIC – representing model fit – improved from 188,623 to 186,096 (-2,527, $p < 0.001$) by adding a quadratic time effect per patient; the difference in models is illustrated in Figure 1 for three patients. Model AIC could be further reduced to 185,785 (-311, $p < 0.001$) by adding a quadratic time effect at the population level. This indicates that as well as the patient-level trajectory being non-linear, the population rate of decline is not constant during follow-up. These differences in model fit were consistent across cohorts (all $p < 0.001$, Table S2(a)), all supporting a non-linear effect over time. As a

Table 1. Patient characteristics at initial ALSFRS-R assessment.

Characteristic	PRECISION ALS (N = 7,030)	Missing data
Age, *years*	65 (12)	0 (0.0%)
Sex, *male*	3,960 (56%)	1 (0.0%)
Site of symptom onset, *bulbar*	2,251 (32%)	102 (1.5%)
Symptom duration, *months**	13.5 (14.2)	158 (2.3%)
Time since diagnosis, *months**	0.7 (3.2)	864 (12.3%)
ALSFRS-R total score	37.3 (7.6)	0 (0.0%)
Bulbar score	9.8 (2.6)	75 (1.1%)
Fine motor score	8.6 (3.2)	77 (1.1%)
Gross motor score	7.9 (3.3)	77 (1.1%)
Respiratory score	11.0 (2.1)	106 (1.5%)
ΔFRS, *points per month**	−0.59 (0.81)	158 (2.3%)
Vital capacity, *%predicted*	83 (24)	3,330 (47.4%)

Data are given in mean (SD) or frequency (%). *Data are median (interquartile range). Missing data were addressed by multiple imputations and pooled across imputations. Abbreviations. ALSFRS-R = revised ALS functional rating scale; ΔFRS = ALSFRS-R total score – 48/symptom duration (49).

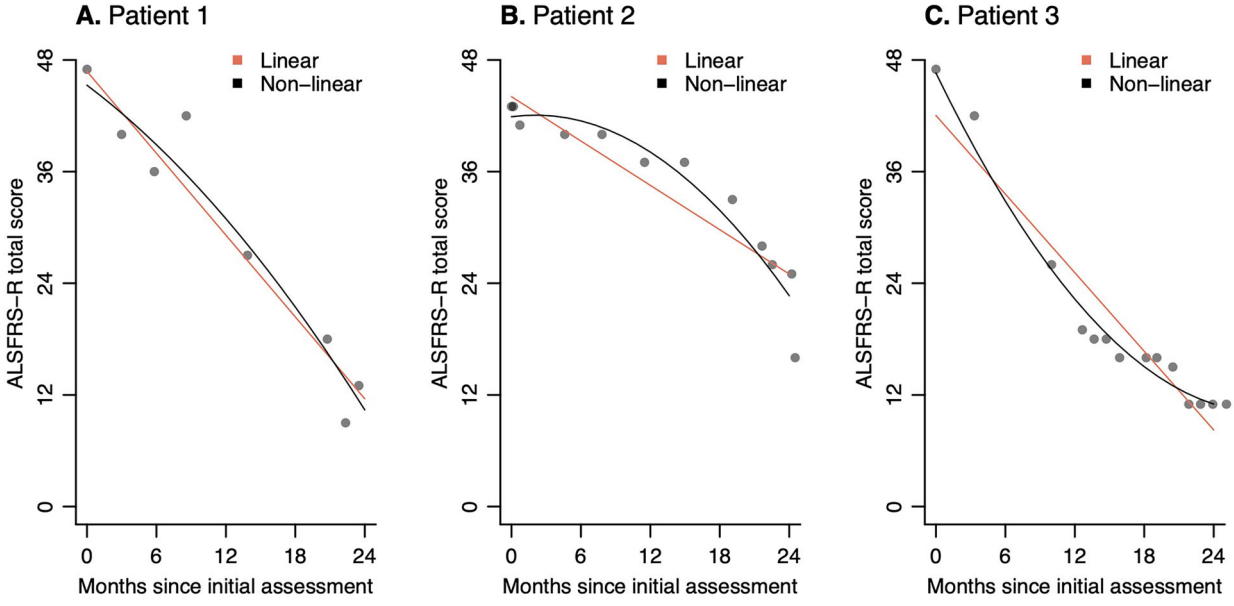

Figure 1. Patient-level trajectories of the ALSFRS-R total score.
The grey dots reflect the observed ALSFRS-R total scores over time for three patients in our database (*panel A-C*). The red solid line reflects an "ordinary" linear slopes model, assuming a linear trajectory – or constant progression rate – over time for each patient. The black solid line assumes a quadratic trajectory over time for each patient, allowing acceleration (*panel B*) and deceleration (*panel C*) of the patient's progression rate over time.

Table 2. Association between the ALSFRS-R total score trajectory and the hazard for death.

	Current ALSFRS-R score			Monthly slope		
Cohort	*Coefficient*	*95% CI*	*P-value*	*Coefficient*	*95% CI*	*P-value*
All sites	0.912	0.908 – 0.916	< 0.001	0.546	0.516 – 0.577	< 0.001
Bellvitge	0.875	0.860 – 0.892	< 0.001	0.437	0.356 – 0.537	< 0.001
Karolinska	0.919	0.908 – 0.930	< 0.001	0.686	0.594 – 0.791	< 0.001
Leuven	0.896	0.887 – 0.906	< 0.001	0.407	0.355 – 0.468	< 0.001
Sheffield	0.915	0.907 – 0.922	< 0.001	0.521	0.461 – 0.589	< 0.001
Tours	0.896	0.888 – 0.905	< 0.001	0.385	0.339 – 0.438	< 0.001
Trinity	0.914	0.906 – 0.922	< 0.001	0.472	0.417 – 0.534	< 0.001
Turin	0.918	0.913 – 0.923	< 0.001	0.647	0.599 – 0.699	< 0.001

Abbreviation: CI = Confidence interval.

sensitivity analysis, the follow-up period was limited to six months, yielding similar findings at the individual patient level but with less pronounced differences at the population level (Table S2(b)).

When averaged across patients and cohorts, the mean rate of decline over 24 months was 0.89 ALSFRS-R points per month (95% CI 0.88 to 0.90), the fastest rate of decline being observed

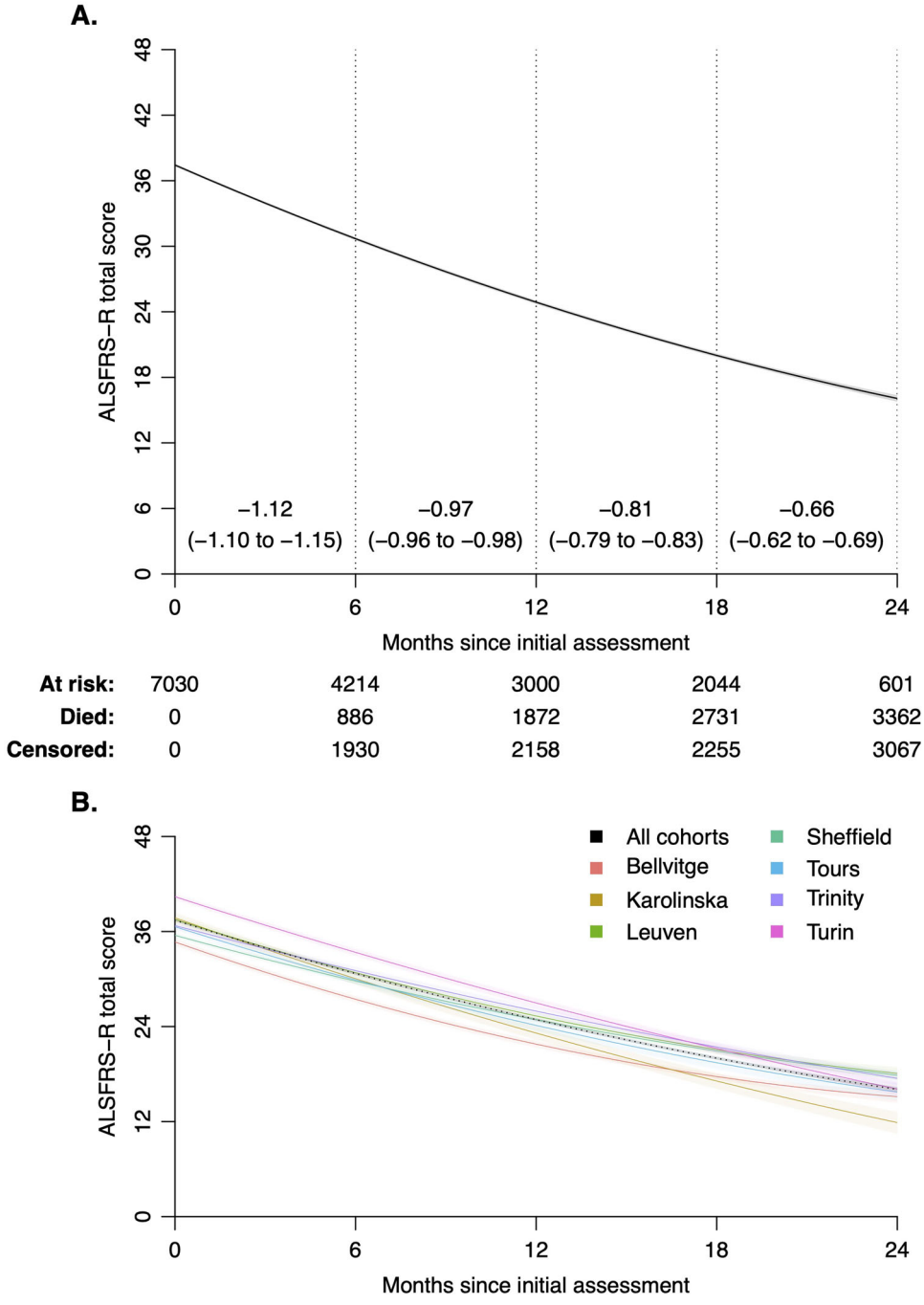

Figure 2. Natural history of the ALSFRS-R total score since first assessment.
Estimated progression of the ALSFRS-R total score over time, adjusted for mortality (*panel A*). The numbers between the dotted lines reflect the average rate in points per month in the respective time interval; in brackets, the 95% confidence interval. The baseline ALSFRS-R score differed between sites, though with similar rates of progression (*panel B*); the dotted line reflects the population average (same as *panel A*).

during the first year after baseline (Figure 2(A)). Interestingly, the baseline ALSFRS-R total score differed significantly between cohorts ($p < 0.001$), ranging from 34.7 (Bellvitge) to 40.4 (Turin), yet overall progression rates had similar trajectories ($p = 0.83$ for site by time interaction, Figure 2(B)); cohort-specific estimates are provided in Table S5. Overall, 95% of the patients had a 24-month averaged rate of decline since initial assessment between −1.96 and −0.04 points per month; the 25th and 75th percentile were −1.24 and −0.54, respectively (Figure S2); in 65.9% of the patients, the rate decelerated over time. The final model output is provided in Table S6. Results were similar in a "trial-eligible" cohort, defined as having a symptom duration ≤36 months, a vital capacity ≥60%, and being younger than 80 years at baseline (Table S7); the mean rate of decline over 24 months was 0.98 ALSFRS-R points per month (95% CI 0.96 to 0.99).

As shown in Figure 3, we explored six patient characteristics available at initial assessment which have been reported in the literature to influence ALSFRS-R progression rate (29,30). For illustrative

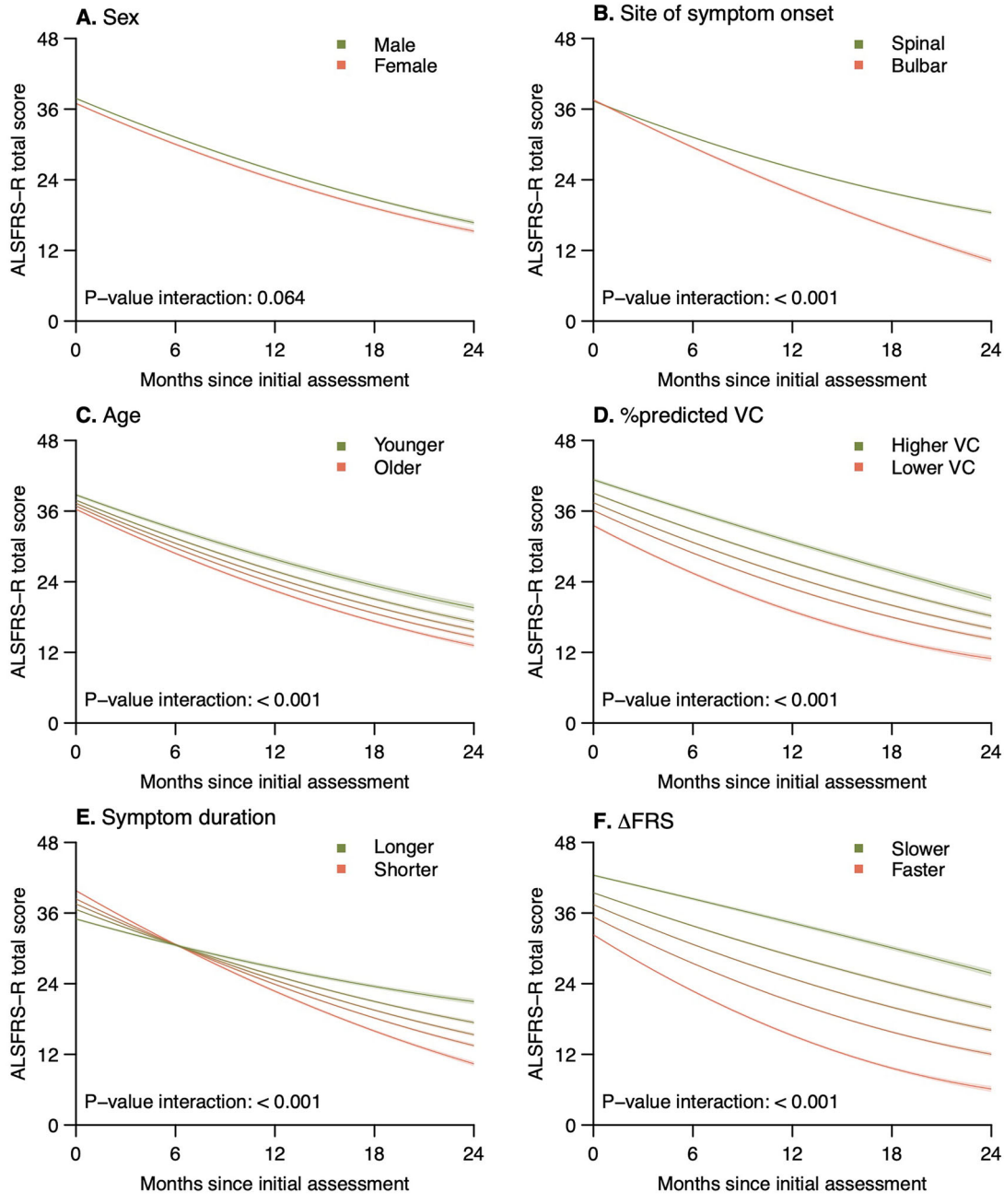

Figure 3. Association between baseline characteristics and ALSFRS-R progression rate.
Univariate associations between baseline covariates and the ALSFRS-R total score; continuous variables have been stratified into five equal percentile groups. The *p*-value is based on a likelihood ratio test with two degrees of freedom to evaluate the interaction terms between the baseline covariate with linear and quadratic time.

purposes, continuous variables have been depicted as five equal percentile groups. All factors were strongly associated with the progression rate over a 24-month period (univariately), except for sex ($p = 0.064$). There was, however, a time-invariant difference between males and females of 0.83 points (95% CI 0.59 to 1.06, $p < 0.001$). Similar results were obtained when the analysis was restricted to the subset of complete cases without missing data (Figure S3). Faster progression rates were also observed among patients known to be carriers of *C9orf72* ($p < 0.001$), and the expected slower progression rates among European patients known to be carriers of *SOD1* ($p < 0.001$) (31); differential progression rates were less evident for *FUS* and *TARDBP* carriers, potentially as a result of their low prevalence (Figure S4).

Association between ALSFRS-R total score and survival

Overall, two components of the modeled ALSFRS-R trajectory were found to affect the patient's overall probability of survival (Table S3 and Table S4): (1) the actual value of the ALSFRS-R total score at a certain point in time, and (2) the rate of change at that time; Table 2 provides the hazard ratios for both components. As can be seen, with every point increase in the ALSFRS-R

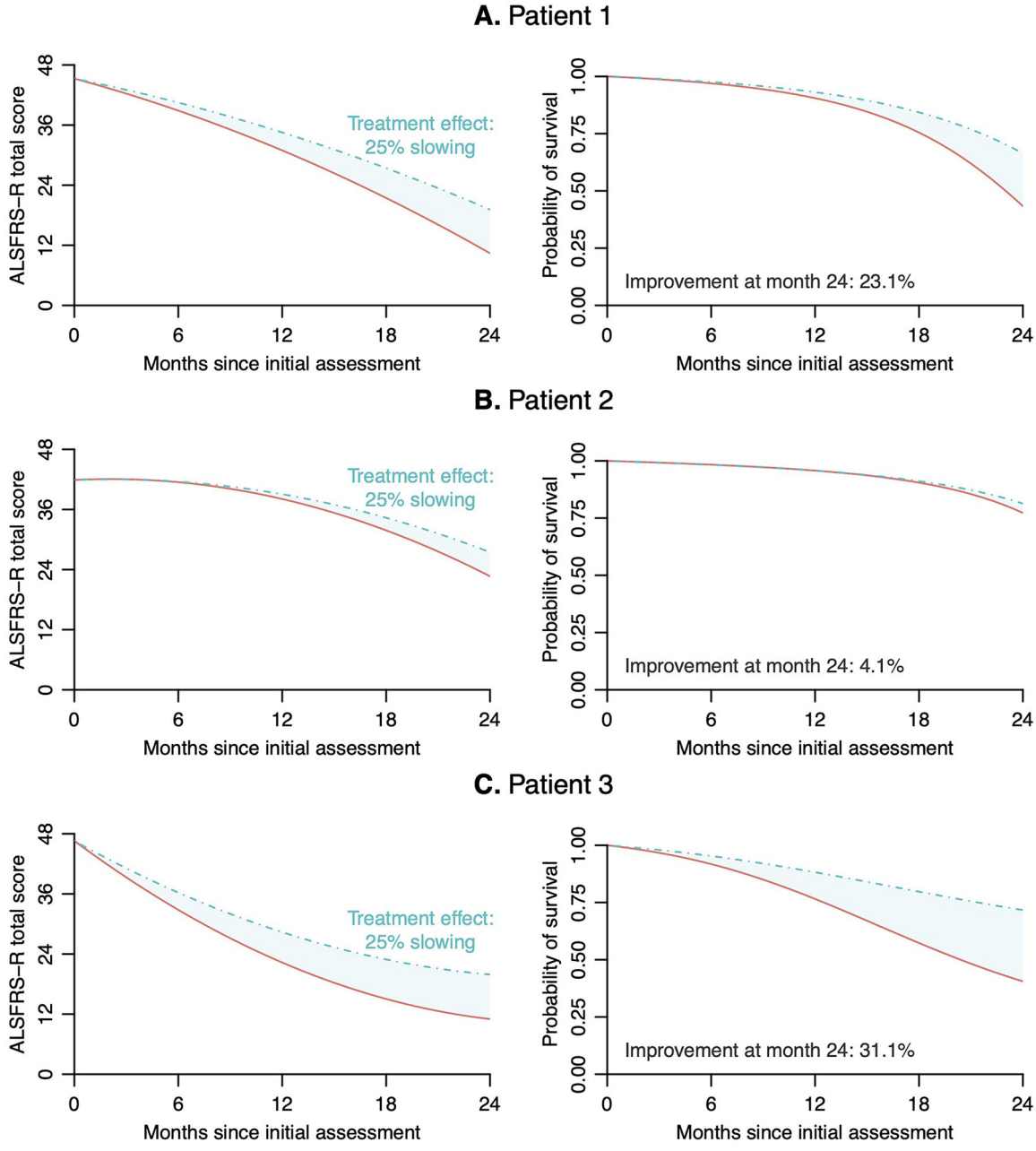

Figure 4. Association between ALSFRS-R and the probability of survival.
Translation of treatment benefit on the ALSFRS-R total score to the patient's probability of survival. As both the current value of the ALSFRS-R and its progression rate are associated with the probability of survival, treatment effects have a differential impact on the patient's life expectancy. Patients 1 – 3 are the same as those in Figure 1.

total score (e.g., increasing the total score from 43 to 44), the hazard decreases by 8.8% (HR 0.912, 95% CI 0.908 to 0.916, $p < 0.001$). Relatedly, with every point reduction in monthly progression rate (e.g., reducing progression rate from −1.5 to −0.5 points per month), the patient's hazard decreases by 45.4% (HR 0.546, 95% CI 0.516 to 0.577, $p < 0.001$).

This relationship is illustrated in Figure 4 for the three patients from Figure 1. Based on the patient's modeled ALSFRS-R trajectory, we can extrapolate their trajectory to a probability of survival (*red line*), or estimate the survival benefit of a hypothetical treatment effect that reduces the patient's progression rate by, say, 25% (*blue line*). As can be seen, depending on the patient's trajectory, such a treatment leads to different absolute increases in the patient's 24-month survival probability. Interestingly, although the actual score and its rate of change were found to be associated with survival at each site (Table 2), the actual hazard ratios differed between sites (both $p < 0.001$). This suggests that a point increase – or reduction in slope – at one site may have a different impact on survival than at another site.

Discussion

In this study, we have characterized the natural history of functional loss in patients with ALS – as

measured by the ALSFRS-R – over a 24-month period following initial assessment in a large, well-defined, multinational cohort of European patients. Although there is considerable variability between patients, functional loss in ALS is non-linear and, at a population-level, follows a decelerating trajectory with faster rates observed at the beginning of follow-up. Moreover, there is a strong interaction between functional loss and life expectancy, where the current functional status and its rate of change at any given time have a direct impact on the patient's probability of survival. Given the pivotal role of functional loss in ALS drug development, these results may help to disentangle treatment benefit from the disease's natural trajectory and refine the analysis of clinical trials.

Earlier work supports the *decelerating* trajectory over time at a population level (32,33). It should be noted, however, that this reflects an average across all patients and is not necessarily applicable to any individual in particular; in fact, 34% of the patients exhibited an *accelerating* pattern. The non-linear and variable rate of decline may not be surprising. First, as the ALSFRS-R is bounded by zero, patients with lower scores have fewer options for losing points, which naturally decelerates their rate. Second, as more domains become affected by ALS, there are more ways patients can lose points, resulting in an accelerating rate over time. This is further supported by the low-to-moderate correlation between the ΔFRS (i.e., the average rate prior to the first assessment) and the subsequent progression rate during follow-up (32,34), with the ΔFRS often being the lower of the two. Third, the ALSFRS-R is not free of measurement error (35), and may be affected by symptomatic treatments or differences in training (36,37). These factors mean patients can exhibit plateaus or small reversals (38,39), all adding to the non-linear trajectory over time.

One major consideration for the average rate of decline is the higher attrition rate among fast-progressing and severely affected patients. This leads to a disproportionate amount of missing data for lower ALSFRS-R scores. If not accounted for, it exacerbates the decelerating trajectory over time, potentially distorting the overall trend. In this study, we addressed informative attrition by directly modeling individual patient trajectories alongside observed survival times. However, other unobserved confounding factors, which could affect the population-level trajectory, may be at play, although these are unlikely to explain the significant variation in non-linear trajectories at the individual patient level.

The natural history of the ALSFRS-R has received considerable attention in the past (30,40–42). In contrast to earlier work, we have focused here primarily on modeling strategies frequently utilized in (randomized) clinical trials. We evaluated key underlying model assumptions, including the linearity of functional loss and its association with death. Previously, these assumptions have only been evaluated to a certain extent, and without replication across independent cohorts (18,32,33,43). They do, however, play a pivotal role in drug evaluation; this was recently highlighted by the FDA's evaluation of Relyvrio (12): the sponsor modeled the functional decline as a linear function, resulting in a mean difference of 2.32 points in favor of active treatment ($p = 0.034$). By changing the linear assumption into a quadratic function, the mean difference decreased to 1.68 points ($p = 0.1134$), a 27.6% difference in effect size which no longer reached nominal significance. Regardless of which model is most accurate, it becomes evident that the pre-specified primary analysis strategy and its underlying assumptions, could have major implications for the success of clinical trials.

The Relyvrio example also demonstrates that linearity is not only relevant in long-term studies. While the average decline over a 6-month follow-up period may appear relatively linear, individual trajectories can vary due to differences in progression rates. In our analysis, we found strong evidence of non-linear trajectories at the individual level over a 6-month period, whereas non-linearity was less pronounced at the group level. Non-linearity is not necessarily problematic and can be addressed with the proper statistical tools. A problem arises if we ignore the non-linearity: this may not only affect study results (44), it also prevents accurate prognostication and may unnecessarily exempt patients from clinical trials (e.g., when using a lead-in period or selecting patients based on the ΔFRS).

In our study, we employed a joint modeling framework to fully encompass these non-linear patient trajectories, while simultaneously addressing informative censoring due to death and missing data due to disease progression. This framework provides direct insight into the patient's probability of survival, allowing both better prognostication and the extrapolation of a theoretical slowing in functional loss (e.g., due to therapeutic intervention) to a change in survival time. Both elements have significant value: they help to improve (1) the accuracy of information patients receive about life expectancy, and (2) the understanding of what a difference in the ALSFRS-R total score means for overall survival.

The strength of our study is the unique database, composed of multiple European cohorts. In contrast to other large datasets, such as the PRO-ACT database (45), the data have been collected at a population-based level, thus providing a good representation of the natural trajectory of the ALSFRS-R total score (46). Moreover, individual cohorts were still identifiable, allowing analyses to be replicated and validated. As data collection was not

protocolized, however, data were less well-structured, resulting in fewer measurements per patient with more variable censoring rates compared to clinical trial data. Although we addressed these limitations in our modeling strategy, unstructured data collection increases variability and it would be of major value to protocolize data collection – including continued training of evaluators – in population-based registries following initiatives such as PRECISION-ALS (https://www.precisionals.ie).

Moreover, the strength of the association between the ALSFRS-R and survival differed between countries (Table 2). This could indicate a potential difference in how the ALSFRS-R is collected (or has been translated) and is used in each country. Having a master version of the ALSFRS-R, with validated backward-forward translated versions and harmonized training, remains a high priority (10,11). Another factor contributing to the differences between countries may be variations in standards of care that impact both ALSFRS-R decline and overall survival (e.g., respiratory support). These relationships could also be affected by certain patient characteristics (47), which may have a different prevalence within each country. Thus, evaluating the impact of care interventions – and the time trends in care changes – along with additional patient characteristics, would provide valuable insights to further elucidate the variability in the natural history of the ALSFRS-R total score and its relationship with survival.

Finally, in our study, we evaluated a relatively simple, non-linear, quadratic time trend. However, patient trajectories may be more complex, and a flexible or spline-based modeling approach might better represent disease progression (48). A disadvantage is that this increases the complexity of the model, potentially complicating its interpretation in clinical trials. A comprehensive simulation study would be valuable, therefore, to help clarify the risks of ignoring or inadequately modeling non-linearity and informative censoring in clinical trials with varying follow-up durations.

In conclusion, in a well-defined, multinational, cohort of European patients we found that functional loss in ALS follows a decelerating trajectory, where the current functional status and its rate of change have a direct impact on the patient's probability of survival. Given the pivotal role in drug development of functional loss, and the ALSFRS-R in particular, these results facilitate the separation of treatment benefit from the disease's natural trajectory, the estimation of the impact of treatment and functional loss on survival, and the refinement of the analysis of clinical trials.

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