Modelling individual amyotrophic lateral sclerosis disease courses in different centers using the D50 progression model

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Introduction: The routinely used Progression Rate (PR) index presumes that progression in ALS is linear and remains fixed over time. However progression in ALS is both curvilinear and vastly heterogeneous (**Fig. 1**).

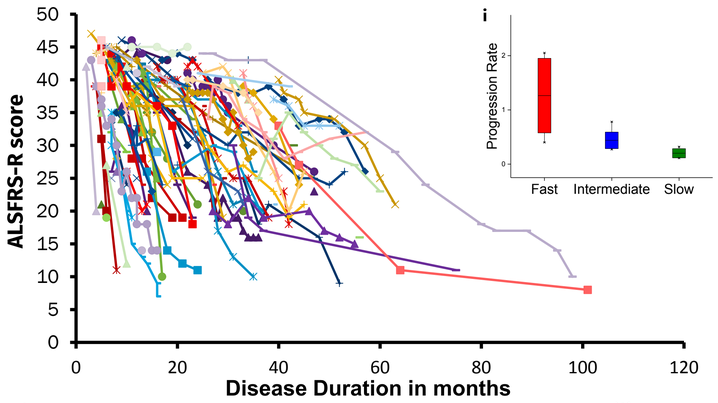


Figure 1: Total ALSFRS-R scores and calculated PRs **(i)** for a subset of individuals across the disease course clearly indicate the non-linearity of functional decline in ALS.

Objectives: To develop a model that uses regularly collected ALSFRS-R scores and reflects progression:
1) across the disease course
2) at the individual level and reduces noise associated with the ALSFRS-R

Methods: A sigmoidal decay function was used to describe the transition from full health to maximum disease for 4,080 patients of different European centers. The model yields following key descriptive parameters:

1) D50: Time taken in months for ALSFRS-score to drop to 24 and **2) dx:** Time constant of ALSFRS-R decay (**Fig. 2A**)
3) Relative D50 (rD50): calculated open-ended value describing individual disease course covered in reference to D50. 0 = disease onset and 0.5 = time-point of halved functionality.
rD50 can also be used to mathematically derive disease phases.
4) Calculated functional state at any time-point of the disease course
5) Calculated functional loss mathematically derived slope of the curve at any time-point of the disease course (**Fig. 2B**)

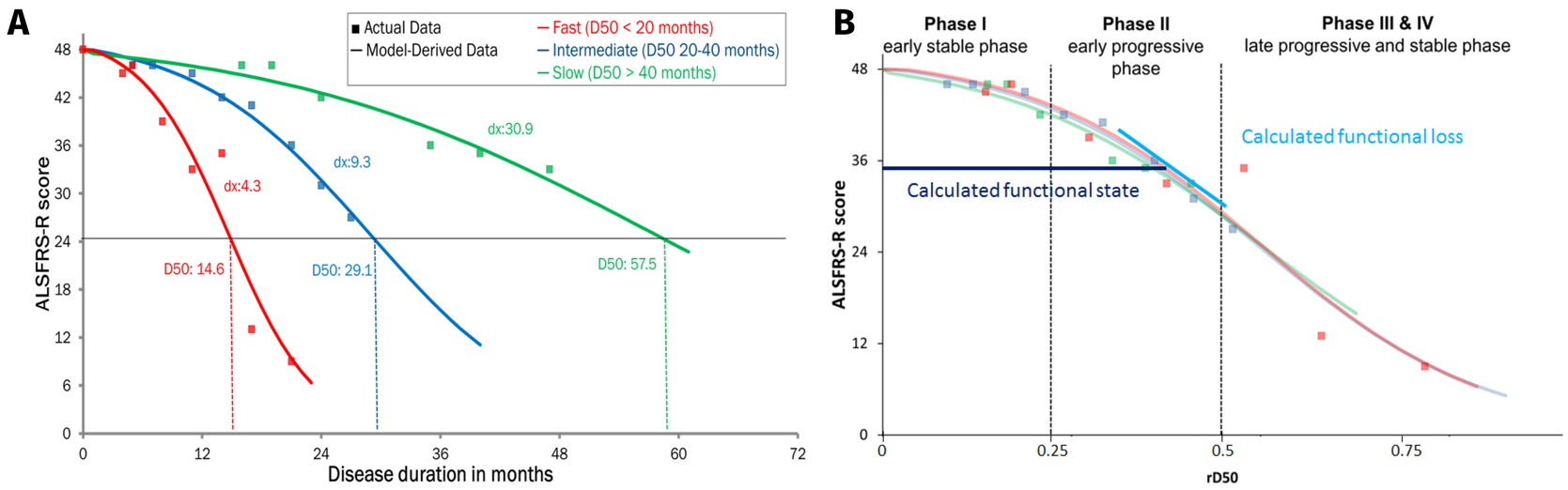


Figure 2: (A) D50 and dx are calculated from actual ALSFRS-R scores for 3 representative patients; a fast, intermediate, and slow progressor.
(B) Normalization with rD50 allows for comparability between patients with vastly different disease time scales and shows that patients proceed through similar phases of functional decline independent of disease aggressiveness.

Results

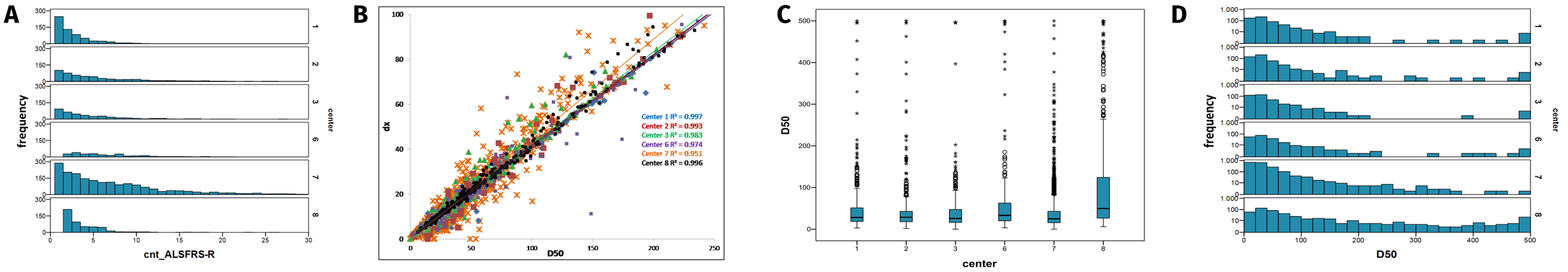
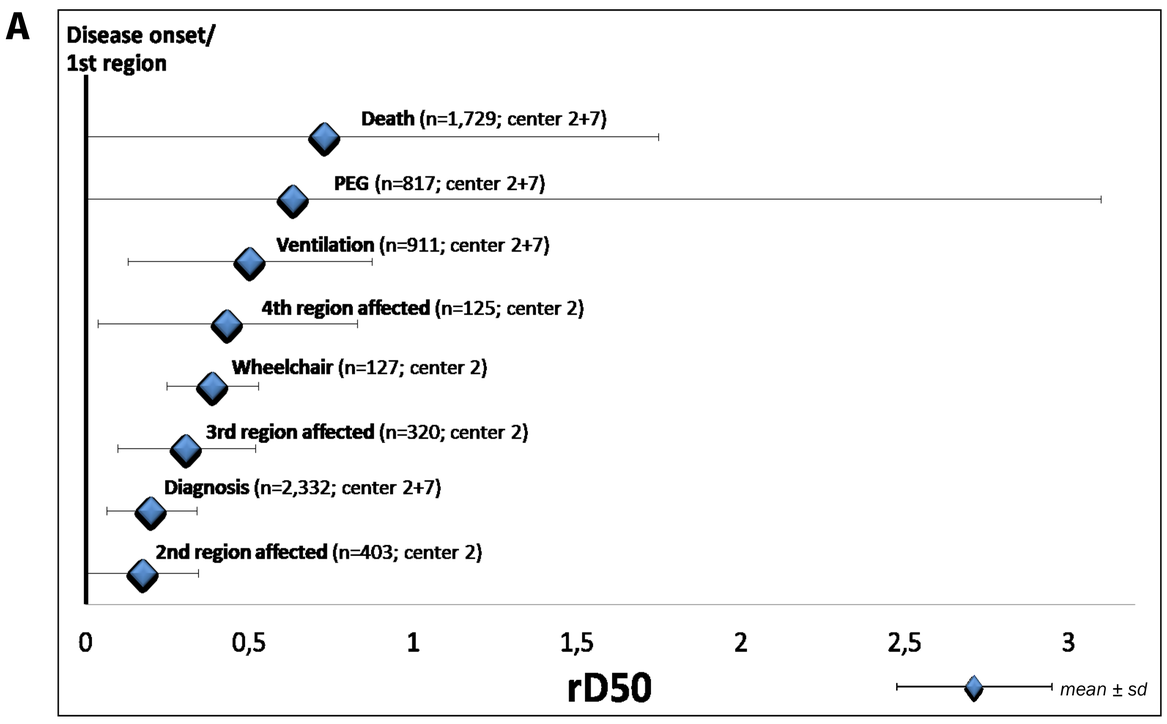


Figure 3: (A) Distribution of frequencies of ALSFRS-R value input of 6 European centers (total ALSFRS-R count = 23,071) **(B)** D50 and dx were calculated for 4,080 patients, with a significant positive correlation between the two parameters ($p<0.001$) **(C)** Distribution of D50 values of each center showing differences between center 6, 8 and 1,2,3,7 ($p<0.05$) **(D)** Distribution of the frequencies (log scaled) of the D50 values showing a high proportion of slow progressing patients (D50>40 months) for individual centers.



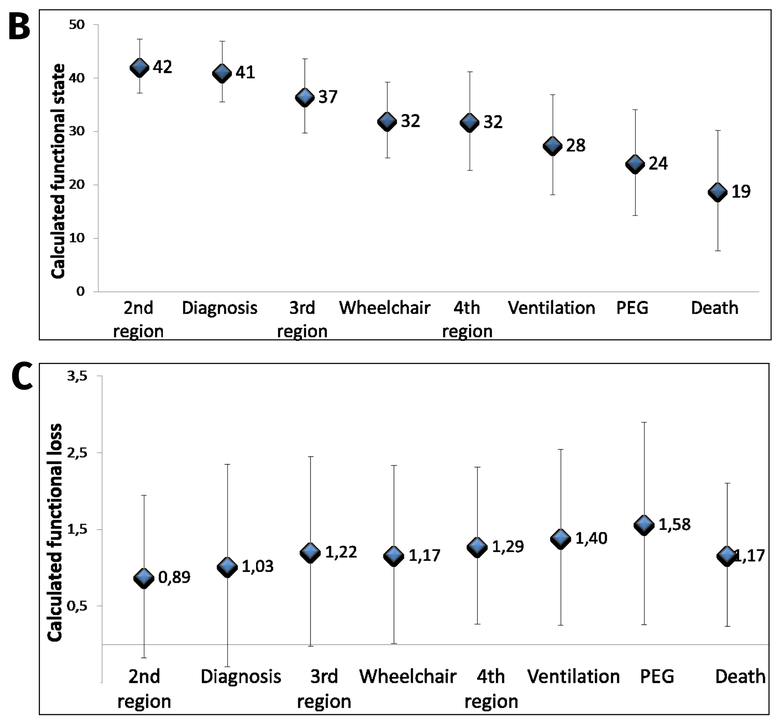


Figure 4:
(A) rD50 represented as mean ± standard deviation for center 2 and 7 for specific disease related events normalized to disease onset.
(B) mean calculated functional state of the patients at the time point of the disease specific event showing a constant decrease and
(C) mean calculated functional loss at the time point of the disease specific event showing a slight increase with high variances

Discussion And Conclusions:

The D50 model provides meaningful descriptors of overall disease aggressiveness, local disease activity, and a unified linear scale to describe disease progression. It a) offers alternative reference points to disease specific events, b) allows the staging of individual events, c) provides a way to pseudo-longitudinally interpret cross-sectional data and d) efficiently compares the composition of cohorts from different geographic regions.
However, D50 and dx correlation strongly depends on the input of ALSFRS-R count where the model forces a fixed ratio by using a single value. Deeper analysis have to assess a reasonable cut-off for D50 in order to cope with very slow progressors.

Acknowledgments
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