



UMC Utrecht

Combining functional loss and mortality *ALS clinical trials*

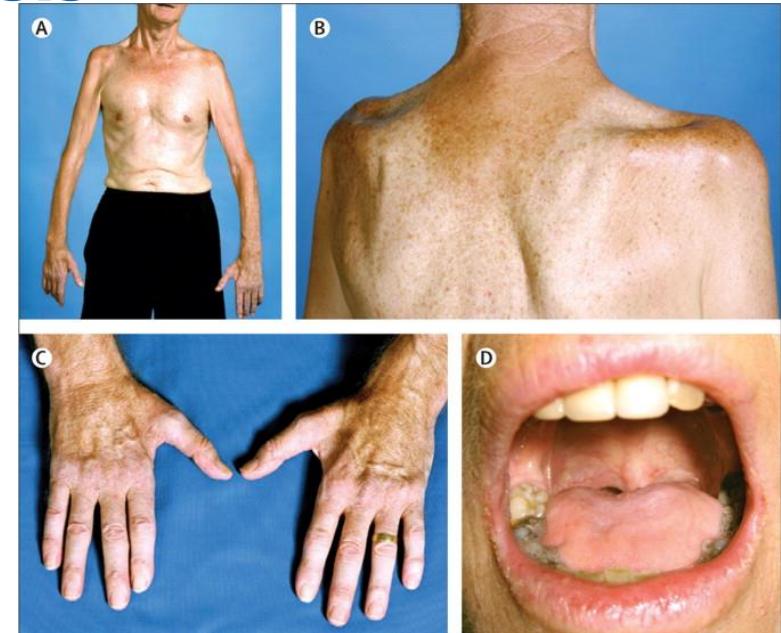
*Ruben van Eijk
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Dimitris Rizopoulos
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University Medical Center Utrecht

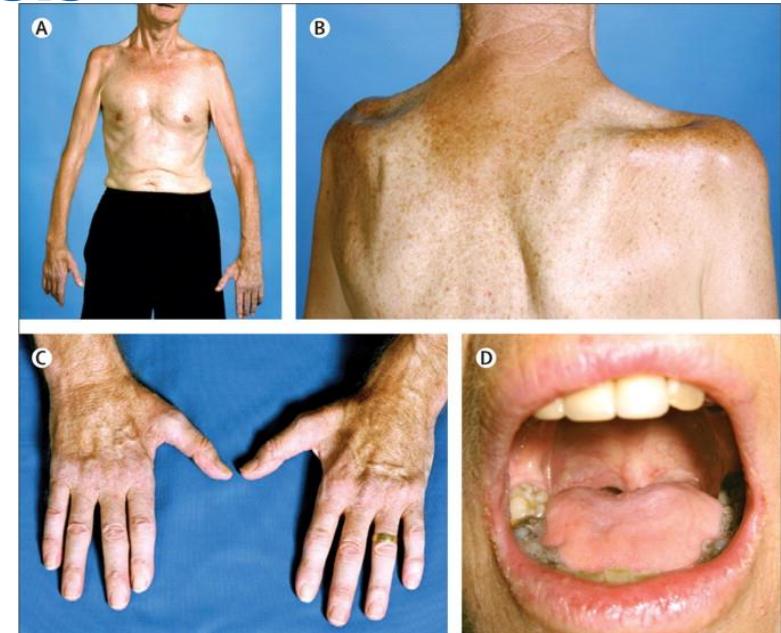
Amyotrophic lateral sclerosis

- Loss of upper and lower motor neurons
- At any adult age
- Progressive weakness
- Median survival is 3 years after onset
- 5-10 % is familial
- 5% overlap FTD
- No effective treatment
- 500 new patients/year in Netherlands
- 1500 patients
- Worldwide similar incidence (300,000 worldwide)
- 1:300 die of ALS



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- Lou Gehrig's disease





ALS Clinical Trials

Primary outcomes

1. Survival

- 12 months: 85%-90% deceased
- 18 months: 60%-75% deceased

2. Functional decline

- Daily functioning
- Muscle strength
- Lung function

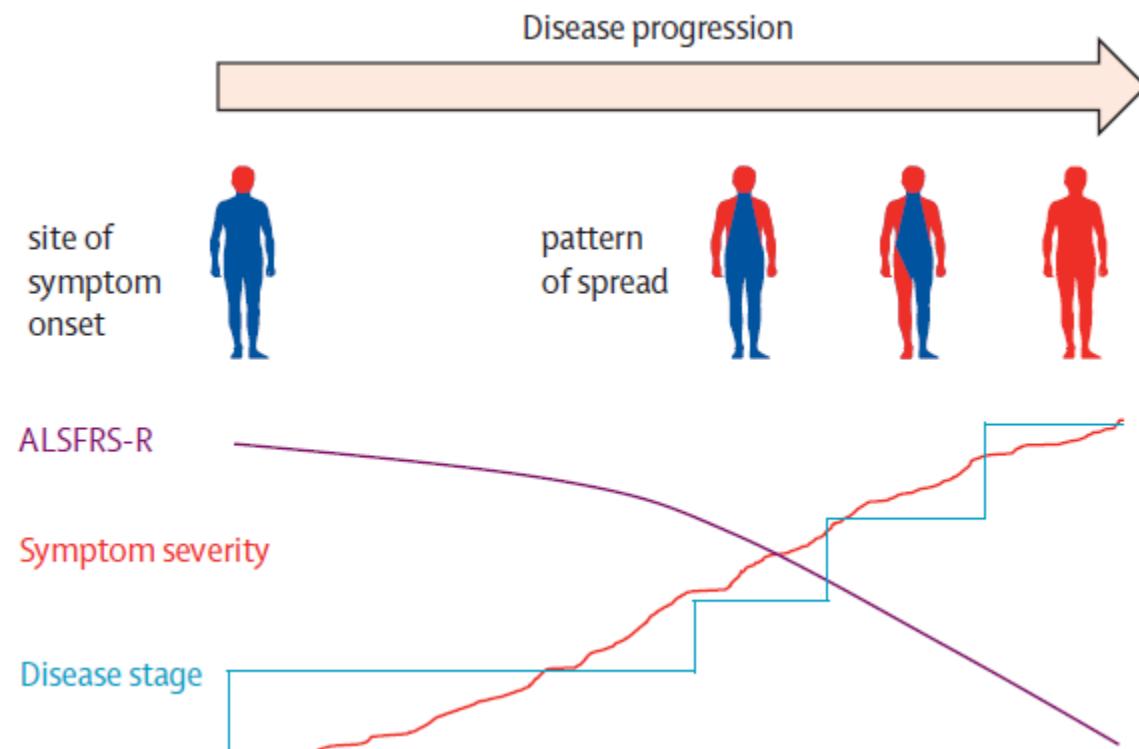
3. No 'responders'

Measuring daily functioning

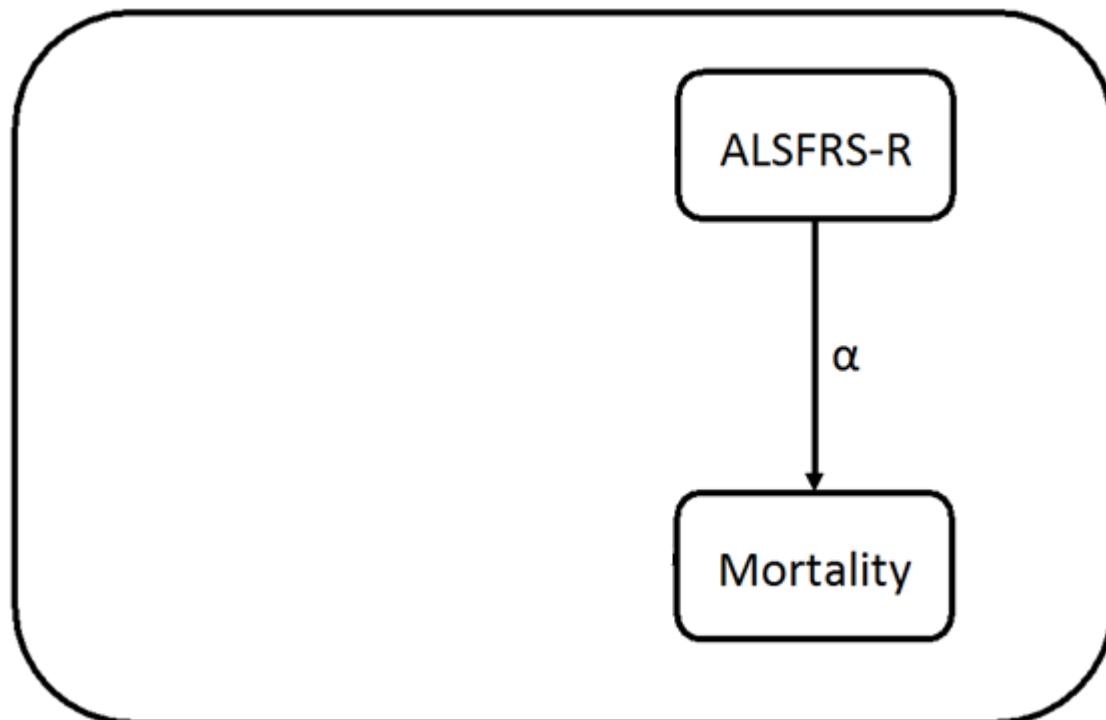
ALS functional rating scale (**ALSFRS-R**)

1. Bulbar
 - Swallowing, speech
2. Fine motor
 - Handwriting, dressing
3. Gross motor
 - Walking
4. Respiratory
 - Respiratory support
 - Breathing difficulties

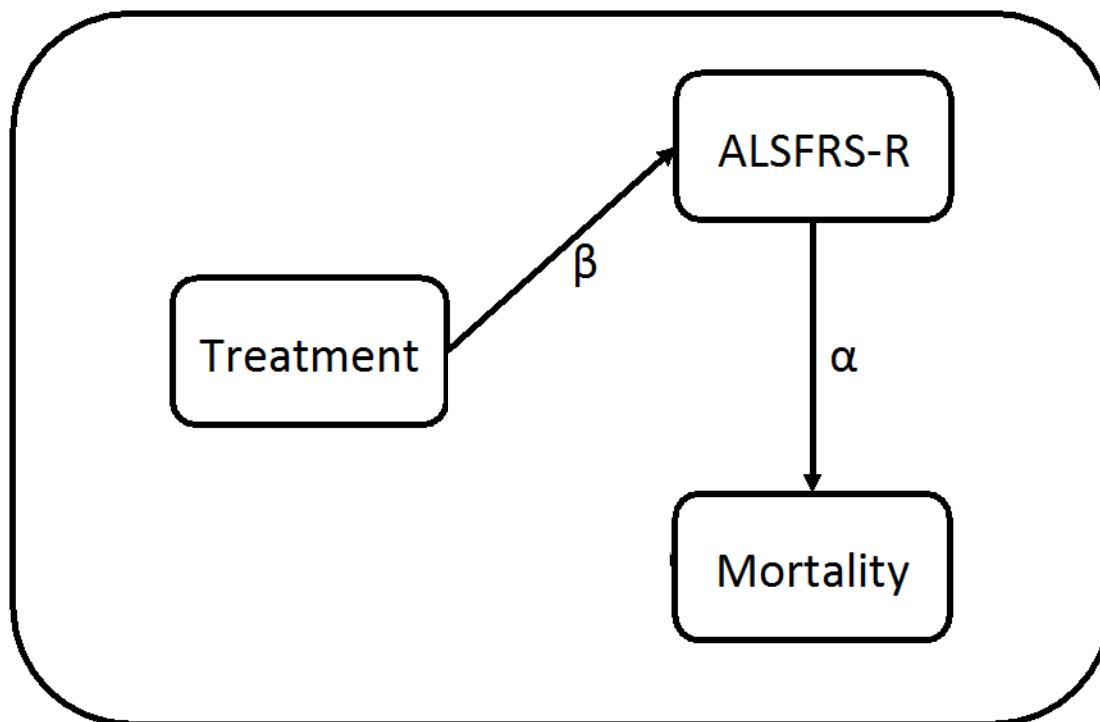
Disease progression



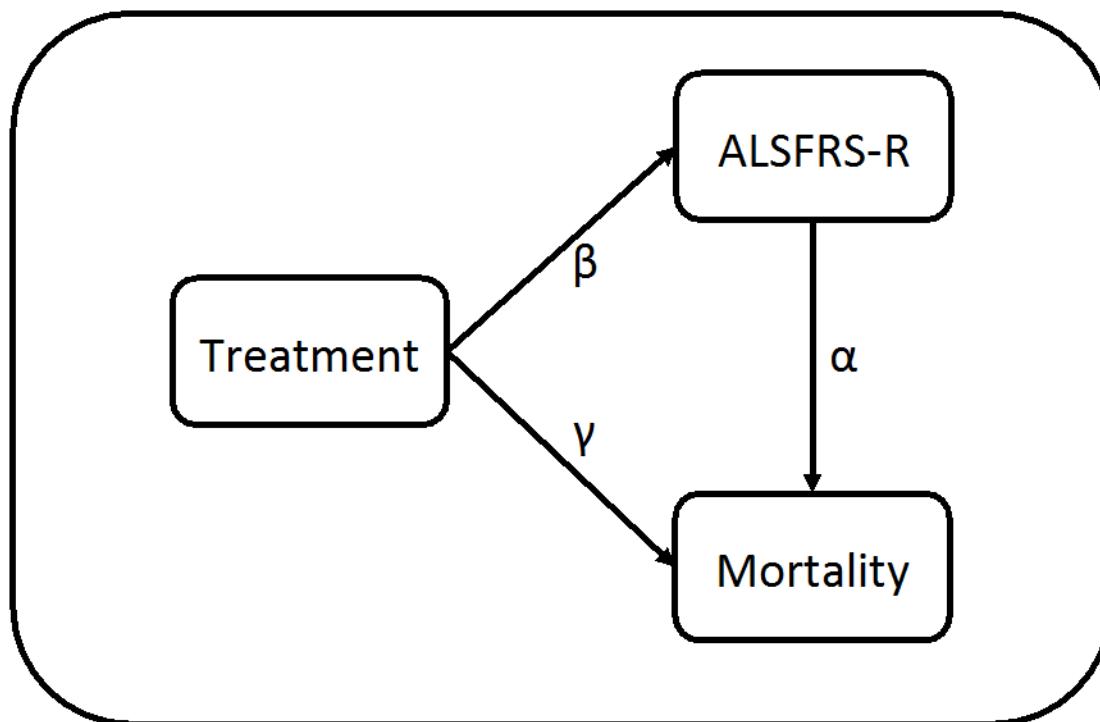
Functional loss, survival and treatment



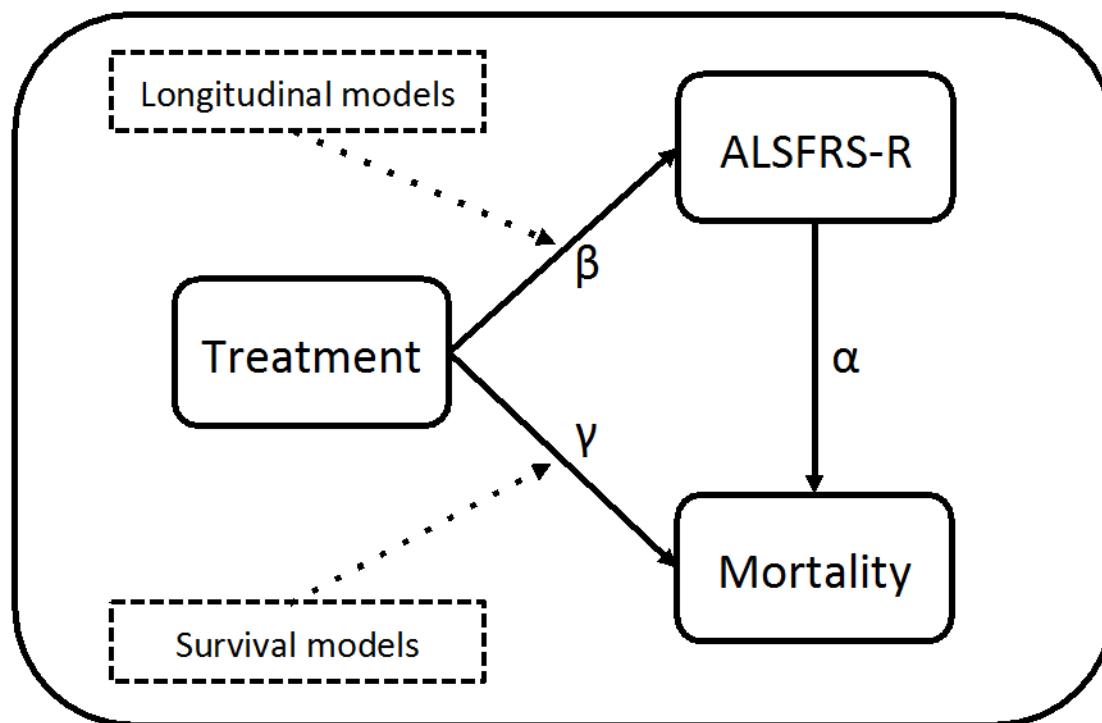
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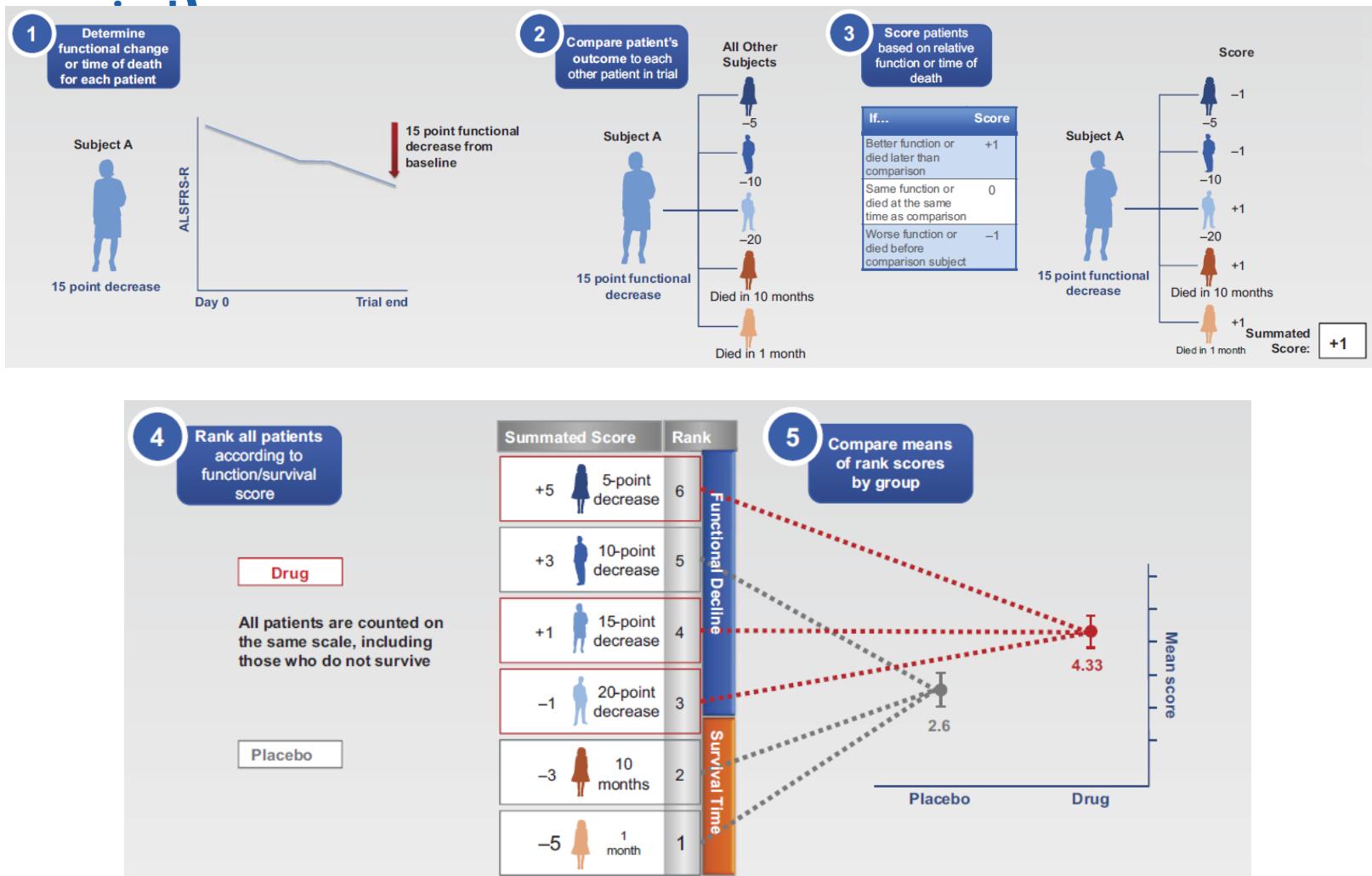
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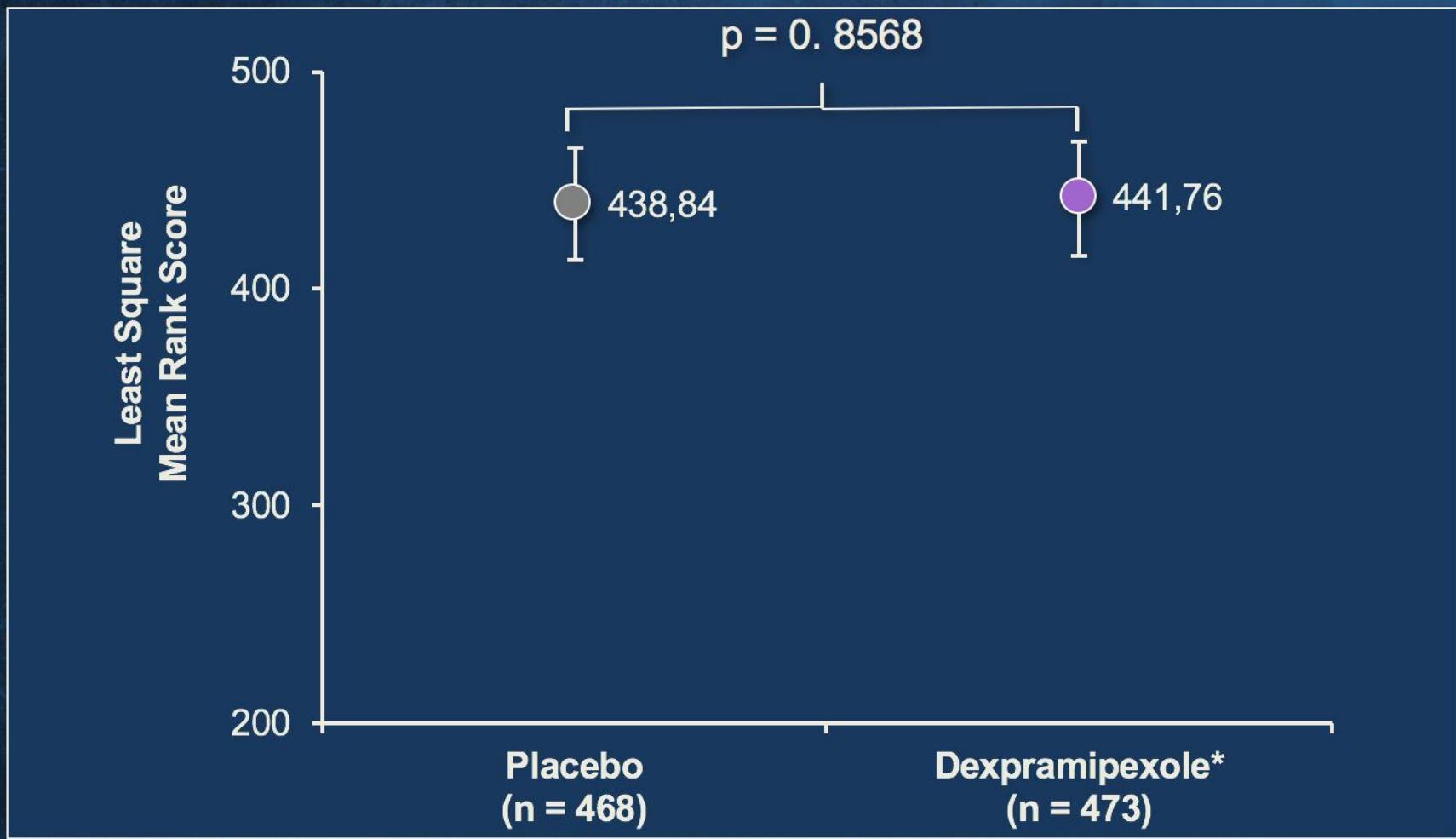
Functional loss, survival and treatment



Solution 1: CAFS (combined assessment of function and survival)

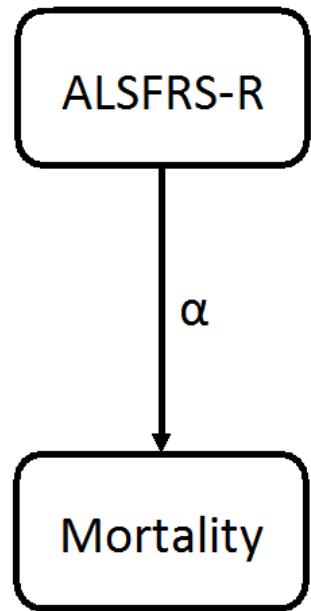


No Effect on CAFS Through 12 Months was Demonstrated With Dexramipexole

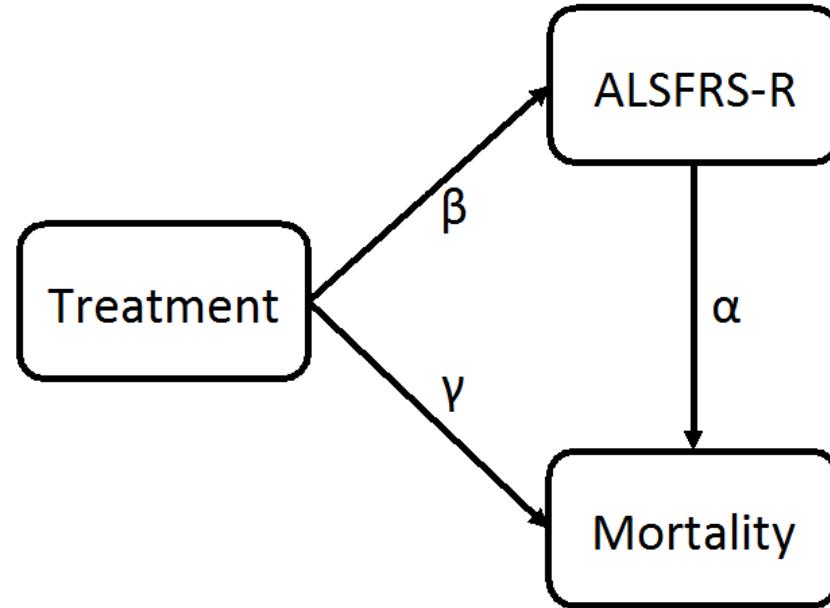


Solution 2: Joint model test

Joint model 1



Joint Model 2



Likelihood ratio test:

Chi-square = $-2 * [\log \text{Likelihood M2} - \log \text{Likelihood M1}]$,
2 degrees of freedom



Solution 3&4

Solution 3: composite endpoint

→ Time to:

- Death
- 6-point loss on ALSFRS-R

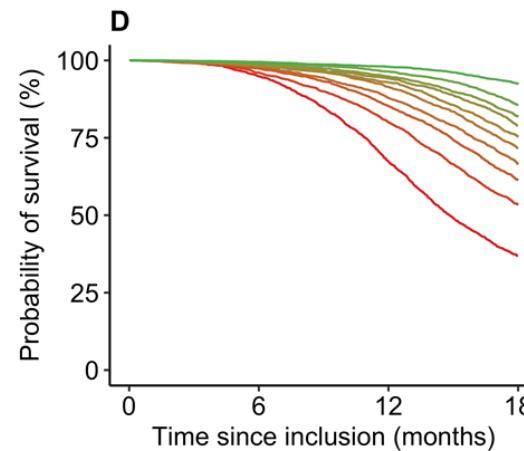
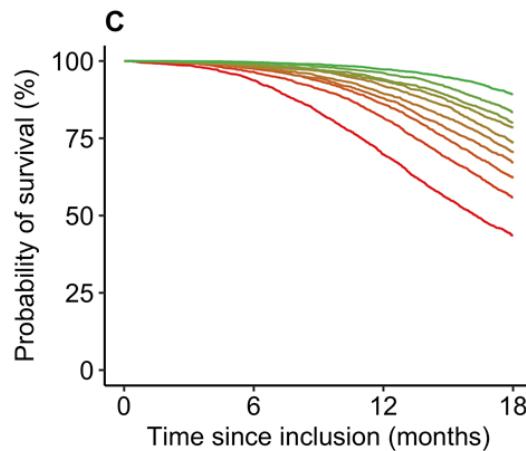
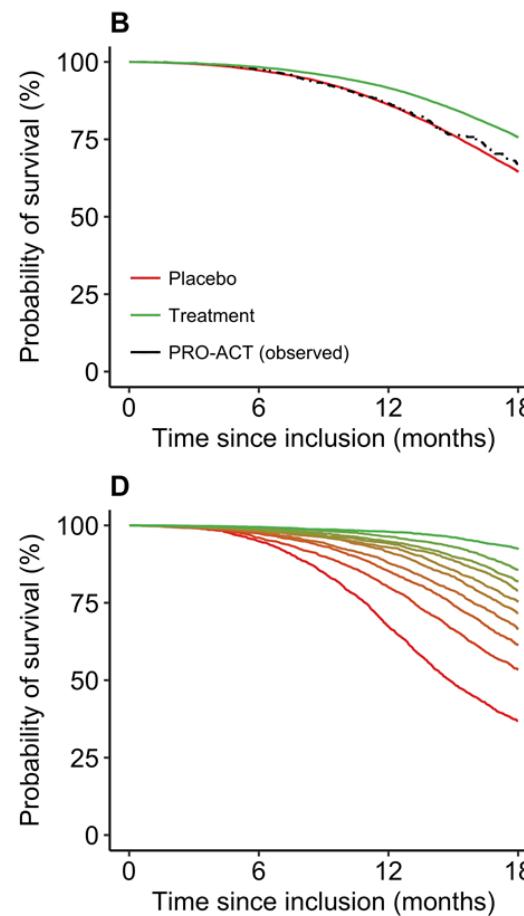
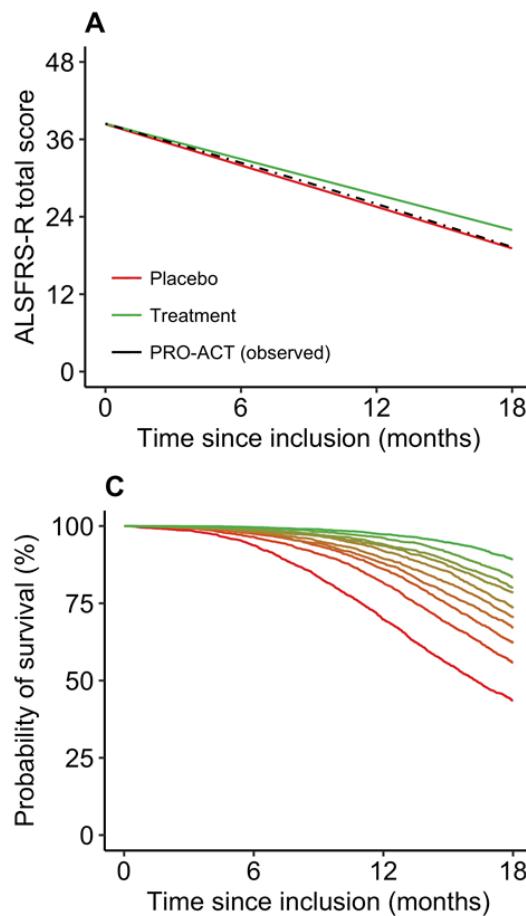
Solution 4: testing both classical models (LME/Cox)

1. LME model $p < 0.0253$ **OR**
2. Cox model $p < 0.0253$

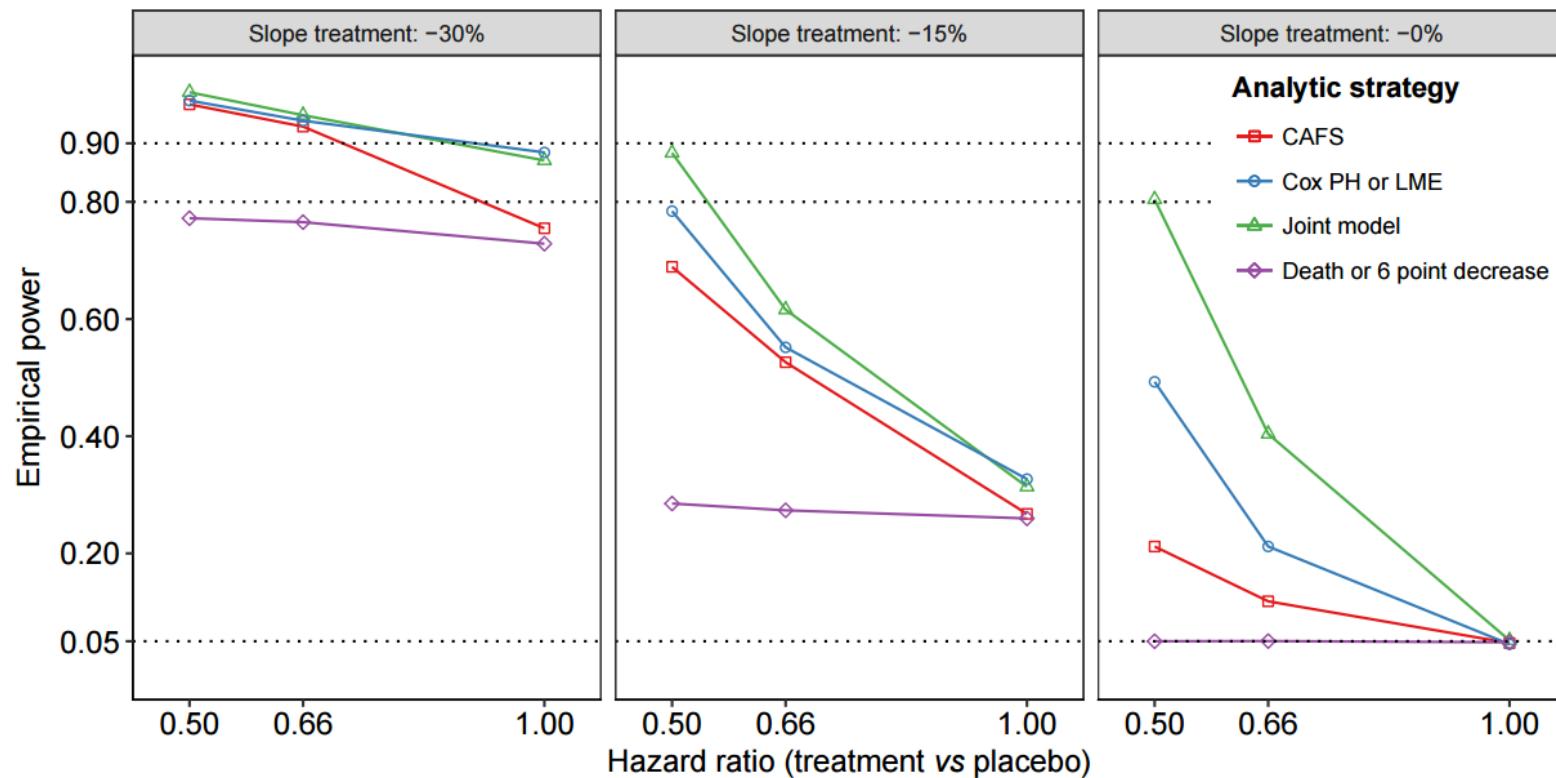
($0.0253 = \text{Šidák-correction for multiple testing}$)



Simulation study PRO-ACT database (n = 1469)



Nine different treatment scenarios



$N = 150$ per arm

Monthly follow-up for 18 months

Joint models can increase emp. power

.... also over classical methods, i.e.:

Pure survival benefit (HR 0.67), 80% power, sample size:

- Cox PH **1282** patients
- CAFS **3922** patients
- JM test **800** patients

Conclusions

1. Joint models are highly consistent across scenarios
2. Classical methods may miss important treatment effects
3. Joint models may circumvent pitfalls encountered by other combining strategies
4. Joint model test could be easily applied in other fields



UMC Utrecht

Personalized prediction of survival in ALS patients



University Medical Center Utrecht

Objective

- Prediction of survival in individual patients



Objective

- Prediction of survival in individual patients
- Advantages:
 - Personalized medicine
 - Timing of interventions
 - Stratification in trials
 - Identification of subgroups and population differences



Variable selection

- **Clinical:** gender, site of onset, age at onset, definite ALS, diagnostic delay, forced vital capacity, ALSFRS slope, premorbid BMI, current smoking and cigarette pack years
- **Cognitive:** FTD, VFI, FAB, ALSFTD-Q
- **Genetic:** C9orf72 repeat expansion, UNC13A (C/C)



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Collaborators & participants

Country, PI	N
Belgium, Philip van Damme	833
France, Phillippe Corcia	190
France, Phillippe Couratier	202
Germany, Albert Ludolph	443
Germany, Julian Großkreutz	343
Germany, Susanne Petri	506
Italy, Adriano Chiò	1022
Country, PI	N
Ireland, Orla Hardiman	1818
Portugal, Mamede de Carvalho	594
Switzerland, Markus Weber	286
The Netherlands, Leonard	1936
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Total

9 counties

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14 datasets

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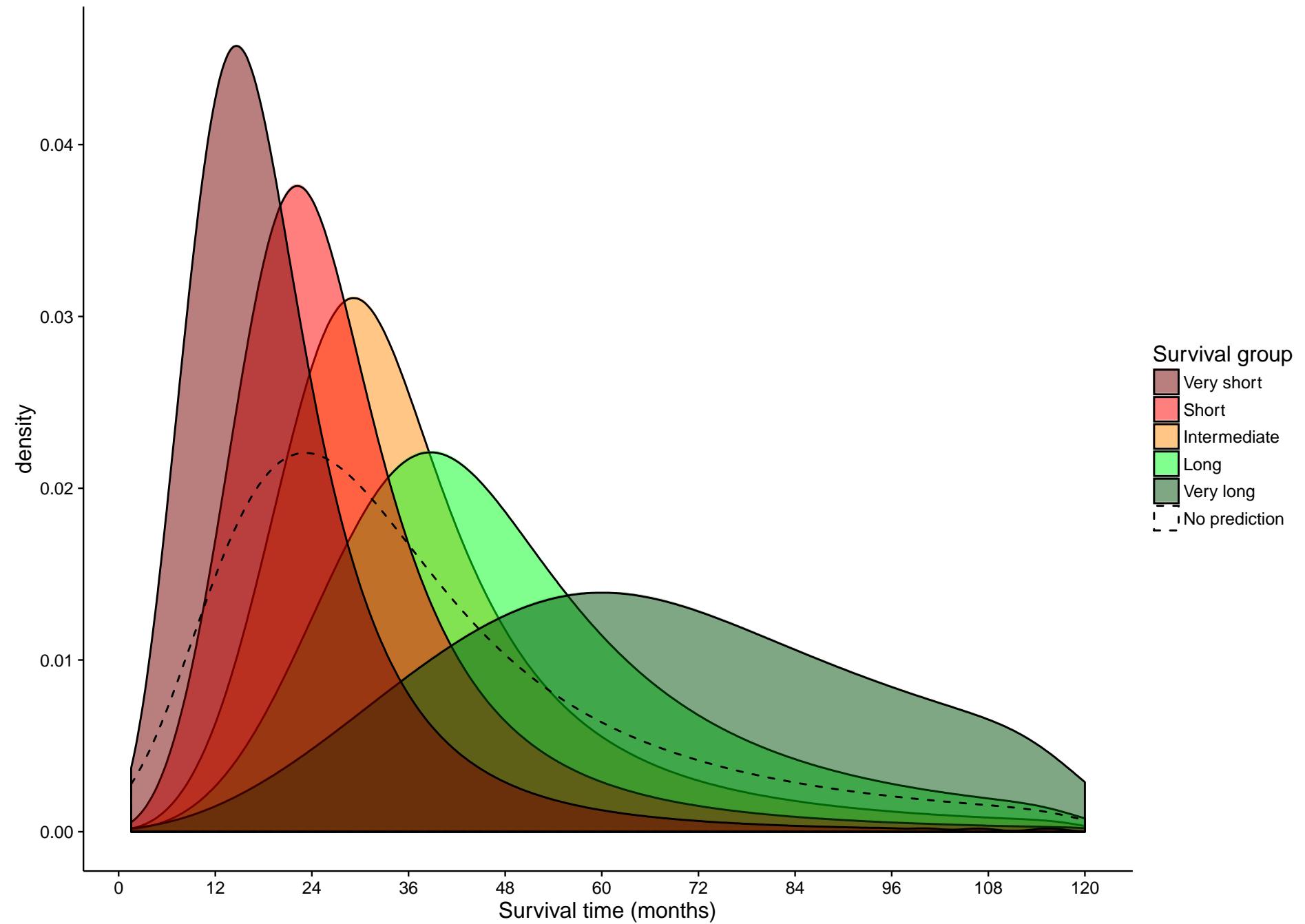
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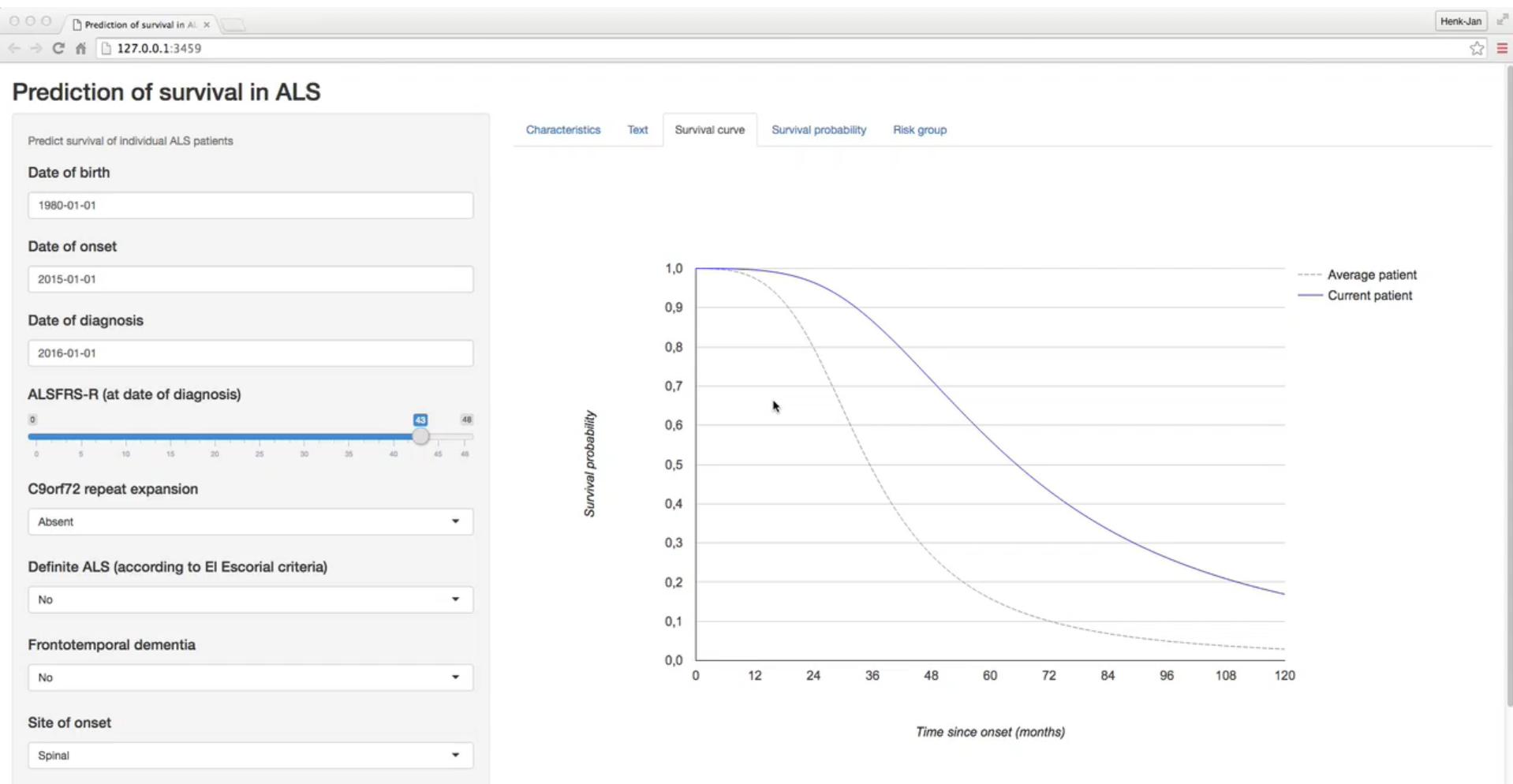
9 counties

14 datasets

11475 patients



Survival prediction tool



Conclusion

- Prediction of survival of individual ALS patients based on 8 different clinical, cognitive and genetic markers is:
 - Reliable
 - Generalizable
 - Easy (with online tool)

