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Title: Overall survival in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study

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Abstract: Summary
Background:
Spinocerebellar ataxias (SCAs) are dominantly inherited progressive ataxia disorders that can lead to premature death. We aimed to study the overall survival of the most common spinocerebellar ataxias: SCA1, SCA2, SCA3, and SCA6. We also aimed to identify the strongest contributing predictors that influence overall survival.
Methods:
In this longitudinal cohort study (EUROSCA), we enrolled men and women, aged 18 years or older, with positive genetic test results for SCA1, SCA2, SCA3, or SCA6 and progressive, otherwise unexplained, ataxias from 17 ataxia referral centers in ten European countries. Survival was defined as the time from enrollment to death for any reason. We used the Cox regression model adjusted for age at baseline to analyze survival. We used prognostic factors with P < 0*05 from multivariate model to build nomograms and assessed their performance based on discrimination and calibration. This study is registered with ClinicalTrials.gov, number NCT02440763.
Findings:
Between July 1, 2005, and Aug 31, 2006, 525 patients with SCA1, SCA2, SCA3, or SCA6 were enrolled and followed. The 10-year survival rate was 57% (95 %CI: 47 - 69) for SCA1, 74% (67 - 81) for SCA2, 73% (65 - 82) for SCA3, and 87% (80 - 94) for SCA6. Factors associated with shorter survival were dysphagia (HR: 4*52 [95%CI=1*83 - 11*15]) and a higher value for the scale for the assessment and rating of ataxia (SARA) score (1*26 [1*19 - 1*33]) for SCA1; older age at inclusion (1*04 [1*01 - 1*08]), longer CAG repeat number (1*16 [1*03 - 1*31]), and higher SARA score (1*15 [1*10 - 1*20]) for SCA2; older age at inclusion (1*44 [1*20 - 1*74]), dystonia (2*65 [1*21 - 5*53]), higher SARA score (1*26 [1*17 -

1*35]), and negative interaction between CAG and age at inclusion (0*994 [0*991 - 0*997]) for SCA3; and higher SARA score (1*17 [1*08 - 1*27]) for SCA6. The nomogram-predicted probability of 10-year survival showed good discrimination (c-index equal to 0*905 ± 0*027, 0*822 ± 0*032, 0*891 ± 0*021 and 0*825 ± 0*054 for SCA1, 2, 3, and 6, respectively) and excellent calibration: in each genotype, the predicted probability of five- and 10-year survival was very close to the actual observed survival.
Interpretation:
Our study provides quantitative data on the survival of the most common spinocerebellar ataxias based on a follow-up period that exceeds those of the previous studies. These results have substantial implications for the design of future interventional studies of SCA; the prognostic survival nomogram would be useful for patient selection and stratification but need validation in external population.
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Keywords: EUROSCA study, spinocerebellar ataxia, survival data, prognosis factors, nomogram.

Summary

Background:

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Interpretation:

Our study provides quantitative data on the survival of the most common spinocerebellar ataxias based on a follow-up period that exceeds those of the previous studies. These results have substantial implications for the design of future interventional studies of SCA; the prognostic survival nomogram would be useful for patient selection and stratification but need validation in external population.

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Panel: Research in context

Evidence before this study

We searched PubMed using the search terms [“spinocerebellar ataxia” OR “dominant ataxia” OR “Machado-Joseph disease” AND “survival”] for reports published before October 31, 2017. Only peer-reviewed, English-language reports of studies performed in patients were considered. Four studies were identified: two were restricted to a single genotype (SCA2 and SCA3), the third focused on index cases with known SCA mutations and affected parents of SCA and analyzed SCAs due to polyglutamine expansion as a group, and the last was an international retrospective study with short follow-up. These studies were very heterogeneous in terms of design, population follow-up, and methods. Few predictors of death were identified: gender, year of birth, age at onset and repeat lengths of the expanded allele.

Added value of this study

In this European, multicenter, longitudinal study (EUROSCA) we prospectively investigated a large cohort of patients with SCA1, SCA2, SCA3, and SCA6 for 10 years. Survival rates differed with respect to genotype. A higher SARA score at baseline was associated with shorter survival for all genotypes. Nomograms constructed from these data allowed precise prediction of survival on an individual basis.

Implications of all available evidence

The available data provide quantitative information on overall survival of patients with SCA1, SCA2, SCA3, and SCA6, and allowed the identification of predictors of survival. The prognostic nomograms will help researchers to optimize the design of future clinical trials and need validation in external population to assist clinicians in counseling patients and their families.

Introduction

Spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of dominantly inherited autosomal progressive ataxia disorders. Several genetically distinct SCAs have been defined, the most common being SCA1, SCA2, SCA3, and SCA6. They are caused by translated CAG repeat expansions that code for elongated polyglutamine tracts within the various proteins associated with each type. In addition, there are SCAs caused by non-translated repeat expansions or conventional mutations. Clinically, they are characterized by progressive balance problems and incoordination, with onset most commonly during adulthood, that lead to severe disability and premature death.[1]

Although life expectancy of SCA patients with these subtypes is substantially reduced, there are only a few studies that have estimated survival or identified factors that influence survival. Significantly decreased survival associated with CAG repeat number, age at onset, and year of birth was observed for Brazilian SCA3 patients.[2] Similar findings were obtained for Cuban SCA2 patients, except for the effect of year of birth on survival.[3] A recent study of 446 index cases with known SCA mutations and 509 affected relatives reported a lower age of death in patients with polyglutamine expansion than in those with other types of mutations.[4] In addition, among the polyglutamine SCA cases, survival was significantly shorter for patients with SCA1 than those with SCA2, SCA3, SCA6, or SCA7.[4]

The EUROSCA natural history study is a European multicenter longitudinal cohort study of patients with SCA1, SCA2, SCA3, and SCA6. It was initiated in 2005 with the goal of characterizing the natural history of the disease and identifying prognostic factors. We recorded phenotypical differences between genotypes at baseline and identified factors that determined disease severity. Analyses of longitudinal data after two[5] and eight[6] years allowed us to establish genotype-specific progression rates and identify factors that determine the course of the disease. In this study, we report survival data of the EUROSCA participants based on an observational period of 10 years. The aim of this study was to (a) quantify overall survival of patients with SCA1, SCA2, SCA3, or SCA6, (b) identify prognostic factors that influence survival, and (c) develop a prognostic model that allows prediction of individual survival based on genetic and clinical characteristics.

Methods

Study design and population

The study population consisted of 525 SCA patients recruited from the longitudinal multicenter (17 European centers) EUROSCA prospective cohort study[7] between July 1, 2005 and Aug 31, 2006. Patients were identified with the help of an electronic patient registry that contained data for all patients with spinocerebellar ataxias who had been in contact with one of the study centers. These patients suffered from progressive, otherwise unexplained, ataxia and had a positive molecular genetic test for SCA1 (n = 117), SCA2 (n = 162), SCA3 (n = 139), or SCA6 (n = 107). Assessments were performed according to a written study protocol. Patients were seen at baseline and followed by annual visits for three years. Afterwards, study participants entered an extension phase in which study assessments were performed during routine visits, resulting in irregular intervals between the visits. The database was locked in November 03, 2016, after a maximum observation period of 11 years. The ethics committees of the participating centers approved the study. Written informed consent was obtained from all study participants at enrollment.

Outcome and predictor variables

The clinical outcome was overall survival. We updated the vital status available in the electronic EUROSCA patient registry to avoid survival bias. Thus, we retrieved the updated vital status from the electronic database when available, through interviews of family members, and by interrogation of records from civil registry offices when feasible. As candidate predictors we selected gender, age at onset and repeat lengths of the expended alleles which have been reported as predictors of death in previously published studies.[2-4] As additional candidates, we selected disease duration, and factors that characterize the neurological phenotype (SARA, INAS, individual non-ataxia signs), mood (PHQ-9) and physical state (BMI, disease stage) of the study participants. "Any use of physiotherapy" was included, because it is the only known therapeutic intervention in ataxia. The complete list of candidate predictors is given in table 1 of the appendix. Demographical data included age, age at ataxia onset, gender, disease duration, disease stage at enrollment, and use of physiotherapy at any time. Body mass index (BMI) at baseline was calculated using the formula [weight/height^2]. Scores on the scale for the assessment and rating of ataxia (SARA)[7], total scores on the inventory of non-ataxia signs (INAS, 0-16), and individual non-ataxia signs, as given in the INAS, including reported abnormalities, such as dysphagia and double vision,[8] were recorded at baseline. To assess the severity of depressive symptoms, the depression scale of the Patient Health Questionnaire (PHQ-9) was used. [9] The PHQ-9 is a 9-item self-rating questionnaire that simply scores each of the nine DSM-IV criteria for depressive disorders. The severity of depression is calculated by assigning scores of 0, 1, 2, and 3, to the response categories "not at all", "several days", "more than half the days" and "nearly every day" respectively. The sum score ranges from 0 (absence of depression) to 27 (severe depression). Repeat lengths of the expanded and normal alleles were determined at the Institute of Medical Genetics and Applied Genomics of the University of Tubingen (Tubingen, Germany).

Data analysis

Mean (standard deviation) or frequencies (percentages) were used to describe the continuous and categorical variables at baseline. Survival was calculated from the date of enrollment to death for any reason. Data for patients who were alive or lost to follow-up were censored. Time from enrollment was used as the time scale. Survival was estimated using the Kaplan-Meier method and compared using a log-rank test. Cox- proportional-hazard models adjusted for age at baseline were used to study prognostic factors, and then candidates with P <0.10 were entered in to the multivariate Cox regression. The strongest contributing predictors for death from multivariate regression were selected through backward procedure based on the lowest Akaike information criterion (AIC). Because the backward selection models heavily relies on statistical significance which in turn depends on statistical power, we computed a posteriori statistical power to highlight an increase in the risk of death of 2 (HR = 2) for any binary variable with a proportion of patient of 50% in each group. Subsequent analyses were performed separately for each genotype, as survival differed between genotypes. Assumptions of hazard proportionality and log-linearity were verified.

A nomogram that included the selected prognostic factors was constructed from each final Cox model to estimate the probability of survival after five and 10 years. A raw prognostic score was computed by summing the contribution of each individual factor, based on the points given for each factor in the nomogram. We divided the patients of each genotype into three prognostic risk groups to provide a reasonable spread of risk. Thus, various cut-offs for the risk score were explored based on the optimal cut-off using the three-risk group approach.[9] The distribution of 55%, 25%, and 20% for prognostic risk group 1 (*good prognosis*), 2 (*intermediate prognosis*), and 3 (*poor prognosis*), respectively, was used, as they were the most discriminative relative to the *c*-index (appendix). We performed calibration plots and computed the discrimination *c*-index to assess the performance of the nomograms. One thousand random samples of the population were used to derive the 95% confidence interval bootstrap percentile for the *c*-index. [11,12] The multivariate model was internally validated using the 1,000-samples bootstrap procedure.

All data analyses were performed using SAS version 9·4 (SAS institute) and the R package. Values of $P < 0{\cdot}05$ were considered to be statistically significant and all tests were two-sided.

Role of the funding source

The sponsors of the study had no role in the design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results:

Between July 1, 2005, and Aug 31, 2006, we enrolled 525 patients with SCA1, SCA2, SCA3, or SCA6. Table 1 shows the clinical and demographical data. During the follow-up, 66 (13%) patients were lost to follow-up and 121 (23%) died: 36 (31%) with SCA1, 38 (24%) with SCA2, 34 (25%) with SCA3, and 13 (12 %) with SCA6. The causes of death were reported for 47% (57/121) of cases. Among them, pulmonary diseases (pneumonia or pulmonary insufficiency) were the most frequent (six in SCA1, four in SCA2, seven in SCA3, and one in SCA6), followed by unknown causes (three in SCA1, three in SCA2, six in SCA3, and two in SCA6), cardiac (five in SCA3 and three in SCA6), cancer (one in SCA1, two in SCA2, and three in SCA6), sepsis/cachexia (one in SCA1, one in SCA2, and two in SCA6), gastric (two in SCA2), suicide (one in SCA1 and one in SCA2), stroke (one in SCA2 and one in SCA3), and renal (one in SCA2).

The five-year survival rate was 80% (95% CI: 72 – 88) for SCA1, 87% (95% CI: 82 – 93) for SCA2, 87% (95% CI: 82 – 93) for SCA3, and 98% (95% CI: 95 – 100) for SCA6. The corresponding 10-year survival rate was 57% (95% CI: 47 – 69), 74% (95% CI: 67 – 81), 73% (95% CI: 65 – 82), and 87% (95% CI: 80 – 94). Overall, survival was significantly different between SCAs (figure 1, $p = 0{\cdot}0002$). The risk of death was higher for SCA1 (HR: 3·79, 95% CI: 2·01 – 7·15), SCA2 (HR: 2·13, 95% CI: 1·13 – 4·00), and SCA3 (HR: 2·46, 95% CI: 1·30 – 4·66) than SCA6· Moreover, the risk of death for SCA1 was higher than that for SCA2 (HR: 1·80, 95% CI: 1·14 – 2·8) or SCA3 (HR: 1·63, 95% CI: 1·02 – 2·61), whereas it was similar between SCA2 and SCA3 (HR: 0·91, 95% CI: 0·57 – 1·44).

We applied univariate Cox regression modeling adjusted for age at baseline to identify predictors for death for each genotype. For SCA1, 19 of 28 evaluated predictors were associated with survival (appendix): CAG repeat number, age at onset, disease duration, BMI, disease stage, PHQ9 sum score, SARA score, number of non-ataxia signs, and the following individual non-ataxia signs: areflexia, paresis, muscle atrophy, fasciculation, myoclonus, chorea/dyskinesia, dystonia, resting tremor, urinary dysfunction, cognitive impairment and dysphagia (appendix). A predictive model obtained from the multivariate Cox analysis, adjusted on age at baseline identified two strongest contributing risk factors for death (table 2): dysphagia (HR: 4·52, 95% CI: 1·83 – 11·15; $p = 0{\cdot}0011$) and higher SARA score (HR: 1·26, 95% CI: 1·19 – 1·33; $p < 0{\cdot}0001$).

For SCA2, the significant predictors in the univariate analysis were CAG repeat number, age at onset, disease duration, disease stage, SARA score, number of non-ataxia signs, and the following individual non-ataxia signs: paresis, muscle atrophy, fasciculation, myoclonus, rigidity, chorea/dyskinesia, dystonia and cognitive impairment (appendix). The strongest contributing risk factors for death (table 2) were older age at inclusion (HR: 1·04, 95% CI: 1·01 – 1·08; $p = 0{\cdot}0130$), longer CAG repeat number (HR: 1·16, 95% CI: 1·03 – 1·31; $p = 0{\cdot}0158$), and higher SARA score (HR: 1·15, 95% CI: 1·10 – 1·20; $p < 0{\cdot}0001$).

For SCA3, CAG repeat number, age at onset, disease duration, disease stage, PHQ9 sum score, SARA score, number of non-ataxia signs, and the following individual non-ataxia signs: extensor plantar signs, spasticity, paresis, muscle atrophy, fasciculation, rigidity, chorea/dyskinesia, dystonia and brainstem oculomotor were significant predictors of death in the univariate analysis (appendix). The strongest contributing risk factors (table 2) were older age at inclusion (HR: 1·44, 95% CI: 1·20 – 1·74; $p = 0{\cdot}0001$), dystonia (HR: 2·65, 95% CI: 1·21 – 5·53; $p = 0{\cdot}0151$), higher SARA score (HR: 1·26, 95% CI: 1·17 – 1·35; $p < 0{\cdot}0001$), and a negative interaction between CAG repeat number and age at inclusion (HR: 0·994, 95% CI: 0·991 – 0·997; $p < 0{\cdot}0001$). Patients with CAG-expanded alleles with less than 62 repeats had a higher risk of death for older age at inclusion, whereas those with more than 62 repeats had a higher risk of death for younger age at inclusion, independently of the severity of the disease. In addition, there was an age-dependent effect on the risk of death associated with CAG-expanded alleles: the older the age at baseline, the weaker the effect of CAG-expanded alleles on the risk of death, and conversely, the younger the age at baseline, the stronger the effect.

In SCA6, disease stage, SARA score and rigidity were significantly associated with survival in Cox univariate analyses, whereas urinary dysfunction ($p = 0{\cdot}06$) and cognitive impairment ($p = 0{\cdot}07$) were borderline (appendix). The only contributing risk factor for death was a higher SARA score (HR: 1·17, 95% CI: 1·08 – 1·27; $p = 0{\cdot}0001$) (table 2).

A posteriori statistical power to highlight an increase in the risk of death of 2 (HR = 2) for any binary variable with a proportion of patient of 50% in each group was 55%, 58%, 53% and 24% for SCA1, 2, 3 and 6 respectively.

We built nomograms that included all selected factors from the final Cox models to predict the probability of five- and 10-year survival for each genotype (appendix). The nomograms showed that the SARA score contributed the most strongly to the prognosis for SCA1, SCA2, and SCA6, whereas age at baseline and its interaction with CAG were the strongest factors for SCA3. The number of CAG repeats and age at baseline had a moderate impact on the survival of SCA2 patients, whereas dysphagia and dystonia had a low impact on the survival of SCA1 and SCA3 patients,

respectively. A raw score was computed from the nomograms, and the patients were classified into three risk categories: *good, intermediate*, and *poor prognosis* based on the thresholds defined in the appendix. For example, a 50-year-old SCA1 patient (3 points) with dysphagia (17 points) and a SARA score of 20 (50 points) has 70 points, placing him in the *intermediate* group with a probability of five and 10-year survival of 80% (95% CI 73 – 87) and 5% (95% CI 1 – 9), respectively (appendix).

The prognostic nomograms had good discriminatory capacity for all SCAs (appendix). The adjusted nomograms *c-index* for predicting death at 10 years was 0·905 ± 0·027, 0·822 ± 0·032 0·891 ± 0·021 and 0·825 ± 0·054 for SCA1, 2, 3, and 6, respectively. Moreover, the Kaplan-Meier curves of the three stratification risk groups were clearly separated (figure 2). The calibration plots showed excellent agreement between the nomogram prediction and the actual predicted probability of five- and 10-year survival (appendix). The uncertainties measured by the bootstrapping procedure in the internal validation were close to the estimated HR, except for a slight deviation for the dysphagia parameter in SCA1 patients (table 2), suggesting robustness of the final model.

Discussion:

This study provides data on the overall survival of patients suffering from SCA1, SCA2, SCA3, or SCA6, based on 10-year longitudinal findings of the EUROSCA cohort. Strengths of our study include the large number of patients and the prospective design of the study. The 10-year observational period may appear to be short, given an estimated survival of SCA patients of 20 to 30 years after ataxia onset.[4,13] However, the average disease duration of study participants at inclusion was 10 years. Thus, we followed the patients up to an average of 20 years after ataxia onset. The information on vital status in the study database was incomplete, because most of the deceased patients had not attended the study centers in the years before death. We therefore used alternative approaches, including interviews of family members and records from civil registry offices to update the information on vital status. This allowed us to recover 40% (49/121) of the deaths and reduced the bias due to censorship, which is one of the major sources of bias in survival analyses. The other possible sources of bias were the bias due to the omission of a balanced covariate and the missing of a covariate being a confounder.[13] We were unable to consider all potential covariates in our model. For example, clinical signs other than those assessed by the used scales, imaging and biomarker data were not available.

In survival analysis, there is an ongoing debate on the choice of the optimal time scale. In this study, we used time-on-study rather than disease duration or chronological age as the time scale. Various simulation studies[14–16] have shown the time-on-study time scale, adjusted for age at inclusion, to be the best as it is the most robust against misspecification (small bias) and is more suitable than other time scales to measure predictive discrimination, such as the time-dependent Area Under the Curve (AUC). We compared the different time scales to choose the most appropriate for our data. Our empirical results agreed with the simulation studies in that the time-on-study was the best.

Survival was shortest for SCA1, intermediate for SCA2 and SCA3, and longest for SCA6. These results corroborate the finding reported by Monin *et al.*[4] that the age at death was lower in SCA1 than in other SCAs due to polyglutamine expansions. These findings characterize SCA1 as the disease with the least favorable prognosis among the polyglutamine SCAs. Correspondingly, two longitudinal studies found that the progression of ataxia severity in SCA1 was faster than in SCA2, SCA3, or SCA6.[5,6,17] The 10-year death rate of the SCA2 patients of our cohort (24%) was lower than that of a Cuban SCA2 cohort (29%). Similarly, the death rate for SCA3 (25%) was lower than that of a Brazilian cohort (35%). Possible reasons for these discrepancies are selection bias, genetic background, and differences between health care systems.

We used Cox regression modelling to identify predictors for death in each genotype. For SCA1 patients, ataxia severity measured with SARA and the presence of dysphagia increased the risk of death. These findings are contrary to the results of an international retrospective study.[12] However, this study used different time scales and did not include clinical findings in the statistical models. For SCA2, the risk of death increased with older age at inclusion, longer CAG repeat number, and severity of ataxia. Longer CAG repeats were similarly found to be a risk factor for death in a Cuban SCA2 cohort.[3] We were unable to confirm the effect of being female on death that was reported in the international retrospective study.[12] For SCA3, predictors of shorter survival identified by univariate Cox analysis, such as early age of onset and long CAG repeat length, overlapped with factors reported in the Brazilian SCA3 study.[2] None of the previous studies reported predictors for the risk of death in SCA6 patients. We found that only the severity of ataxia at baseline affected survival. The finding that the severity of ataxia at baseline measured with SARA was a predictor of survival in all genotypes underlines the clinical relevance and predictive power of SARA. In our analysis, we failed to find an effect on of physiotherapy on survival, although previous studies had shown a temporary symptomatic effect.[19,20] We do not exclude to have missed some risk factors due to lack of power.

Nomograms are widely used prognostic tools in various fields of medicine. For example, there are nomograms that allow prediction of lymph node metastasis in cancer patients. These nomograms may assist physicians in decisions on surgical management. [22–24] More recently, a prognosis nomogram was developed to predict individual outcomes after antiepileptic drug withdrawal in people with epilepsy. [25]One main limit of the nomogram is that it assumes that outcomes remain constant over time. Consequently, its accuracy becomes less good over time probably because of changes in natural history of the disease, early diagnosis detection and improvements in therapy. [21] We constructed nomograms for each genotype that allowed predicting individual survival with high precision based on a number of easily accessible factors identified in the Cox models. Nomograms were constructed in a rigorous methodological framework, including the choice of the candidate predictors and time scale.[16] The nomograms had good discriminatory capacity, and there was excellent agreement between the nomogram prediction and actual survival. DR Cox proposed to use the following distribution: 27%, 49·5%, and 27%, when categorizing the prognostic score in three groups.[10] This distribution was not appropriate for our data, as we had a large number of patients with good prognoses. We chose the distribution that optimized the separation of the Kaplan Meier curves and thus retained the distribution with the largest *c*-index (appendix). However, the nomograms need to be externally validated on independent samples including non-

European patients to determine the generalizability of the model.[10,11] They may be further improved by the incorporation of imaging data and biomarkers.

Our data extend the knowledge of the biological characteristics of SCA1, SCA2, SCA3, and SCA6. The nomograms are easy-to-use tools that may facilitate selection and stratification of patients for future clinical trials.

Contributors

ADi designed and executed the statistical analysis, and wrote the first draft of the report and reviewed the report; HJ and TS-H contibuted to the conception, organisation, and execution of the research project and reviewed and commanted on the statistical analysis and the report; AC, RL, ADu, AB, PC, CeM, CaM, LN, MarP, MR, ASo, ASu, LS, HH, BM, AF, AA, JI, JB, BPvdW, DT, SB, MP, JBS, PB, PG and K-JS organised and did the research project and reviewed and commented on the statistical analysis and the report; TK conceived, organised, and did the research project, and designed, reviewed, and commanted on the statistical analysis and wrote the first draft of the report and reviewed the report; STdM contibuted to the conception of the research project wrote the first draft of the report and reviewed the report.

Declaration of interests

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Table 1: Population characteristics at baseline

	SCA1 (n=117)	SCA 2 (n=162)	SCA 3 (n=139)	SCA 6 (n=107)
Gender (n, %male)	71 (61)	74 (46)	73 (53)	58 (54)
Age (years)	46·3 ± 12·2	46·4 ± 13·3	48·8 ± 11·8	65·0 ± 10·9
Age at onset (years)	36·7 ± 10·4	35·2 ± 12·5	37·0 ± 11·3	54·3 ± 10·6
Disease duration (years)	9·5 ± 5·7	11·1 ± 6·0	11·7 ± 6·0	10·7 ± 6·9
Number of CAG repeats	47·6 ± 5·6	39·4 ± 3·5	69·1 ± 4·6	22·5 ± 2·2
BMI (kg/m^2)	24·4 ± 4·1	25·1 ± 4·3	23·1 ± 4·0	25·7 ± 4·1
SARA score	15·6 ± 9·1	15·7 ± 8·0	15·1 ± 8·5	15·2 ± 6·8
PHQ-9 sum score	6·7 ± 6·4	5·5 ± 4·9	6·9 ± 6·2	5·3 ± 5·4
Any physiotherapy use (yes)	43 (37)	75 (46)	75 (54)	51 (48)
Number of non-ataxia signs	4·8 ± 2·2	4·2 ± 2·2	4·9 ± 2·6	1·9 ± 1·6
Death (n, % yes)	36 (31)	38 (24)	34 (25)	13 (12)
Median follow-up (years), 95% CI	9·9 (6·9 10·1)	10·2 (10·1 10·3)	10·2 (10·1 10·4)	10·2 (10·1 10·3)

The categorical variable are shown as n (%), the continuous variables as mean (SD). SARA = Scale for the Assessment and Rating of Ataxia. SCA = spinocerebellar ataxia.

Table 2: Multivariate Cox model

				[§]Max score in		Internal validation	
Parameters	**HR**	**95 % CI**	**p-value**	**nomogram**	**Median (IQR)**	**BHR**	**BCI HR 95 %**
SCA1							
Age at baseline (years)	1.01	0.98 1.04	0.53021	6	46 (37 55)	1.003	0.975 1.033
Dysphagia (yes)	4.52	1.83 11.15	**0.00107**	17	0 (1 1)	7.029	1.939 41.81
SARA score	1.26	1.19 1.33	**<.0001**	100	13.5 (8.5 20.5)	1.288	1.201 1.382
SCA2							
Age at baseline (years)	1.04	1.01 1.08	**0.01300**	51	47.5 (37 54)	1.045	1.009 1.082
CAG (number repeats)	1.16	1.03 1.31	**0.01580**	53	39 (37 41)	1.172	1.028 1.337
SARA score	1.15	1.10 1.20	**<.0001**	100	14 (10 19.5)	1.155	1.103 1.210
SCA3							
Age at baseline (years)	1.44	1.20 1.74	**0.0001**	100	48 (40 56)	1.692	1.179 2.486
Dystonia (yes)	2.65	1.21 5.53	**0.0151**	4	0 (0 0)	2.898	1.132 7.341
SARA score	1.26	1.17 1.35	**<.0001**	33	14 (10 20.5)	1.295	1.189 1.406
CAG (number repeats)	1.04	0.89 1.21	0.6501	5	69 (66 72)	1.151	0.867 1.533
Interaction Age*CAG	0.994	0.991 0.997	**<.0001**	86	3328 (2850 3776)	0.993	0.988 0.998
SCA6							
Age at baseline (years)	1.02	0.95 1.08	0.6426	14	67 (58 73)	1.018	0.947 1.096
SARA score	1.17	1.08 1.27	**0.0001**	100	14 (10.5 19)	1.187	1.080 1.306

HR: hazard ratio, CI: confidence interval, BHR: bootstrap hazard ratio, BCI: bootstrap confidence interval; [§]Maximum number for the highest observed value attributed by a nomogram for each predictor.

Main figures:

Figure 1: Overall survival from enrollment according to genotype

Figure 2: Overall survival from enrollment according to the characterization score from nomograms by genotype

Appendix

Figure 1: Prognostic nomograms to predict the probability of individual overall survival of patients with spinocerebellar ataxia type 1, 2, 3, and 6.

Points are assigned to each risk factor by drawing a line upward from the corresponding value to the 'Points' line. The total sum point for the three factors is plotted on the 'Total points' line. A line is drawn down to read the corresponding predictions of the probability of five- and 10-year survival.

For example, a 50-year-old SCA1 patient (3 points) with dysphagia (17 points) and a SARA score of 20 (50 points) has 70 points (3 + 17 + 50), placing him in the *intermediate* group with a probability of five- (blue line) and 10-year (red line) survival of 80% and 5%, respectively.

Figure 2: Calibration plots for predicting ataxia patient overall survival at each time point by genotype.

The X-axis shows the nomogram predicted probability of survival. Patients were grouped by quartiles of predicted risk. The Y-axis is the actual probability of five- (blue) and 10-year (red) survival estimated by the Kaplan-Meier method. The solid line represents the values from the nomograms with their 95% CI. A plot along a 45-degree line (dotted line) would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes.

Table 1: Univariate Cox model in SCAs of the 28 potential predictors of death

Table 2: Various range and threshold prognostic score computed from nomograms

Table 3: Discrimination measures and β estimates with their SE from the Cox model

Table 4: Individual non-ataxia signs characteristics at baseline

Table 5: Predicted probability and actual observed survival of five- and 10-year

Overall survival in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study

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Keywords: EUROSCA study, spinocerebellar ataxia, survival data, prognosis factors, nomogram.

Summary

Background:

Spinocerebellar ataxias (SCAs) are dominantly inherited progressive ataxia disorders that can lead to premature death. We aimed to study the overall survival of the most common spinocerebellar ataxias: SCA1, SCA2, SCA3, and SCA6. We also aimed to identify the strongest contributing predictors that influence overall survival.

Methods:

In this longitudinal cohort study (EUROSCA), we enrolled men and women, aged 18 years or older, with positive genetic test results for SCA1, SCA2, SCA3, or SCA6 and progressive, otherwise unexplained, ataxias from 17 ataxia referral centers in ten European countries. Survival was defined as the time from enrollment to death for any reason. We used the Cox regression model adjusted for age at baseline to analyze survival. We used prognostic factors with $P <$ 0·05 from multivariate model to build nomograms and assessed their performance based on discrimination and calibration. This study is registered with ClinicalTrials.gov, number NCT02440763.

Findings:

Between July 1, 2005, and Aug 31, 2006, 525 patients with SCA1, SCA2, SCA3, or SCA6 were enrolled and followed. The 10-year survival rate was 57% (95 %CI: 47 – 69) for SCA1, 74% (67 – 81) for SCA2, 73% (65 – 82) for SCA3, and 87% (80 – 94) for SCA6. Factors associated with shorter survival were dysphagia (HR: 4·52 [95%CI=1·83 – 11·15]) and a higher value for the scale for the assessment and rating of ataxia (SARA) score (1·26 [1·19 – 1·33]) for SCA1; older age at inclusion (1·04 [1·01 – 1·08]), longer CAG repeat number (1·16 [1·03 – 1·31]), and higher SARA score (1·15 [1·10 – 1·20]) for SCA2; older age at inclusion (1·44 [1·20 – 1·74]), dystonia (2·65 [1·21 – 5·53]), higher SARA score (1·26 [1·17 – 1·35]), and negative interaction between CAG and age at inclusion (0·994 [0·991 – 0·997]) for SCA3; and higher SARA score (1·17 [1·08 – 1·27]) for SCA6. The nomogram-predicted probability of 10-year survival showed good discrimination (*c-index* equal to 0·905 ± 0·027, 0·822 ± 0·032, 0·891 ± 0·021 and 0·825 ± 0·054 for SCA1, 2, 3, and 6, respectively) and excellent calibration: in each genotype, the predicted probability of five- and 10-year survival was very close to the actual observed survival.

Interpretation:

Our study provides quantitative data on the survival of the most common spinocerebellar ataxias based on a follow-up period that exceeds those of the previous studies. These results have substantial implications for the design of future interventional studies of SCA; the prognostic survival nomogram would be useful for patient selection and stratification but need validation in external population.

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Panel: Research in context

Evidence before this study

We searched PubMed using the search terms [“spinocerebellar ataxia” OR “dominant ataxia” OR “Machado-Joseph disease” AND “survival”] for reports published before October 31, 2017. Only peer-reviewed, English-language reports of studies performed in patients were considered. Four studies were identified: two were restricted to a single genotype (SCA2 and SCA3), the third focused on index cases with known SCA mutations and affected parents of SCA and analyzed SCAs due to polyglutamine expansion as a group, and the last was an international retrospective study with short follow-up. These studies were very heterogeneous in terms of design, population follow-up, and methods. Few predictors of death were identified: gender, year of birth, age at onset and repeat lengths of the expanded allele.

Added value of this study

In this European, multicenter, longitudinal study (EUROSCA) we prospectively investigated a large cohort of patients with SCA1, SCA2, SCA3, and SCA6 for 10 years. Survival rates differed with respect to genotype. A higher SARA score at baseline was associated with shorter survival for all genotypes. Nomograms constructed from these data allowed precise prediction of survival on an individual basis.

Implications of all available evidence

The available data provide quantitative information on overall survival of patients with SCA1, SCA2, SCA3, and SCA6, and allowed the identification of predictors of survival. The prognostic nomograms will help researchers to optimize the design of future clinical trials and need validation in external population to assist clinicians in counseling patients and their families.

Introduction

Spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of dominantly inherited autosomal progressive ataxia disorders. Several genetically distinct SCAs have been defined, the most common being SCA1, SCA2, SCA3, and SCA6. They are caused by translated CAG repeat expansions that code for elongated polyglutamine tracts within the various proteins associated with each type. In addition, there are SCAs caused by non-translated repeat expansions or conventional mutations. Clinically, they are characterized by progressive balance problems and incoordination, with onset most commonly during adulthood, that lead to severe disability and premature death.[1]

Although life expectancy of SCA patients with these subtypes is substantially reduced, there are only a few studies that have estimated survival or identified factors that influence survival. Significantly decreased survival associated with CAG repeat number, age at onset, and year of birth was observed for Brazilian SCA3 patients.[2] Similar findings were obtained for Cuban SCA2 patients, except for the effect of year of birth on survival.[3] A recent study of 446 index cases with known SCA mutations and 509 affected relatives reported a lower age of death in patients with polyglutamine expansion than in those with other types of mutations.[4] In addition, among the polyglutamine SCA cases, survival was significantly shorter for patients with SCA1 than those with SCA2, SCA3, SCA6, or SCA7.[4]

The EUROSCA natural history study is a European multicenter longitudinal cohort study of patients with SCA1, SCA2, SCA3, and SCA6. It was initiated in 2005 with the goal of characterizing the natural history of the disease and identifying prognostic factors. We recorded phenotypical differences between genotypes at baseline and identified factors that determined disease severity. Analyses of longitudinal data after two[5] and eight[6] years allowed us to establish genotype-specific progression rates and identify factors that determine the course of the disease. In this study, we report survival data of the EUROSCA participants based on an observational period of 10 years. The aim of this study was to (a) quantify overall survival of patients with SCA1, SCA2, SCA3, or SCA6, (b) identify prognostic factors that influence survival, and (c) develop a prognostic model that allows prediction of individual survival based on genetic and clinical characteristics.

Methods

Study design and population

The study population consisted of 525 SCA patients recruited from the longitudinal multicenter (17 European centers) EUROSCA prospective cohort study[7] between July 1, 2005 and Aug 31, 2006. Patients were identified with the help of an electronic patient registry that contained data for all patients with spinocerebellar ataxias who had been in contact with one of the study centers. These patients suffered from progressive, otherwise unexplained, ataxia and had a positive molecular genetic test for SCA1 (n = 117), SCA2 (n = 162), SCA3 (n = 139), or SCA6 (n = 107). Assessments were performed according to a written study protocol. Patients were seen at baseline and followed by annual visits for three years. Afterwards, study participants entered an extension phase in which study assessments were performed during routine visits, resulting in irregular intervals between the visits. The database was locked in November 03, 2016, after a maximum observation period of 11 years. The ethics committees of the participating centers approved the study. Written informed consent was obtained from all study participants at enrollment.

Outcome and predictor variables

The clinical outcome was overall survival. We updated the vital status available in the electronic EUROSCA patient registry to avoid survival bias. Thus, we retrieved the updated vital status from the electronic database when available, through interviews of family members, and by interrogation of records from civil registry offices when feasible. As candidate predictors we selected gender, age at onset and repeat lengths of the expended alleles which have been reported as predictors of death in previously published studies.[2-4] As additional candidates, we selected disease duration, and factors that characterize the neurological phenotype (SARA, INAS, individual non-ataxia signs), mood (PHQ-9) and physical state (BMI, disease stage) of the study participants. "Any use of physiotherapy" was included, because it is the only known therapeutic intervention in ataxia. The complete list of candidate predictors is given in table 1 of the appendix~~From previous studies and available data from the EUROSCA cohort,[6] 28 candidates predictors for death were selected~~. Demographical data included age, age at ataxia onset, gender, disease duration, disease stage at enrollment, and use of physiotherapy at any time. Body mass index (BMI) at baseline was calculated using the formula [weight/height^2]. Scores on the scale for the assessment and rating of ataxia (SARA)[7], total scores on the inventory of non-ataxia signs (INAS, 0-16), and individual non-ataxia signs, as given in the INAS, including reported abnormalities, such as dysphagia and double vision,[8] were recorded at baseline. To assess the severity of depressive symptoms, the depression scale of the Patient Health Questionnaire (PHQ-9) was used. [9] The PHQ-9 is a 9-item self-rating questionnaire that simply scores each of the nine DSM-IV criteria for depressive disorders. The severity of depression is calculated by assigning scores of 0, 1, 2, and 3, to the response categories "not at all", "several days", "more than half the days" and "nearly every day" respectively. The sum score ranges from 0 (absence of depression) to 27 (severe depression). Repeat lengths of the expanded and normal alleles were determined at the Institute of Medical Genetics and Applied Genomics of the University of Tubingen (Tubingen, Germany).

Data analysis

Mean (standard deviation) or frequencies (percentages) were used to describe the continuous and categorical variables at baseline. Survival was calculated from the date of enrollment to death for any reason. Data for patients who were alive or lost to follow-up were censored. Time from enrollment was used as the time scale. Survival was estimated using the Kaplan-Meier method and compared using a log-rank test. Cox- proportional-hazard models adjusted for age at baseline were used to study prognostic factors, and then candidates with P <0.10 were entered in to the multivariate Cox regression. The strongest contributing predictors for death from multivariate regression were selected through backward procedure based on the lowest Akaike information criterion (AIC). Because the backward selection models heavily relies on statistical significance which in turn depends on statistical power, we computed a posteriori statistical power to highlight an increase in the risk of death of 2 (HR = 2) for any binary variable with a proportion of patient of 50% in each group. Subsequent analyses were performed separately for each genotype, as survival differed between genotypes. Assumptions of hazard proportionality and log-linearity were verified.

A nomogram that included the selected prognostic factors was constructed from each final Cox model to estimate the probability of survival after five and 10 years. A raw prognostic score was computed by summing the contribution of each individual factor, based on the points given for each factor in the nomogram. We divided the patients of each genotype into three prognostic risk groups to provide a reasonable spread of risk. Thus, various cut-offs for the risk score were explored based on the optimal cut-off using the three-risk group approach.[9] The distribution of 55%, 25%, and 20% for prognostic risk group 1 (*good prognosis*), 2 (*intermediate prognosis*), and 3 (*poor prognosis*), respectively, was used, as they were the most discriminative relative to the *c*-index (appendix). We performed calibration plots and computed the discrimination *c*-index to assess the performance of the nomograms. One thousand random samples of the

population were used to derive the 95% confidence interval bootstrap percentile for the *c*-index. [11,12] The multivariate model was internally validated using the 1,000-samples bootstrap procedure.

All data analyses were performed using SAS version 9·4 (SAS institute) and the R package. Values of $P < 0{\cdot}05$ were considered to be statistically significant and all tests were two-sided.

Role of the funding source

The sponsors of the study had no role in the design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results:

Between July 1, 2005, and Aug 31, 2006, we enrolled 525 patients with SCA1, SCA2, SCA3, or SCA6. Table 1 shows the clinical and demographical data. During the follow-up, 66 (13%) patients were lost to follow-up and 121 (23%) died: 36 (31%) with SCA1, 38 (24%) with SCA2, 34 (25%) with SCA3, and 13 (12 %) with SCA6. The causes of death were reported for 47% (57/121) of cases. Among them, pulmonary diseases (pneumonia or pulmonary insufficiency) were the most frequent (six in SCA1, four in SCA2, seven in SCA3, and one in SCA6), followed by unknown causes (three in SCA1, three in SCA2, six in SCA3, and two in SCA6), cardiac (five in SCA3 and three in SCA6), cancer (one in SCA1, two in SCA2, and three in SCA6), sepsis/cachexia (one in SCA1, one in SCA2, and two in SCA6), gastric (two in SCA2), suicide (one in SCA1 and one in SCA2), stroke (one in SCA2 and one in SCA3), and renal (one in SCA2).

The five-year survival rate was 80% (95% CI: 72 – 88) for SCA1, 87% (95% CI: 82 – 93) for SCA2, 87% (95% CI: 82 – 93) for SCA3, and 98% (95% CI: 95 – 100) for SCA6. The corresponding 10-year survival rate was 57% (95% CI: 47 – 69), 74% (95% CI: 67 – 81), 73% (95% CI: 65 – 82), and 87% (95% CI: 80 – 94). Overall, survival was significantly different between SCAs (figure 1, p = 0·0002). The risk of death was higher for SCA1 (HR: 3·79, 95% CI: 2·01 – 7·15), SCA2 (HR: 2·13, 95% CI: 1·13 – 4·00), and SCA3 (HR: 2·46, 95% CI: 1·30 – 4·66) than SCA6· Moreover, the risk of death for SCA1 was higher than that for SCA2 (HR: 1·80, 95% CI: 1·14 – 2·8) or SCA3 (HR: 1·63, 95% CI: 1·02 – 2·61), whereas it was similar between SCA2 and SCA3 (HR: 0·91, 95% CI: 0·57 – 1·44).

We applied univariate Cox regression modeling adjusted for age at baseline to identify predictors for death for each genotype. For SCA1, ~~20~~ 19 of 28 evaluated predictors were associated with survival (appendix): CAG repeat number, age at onset, disease duration, BMI, ~~age at onset, disease progression,~~ disease stage, PHQ9 sum score, SARA score, ~~INAS count~~number of non-ataxia signs, and ~~various~~ the following individual non-ataxia signs: ~~including~~ areflexia, ~~extensor plantar,~~ paresis, muscle atrophy, fasciculation, myoclonus, chorea/dyskinesia, dystonia, resting tremor, urinary dysfunction, cognitive impairment and dysphagia (appendix). A predictive model obtained from the multivariate Cox analysis, adjusted on age at baseline identified two strongest contributing risk factors for death (table 2): dysphagia (HR: 4·52, 95% CI: 1·83 – 11·15; p = 0·0011) and higher SARA score (HR: 1·26, 95% CI: 1·19 – 1·33; p < 0·0001).

For SCA2, the significant predictors in the univariate analysis were CAG repeat number, age at onset, disease ~~progression~~duration, disease stage, SARA score, number of non-ataxia signs~~INAS count~~, and the following ~~various~~ individual non-ataxia signs ~~especially pyramidal and peripheral motor symptoms~~: paresis, muscle atrophy, fasciculation, myoclonus, rigidity, chorea/dyskinesia, dystonia and cognitive impairment (appendix). The strongest contributing risk factors for death (table 2) were older age at inclusion (HR: 1·04, 95% CI: 1·01 – 1·08; p = 0·0130), longer CAG repeat number (HR: 1·16, 95% CI: 1·03 – 1·31; p = 0·0158), and higher SARA score (HR: 1·15, 95% CI: 1·10 – 1·20; p < 0·0001).

For SCA3, CAG repeat number, age at onset, disease ~~progression~~duration, disease stage, PHQ9 sum score~~depressive symptom~~, SARA score, number of non-ataxia signs~~INAS score~~, and the following~~various~~ individual non-ataxia signs: ~~including~~ extensor plantar signs, spasticity, paresis, muscle atrophy, fasciculation, rigidity, chorea/dyskinesia, dystonia , ~~,~~ and brainstem oculomotor ~~and dysphagia~~ were significant predictors of death in the univariate analysis (appendix). The strongest contributing risk factors (table 2) were older age at inclusion (HR: 1·44, 95% CI: 1·20 – 1·74; p = 0·0001), dystonia (HR: 2·65, 95% CI: 1·21 – 5·53; p = 0·0151), higher SARA score (HR: 1·26, 95% CI: 1·17 – 1·35; p < 0·0001), and a negative interaction between CAG repeat number and age at inclusion (HR: 0·994, 95% CI: 0·991 – 0·997; p < 0·0001). Patients with CAG-expanded alleles with less than 62 repeats had a higher risk of death for older age at inclusion, whereas those with more than 62 repeats had a higher risk of death for younger age at inclusion, independently of the severity of the disease. In addition, there was an age-dependent effect on the risk of death associated with CAG-expanded alleles: the older the age at baseline, the weaker the effect of CAG-expanded alleles on the risk of death, and conversely, the younger the age at baseline, the stronger the effect.

In SCA6, disease stage, SARA score and rigidity were significantly associated with survival in Cox univariate analyses, whereas urinary dysfunction (p = 0·06) and cognitive impairment (p = 0·07) were borderline (appendix). The only contributing risk factor for death was a higher SARA score (HR: 1·17, 95% CI: 1·08 – 1·27; p = 0·0001) (table 2).

A posteriori statistical power to highlight an increase in the risk of death of 2 (HR = 2) for any binary variable with a proportion of patient of 50% in each group was 55%, 58%, 53% and 24% for SCA1, 2, 3 and 6 respectively.

We built nomograms that included all selected factors from the final Cox models to predict the probability of five- and 10-year survival for each genotype (appendix). The nomograms showed that the SARA score contributed the most strongly to the prognosis for SCA1, SCA2, and SCA6, whereas age at baseline and its interaction with CAG were the strongest factors for SCA3. The number of CAG repeats and age at baseline had a moderate impact on the survival of

SCA2 patients, whereas dysphagia and dystonia had a low impact on the survival of SCA1 and SCA3 patients, respectively. A raw score was computed from the nomograms, and the patients were classified into three risk categories: *good, intermediate*, and *poor prognosis* based on the thresholds defined in the appendix. For example, a 50-year-old SCA1 patient (3 points) with dysphagia (17 points) and a SARA score of 20 (50 points) has 70 points, placing him in the *intermediate* group with a probability of five and 10-year survival of 80% (95% CI 73 – 87) and 5% (95% CI 1 – 9), respectively (appendix).

The prognostic nomograms had good discriminatory capacity for all SCAs (appendix). The adjusted nomograms *c-index* for predicting death at 10 years was 0·905 ± 0·027, 0·822 ± 0·032 0·891 ± 0·021 and 0·825 ± 0·054 for SCA1, 2, 3, and 6, respectively. Moreover, the Kaplan-Meier curves of the three stratification risk groups were clearly separated (figure 2). The calibration plots showed excellent agreement between the nomogram prediction and the actual predicted probability of five- and 10-year survival (appendix). The uncertainties measured by the bootstrapping procedure in the internal validation were close to the estimated HR, except for a slight deviation for the dysphagia parameter in SCA1 patients (table 2), suggesting robustness of the final model.

Discussion:

This study provides data on the overall survival of patients suffering from SCA1, SCA2, SCA3, or SCA6, based on 10-year longitudinal findings of the EUROSCA cohort. Strengths of our study include the large number of patients and the prospective design of the study. The 10-year observational period may appear to be short, given an estimated survival of SCA patients of 20 to 30 years after ataxia onset.[4,13] However, the average disease duration of study participants at inclusion was 10 years. Thus, we followed the patients up to an average of 20 years after ataxia onset. The information on vital status in the study database was incomplete, because most of the deceased patients had not attended the study centers in the years before death. We therefore used alternative approaches, including interviews of family members and records from civil registry offices to update the information on vital status. This allowed us to recover 40% (49/121) of the deaths and reduced the bias due to censorship, which is one of the major sources of bias in survival analyses. The other possible sources of bias were the bias due to the omission of a balanced covariate and the missing of a covariate being a confounder.[13] We were unable to consider all potential covariates in our model. For example, clinical signs other than those assessed by the used scales, imaging and biomarker data were not available~~These are almost inevitable because we were unable to consider all potential covariates in our model. For example, painful muscle cramps, imaging and biomarker data were not available~~.

In survival analysis, there is an ongoing debate on the choice of the optimal time scale. In this study, we used time-on-study rather than disease duration or chronological age as the time scale. Various simulation studies[14–16] have shown the time-on-study time scale, adjusted for age at inclusion, to be the best as it is the most robust against misspecification (small bias) and is more suitable than other time scales to measure predictive discrimination, such as the time-dependent Area Under the Curve (AUC). We compared the different time scales to choose the most appropriate for our data. Our empirical results agreed with the simulation studies in that the time-on-study was the best.

Survival was shortest for SCA1, intermediate for SCA2 and SCA3, and longest for SCA6. These results corroborate the finding reported by Monin *et al.*[4] that the age at death was lower in SCA1 than in other SCAs due to polyglutamine expansions. These findings characterize SCA1 as the disease with the least favorable prognosis among the polyglutamine SCAs. Correspondingly, two longitudinal studies found that the progression of ataxia severity in SCA1 was faster than in SCA2, SCA3, or SCA6.[5,6,17] The 10-year death rate of the SCA2 patients of our cohort (24%) was lower than that of a Cuban SCA2 cohort (29%). Similarly, the death rate for SCA3 (25%) was lower than that of a Brazilian cohort (35%). Possible reasons for these discrepancies are selection bias, genetic background, and differences between health care systems.

We used Cox regression modelling to identify predictors for death in each genotype. For SCA1 patients, ataxia severity measured with SARA and the presence of dysphagia increased the risk of death. These findings are contrary to the results of an international retrospective study.[12] However, this study used different time scales and did not include clinical findings in the statistical models. For SCA2, the risk of death increased with older age at inclusion, longer CAG repeat number, and severity of ataxia. Longer CAG repeats were similarly found to be a risk factor for death in a Cuban SCA2 cohort.[3] We were unable to confirm the effect of being female on death that was reported in the international retrospective study.[12] For SCA3, predictors of shorter survival identified by univariate Cox analysis, such as early age of onset and long CAG repeat length, overlapped with factors reported in the Brazilian SCA3 study.[2] None of the previous studies reported predictors for the risk of death in SCA6 patients. We found that only the severity of ataxia at baseline affected survival. The finding that the severity of ataxia at baseline measured with SARA was a predictor of survival in all genotypes underlines the clinical relevance and predictive power of SARA. In our analysis, we failed to find an effect on of physiotherapy on survival, although previous studies had shown a temporary symptomatic effect.[19,20] We do not exclude to have missed some risk factors due to lack of power.

Nomograms are widely used prognostic tools in various ~~oncology and other~~ fields of medicine. ~~especially in all aspects of the care of patients[18] including patient's selection both in pre or postoperative phase.[22–24]~~ For example, there are nomograms that allow prediction of lymph node metastasis in cancer patients. These nomograms may assist physicians in decisions on surgical management. [22–24] More recently, a prognosis nomogram was developed to predict individual outcomes after antiepileptic drug withdrawal in people with epilepsy. [25]One main limit of the nomogram is that it assumes that outcomes remain constant over time. Consequently, its accuracy becomes less good over time probably because of changes in natural history of the disease, early diagnosis detection and improvements in therapy. [21] We constructed nomograms for each genotype that allowed predicting individual survival with high precision based on a number of easily accessible factors identified in the Cox models. Nomograms were constructed in a rigorous methodological framework, including the choice of the candidate predictors and time scale.[16] The nomograms had good discriminatory capacity, and there was excellent agreement between the nomogram prediction and actual survival. DR Cox proposed to use the following distribution: 27%, 49·5%, and 27%, when categorizing the prognostic score in three groups.[10] This distribution was not appropriate for our data, as we had a large number of patients with good prognoses.

We chose the distribution that optimized the separation of the Kaplan Meier curves and thus retained the distribution with the largest *c*-index (appendix). However, the nomograms need to be externally validated on independent samples including non-European patients to determine the generalizability of the model.[10,11] They may be further improved by the incorporation of imaging data and biomarkers.

Our data extend the knowledge of the biological characteristics of SCA1, SCA2, SCA3, and SCA6. The nomograms are easy-to-use tools that may facilitate selection and stratification of patients for future clinical trials.

Contributors

ADi designed and executed the statistical analysis, and wrote the first draft of the report and reviewed the report; HJ and TS-H contibuted to the conception, organisation, and execution of the research project and reviewed and commanted on the statistical analysis and the report; AC, RL, ADu, AB, PC, CeM, CaM, LN, MarP, MR, ASo, ASu, LS, HH, BM, AF, AA, JI, JB, BPvdW, DT, SB, MP, JBS, PB, PG and K-JS organised and did the research project and reviewed and commented on the statistical analysis and the report; TK conceived, organised, and did the research project, and designed, reviewed, and commanted on the statistical analysis and wrote the first draft of the report and reviewed the report; STdM contibuted to the conception of the research project wrote the first draft of the report and reviewed the report.

Declaration of interests

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Table 1: Population characteristics at baseline

	SCA1 (n=117)	SCA 2 (n=162)	SCA 3 (n=139)	SCA 6 (n=107)
Gender (n, %male)	71 (61)	74 (46)	73 (53)	58 (54)
Age (years)	46·3 ± 12·2	46·4 ± 13·3	48·8 ± 11·8	65·0 ± 10·9
Age at onset (years)	36·7 ± 10·4	35·2 ± 12·5	37·0 ± 11·3	54·3 ± 10·6
Disease duration (years)	9·5 ± 5·7	11·1 ± 6·0	11·7 ± 6·0	10·7 ± 6·9
Number of CAG repeats	47·6 ± 5·6	39·4 ± 3·5	69·1 ± 4·6	22·5 ± 2·2
BMI (kg/m^2)	24·4 ± 4·1	25·1 ± 4·3	23·1 ± 4·0	25·7 ± 4·1
SARA score	15·6 ± 9·1	15·7 ± 8·0	15·1 ± 8·5	15·2 ± 6·8
PHQ-9 sum score	6·7 ± 6·4	5·5 ± 4·9	6·9 ± 6·2	5·3 ± 5·4
Any physiotherapy use (yes)	43 (37)	75 (46)	75 (54)	51 (48)
Number of non-ataxia signs	4·8 ± 2·2	4·2 ± 2·2	4·9 ± 2·6	1·9 ± 1·6
Death (n, % yes)	36 (31)	38 (24)	34 (25)	13 (12)
Median follow-up (years), 95% CI	9·9 (6·9 10·1)	10·2 (10·1 10·3)	10·2 (10·1 10·4)	10·2 (10·1 10·3)

The categorical variable are shown as n (%), the continuous variables as mean (SD). ~~Data are shown as the mean (SD) or n (%).~~ SARA = Scale for the Assessment and Rating of Ataxia. SCA = spinocerebellar ataxia.

Table 2: Multivariate Cox model

Parameters	HR	95% CI	p-value	$Max score in nomogram	*Range	Internal validation BCI HR 95%
SCA1						
Age at baseline (years)	1·01	0·98 1·04	0·53021	6	18 - 76	0·975 1·033
Dysphagia (yes)	4·52	1·83 11·15	**0·00107**	17	0 - 1	1·939 41·81
SARA score	1·26	1·19 1·33	**<·0001**	100	2 - 40	1·201 1·382
SCA2						
Age at baseline years)	1·04	1·01 1·08	**0·01300**	51	18 - 84	1·009 1·082
CAG (number of repeats)	1·16	1·03 1·31	**0·01580**	53	33 - 52	1·028 1·337
SARA score	1·15	1·10 1·20	**<·0001**	100	2 - 39	1·103 1·210
SCA3						
Age at baseline (years)	1·44	1·20 1·74	**0·0001**	100	14 - 81	1·179 2·486
Dystonia (yes)	2·65	1·21 5·53	**0·0151**	4	0 - 1	1·132 7·341
SARA score	1·26	1·17 1·35	**<·0001**	33	1 - 40	1·189 1·406
CAG	1·04	0·89 1·21	0·6501	5	56 - 91	0·867 1·533
Interaction Age*CAG	0·994	0·991 0·997	**<·0001**	86	1200 – 4900	0·988 0·998
SCA6						
Age at baseline (years)	1·02	0·95 1·08	0·64260	14	37 - 85	0·947 1·096
SARA score	1·17	1·08 1·27	**0·0001**	100	1 - 33	1·080 1·306

*Range is the min and max of the corresponding covariate, HR: hazard ratio, CI: confidence interval, BCI: bootstrap confidence interval; $Maximum number attributed by a nomogram for each predictor.

Parameters	HR	95 % CI	p-value	$Max score in nomogram	Median (IQR)	Internal validation BHR	BCI HR 95 %
SCA1							
Age at baseline (years)	1.01	0.98 1.04	0.53021	6	46 (37 55)	1.003	0.975 1.033
Dysphagia (yes)	4.52	1.83 11.15	**0.00107**	17	0 (1 1)	7.029	1.939 41.81
SARA score	1.26	1.19 1.33	**<.0001**	100	13.5 (8.5 20.5)	1.288	1.201 1.382
SCA2							
Age at baseline (years)	1.04	1.01 1.08	**0.01300**	51	47.5 (37 54)	1.045	1.009 1.082
CAG (number repeats)	1.16	1.03 1.31	**0.01580**	53	39 (37 41)	1.172	1.028 1.337
SARA score	1.15	1.10 1.20	**<.0001**	100	14 (10 19.5)	1.155	1.103 1.210
SCA3							
Age at baseline (years)	1.44	1.20 1.74	**0.0001**	100	48 (40 56)	1.692	1.179 2.486
Dystonia (yes)	2.65	1.21 5.53	**0.0151**	4	0 (0 0)	2.898	1.132 7.341

SARA score	1.26	1.17 1.35	**<.0001**	33	14 (10 20.5)	1.295	1.189 1.406
CAG (number repeats)	1.04	0.89 1.21	0.6501	5	69 (66 72)	1.151	0.867 1.533
Interaction Age*CAG	0.994	0.991 0.997	**<.0001**	86	3328 (2850 3776)	0.993	0.988 0.998
SCA6							
Age at baseline (years)	1.02	0.95 1.08	0.6426	14	67 (58 73)	1.018	0.947 1.096
SARA score	1.17	1.08 1.27	**0.0001**	100	14 (10.5 19)	1.187	1.080 1.306

HR: hazard ratio, CI: confidence interval, BHR: bootstrap hazard ratio, BCI: bootstrap confidence interval; [§]Maximum number for the highest observed value attributed by a nomogram for each predictor.

Main figures:

Figure 1: Overall survival from enrollment according to genotype

Figure 2: Overall survival from enrollment according to the characterization score from nomograms by genotype

Appendix

Figure 1: Prognostic nomograms to predict the probability of individual overall survival of patients with spinocerebellar ataxia type 1, 2, 3, and 6.

Points are assigned to each risk factor by drawing a line upward from the corresponding value to the 'Points' line. The total sum point for the three factors is plotted on the 'Total points' line. A line is drawn down to read the corresponding predictions of the probability of five- and 10-year survival.

For example, a 50-year-old SCA1 patient (3 points) with dysphagia (17 points) and a SARA score of 20 (50 points) has 70 points (3 + 17 + 50), placing him in the *intermediate* group with a probability of five- (blue line) and 10-year (red line) survival of 80% and 5%, respectively.

Figure 2: Calibration plots for predicting ataxia patient overall survival at each time point by genotype.

The X-axis shows the nomogram predicted probability of survival. Patients were grouped by quartiles of predicted risk. The Y-axis is the actual probability of five- (blue) and 10-year (red) survival estimated by the Kaplan-Meier method. The solid line represents the values from the nomograms with their 95% CI. A plot along a 45-degree line (dotted line) would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes.

Table 1: Univariate Cox model in SCAs of the 28 potential predictors of death

Table 2: Various range and threshold prognostic score computed from nomograms

Table 3: Discrimination measures and β estimates with their SE from the Cox model

Table 4: Individual non-ataxia signs characteristics at baseline

Table 5: Predicted probability and actual observed survival of five- and 10-year

***Reply to Reviewers Comments**

Manuscript reference number: THELANCETNEUROLOGY-D-17-00772R1
Title: Overall survival in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study

Point by point answers to the comments of the editor and reviewer are given below. As requested, we have highlighted all modifications in a track mode in the manuscript and indicated the page (highlighted version of the manuscript with) in the letter.
We are grateful to the editor for re-reviewing our paper.
We thank the editor and the reviewer for their positive reviews and helpful comments.

----------Editorial comments----------

1. Please include the following in your revised paper:
a. data to support the statement that calibration was excellent.

To support the statement that calibration was excellent, we have added the following sentence in the Abstract section: "In each genotype, the predicted probability of five- and 10-year survival was very close to the actual observed survival". In addition, we have added a table 5 including the predicted probability and actual observed survival (appendix).

Table 5: Predicted probability and actual observed five- and 10-year survival

		Time prediction			
		5-year survival prediction		10-year survival prediction	
Genotype	§Groups	Predicted	Observed	Predicted	Observed
SCA1					
	1	0.306	0.302	0.000	0.000
	2	0.885	0.881	0.327	0.315
	3	0.980	1.000	0.831	0.867
	4	0.999	1.000	0.952	0.950
SCA2					
	1	0.640	0.630	0.351	0.335
	2	0.937	0.943	0.828	0.823
	3	0.909	0.918	0.816	0.832
	4	0.995	1.000	0.961	0.971
SCA3					
	1	0.584	0.577	0.167	0.144
	2	0.912	0.926	0.758	0.773
	3	0.991	1.000	0.933	0.966
	4	0.999	1.000	0.997	1.000
SCA6					
	1	0.909	0.910	0.700	0.682
	2	0.999	1.000	0.807	0.815
	3	0.999	1.000	0.934	0.955
	4	0.998	1.000	0.990	1.000

§Participants of each genotype were grouped in quartiles based on the risk score from the respective multivariate model.
In each genotype, the predicted probability of five- and 10-year survival was very close to the actual observed survival supporting the statement of a good calibration.

b. clarification in your introduction of the relation between spinocerebellar ataxias and CAG repeat expansions, for non-specialist readers. The first paragraph could be interpreted as suggesting that all SCA is caused by CAG repeat expansions, whereas the second paragraph could be interpreted as meaning that people with SCA can have other types of mutation instead.

To clarify the relation between spinocerebellar ataxias and CAG repeat expansion, we have inserted the following sentence to the first para of the Introduction.

"In addition, there are SCAs caused by non-translated repeat expansions or conventional mutations."

c. a little further clarification of how candidate predictors were selected from previous studies. Did you have some criteria for selection that could be mentioned?

Gender, age at onset and repeat lengths of the expended alleles were predictors of death reported in previously published studies. As additional candidate predictors we selected disease duration, and factors that characterize the neurological phenotype (SARA, INAS, individual non-ataxia signs) and the physical state (BMI, disease stage) of the study participants. "Any use of physiotherapy" was included, because it is the only known therapeutic intervention in ataxia. PHQ-9 was added on request of one of the reviewers.
To clarify how we selected the candidate predictors, we have replaced the sentence of the second paragraph of the Methods "From previous studies [2–4] and available data from the EUROSCA cohort,[6] 28 candidates predictors for death were selected" by the following sentence: "As candidate predictors we selected gender, age at onset and repeat lengths of the expended alleles which have been reported as predictors of death in previously published studies.[2-4] As additional candidates, we selected disease duration, and factors that characterize the neurological phenotype (SARA, INAS, individual non-ataxia signs), mood (PHQ-9) and physical state (BMI, disease stage) of the study participants. "Any use of physiotherapy" was included, because it is the only known therapeutic intervention in ataxia. The complete list of candidate predictors is given in table 1 of the appendix".

d. a complete list of the predictors associated with survival in your main paper, if you have not already done so. I counted 20 predictors in the results third paragraph, but use of "including" suggests that the list is not complete.

Following the first revision, the number of predictors was incorrect due to an error. There are 19 instead of 20 predictors for death since the extensar plantar sign was not associated with the risk of death from the univariate Cox model in SCA1 (appendix and para 3 Results), 14 for SCA2 (appendix and para 4 Results), 16 instead of 17 in SCA3 since dysphagia was not associated with risk of death (appendix and para 5 Results) and 3 for SCA6 (appendix and para 6 Results).

The list of predictors has thus been updated: we have modified the sentence by removing extensar plantar sign (para 3 of the Results) and dysphagia (para 5 of the Results) from the list of potential predictors of death in the main document.

In paragraphs 3, 4 and 5, the word "including" has been deleted.

e. clarification of what is meant by the new text in the first sentence of the discussion fifth paragraph. "especially in all aspects of the care of patients" suggests that nomograms are already widely used for all neurological diseases. By "other fields of medicine", do you mean fields other than oncology or other than neurology? It is also not immediately obvious what is meant by "patient's selection both in pre or postoperative phase". Could you please clarify selection for what - perhaps for surgery before it, but for what after surgery?

We have reformulated the first sentence of the paragraph and added concrete examples of the use of nomograms in oncology and neurology. The beginning of the paragraph now reads, as follows:
"Nomograms are widely used prognostic tools in various fields of medicine.[18] For example, there are nomograms that allow prediction of lymph node metastasis in cancer patients. These nomograms may assist physicians in decisions on surgical management.[22–24] More recently, a prognosis nomogram was developed to predict individual outcomes after antiepileptic drug withdrawal in people with epilepsy.[25]"

2. Could you please confirm (not necessarily in your paper) why PHQ9 has been added as a predictor in the latest revision but it was not included previously?

We have added PHQ9 upon the request of the reviewer 1(3rd question).

Could other relevant predictors have been similarly missed?

This is possible since there may be completely unknown factors. Other factors that are likely to be relevant, such as imaging data, could not be considered because there were not available. This point is addressed in the last part of the first paragraph of the discussion: "We were unable to consider all potential covariates in our model. For example, clinical signs other than those assessed by the used scales, imaging and biomarker data were not available".

And could you please confirm that it is correct that none of the data in your abstract or main paper seem to have changed in light of inclusion of this predictor?

We confirm that the inclusion of PHQ-9 did not change the results from multivariate Cox mode and thus the conclusion from abstract and main paper.

3. Figures, tables, panels, and appendices:
a. please clarify in the legend of table 1 what is shown. For example, the current column headings suggest that the max score values should either be within or the upper limit of the range values in the next column, neither of which seems to be the case. Could the range values be replaced by median (IQR)? And do the 95% CI for the internal validation have corresponding HR values that could be included, or do they always apply to the same HR as given in the first column (in which case, could that be clarified)?

The modifications have been performed as requested (Table 1 and 2).

In the legend of Table 1, we have replaced "Data" by "The categorical variables are shown as n (%), the continuous variables as mean (SD)".

The Table 2 has been modified as follow:
-the max score corresponds to the maximum assigned score by the nomogram. In this column, we have changed the title as "Max assigned score in nomogram". In addition, the legend was modified as follow: "Maximum number for the highest observed value assigned by a nomogram for each predictor".
-the range has been replaced by median (IQR) as requested;
-the Bootstrap Hazard Ratio (BHR) has been added just before its 95% confidence interval.

Table 2: Multivariate Cox model

				[§]Max assigned score in		Internal validation	
Parameters	**HR**	**95 % CI**	**p-value**	**nomogram**	**Median (IQR)**	**BHR**	**BCI HR 95 %**
SCA1							
Age at baseline (years)	1.01	0.98 1.04	0.53021	6	46 (37 55)	1.003	0.975 1.033
Dysphagia (yes)	4.52	1.83 11.15	**0.00107**	17	0 (1 1)	7.029	1.939 41.81
SARA score	1.26	1.19 1.33	**<.0001**	100	13.5 (8.5 20.5)	1.288	1.201 1.382
SCA2							
Age at baseline (years)	1.04	1.01 1.08	**0.01300**	51	47.5 (37 54)	1.045	1.009 1.082
CAG (number repeats)	1.16	1.03 1.31	**0.01580**	53	39 (37 41)	1.172	1.028 1.337
SARA score	1.15	1.10 1.20	**<.0001**	100	14 (10 19.5)	1.155	1.103 1.210
SCA3							
Age at baseline (years)	1.44	1.20 1.74	**0.0001**	100	48 (40 56)	1.692	1.179 2.486
Dystonia (yes)	2.65	1.21 5.53	**0.0151**	4	0 (0 0)	2.898	1.132 7.341
SARA score	1.26	1.17 1.35	**<.0001**	33	14 (10 20.5)	1.295	1.189 1.406
CAG (number repeats)	1.04	0.89 1.21	0.6501	5	69 (66 72)	1.151	0.867 1.533
Interaction Age*CAG	0.994	0.991 0.997	**<.0001**	86	3328 (2850 3776)	0.993	0.988 0.998
SCA6							

Age at baseline (years)	1.02	0.95	1.08	0.6426	14	67 (58 73)		1.018	0.947	1.096
SARA score	1.17	1.08	1.27	**0.0001**	100	14 (10.5 19)		1.187	1.080	1.306

HR: hazard ratio, CI: confidence interval, BHR: bootstrap hazard ratio, BCI: bootstrap confidence interval;
[§]Maximum number for the highest observed value assigned by a nomogram for each predictor.

b. Please supply the figures for your main paper as separate editable files, and please indicate at resubmission what programme was used to create them. For more information on our requirements please see: http://download.thelancet.com/flatcontentassets/authors/artwork-guidelines.pdf
Unfortunately, the current versions do not seem to be editable as supplied in Word or PDF format, as I am unable to select individual parts of the figure.

We have used a SAS macro to create figure 1 and 2: the %NEWSURV SAS program developed by Jeffrey Meyers from Mayo Clinic. The macro is downloadable from the following link:
http://www.sascommunity.org/wiki/Kaplan-Meier_Survival_Plotting_Macro_%25NEWSURV
The figures 1 and 2 have been re-uploaded in pdf vectordrawing format and with the modifications requested.

c. in figure 1, could the "Total" column be omitted to avoid overlap with the numbers at risk below the figure?

The “Total” column has been omitted for both Figures.

d. could "+ Censor" be omitted or explained, for both figures?

The “"+ Censor” has been omitted for both Figures.

e. in figure 2, what is meant by "score1cl" etc?

This is the categorized prognostic group variable. This label as modified for "Prognosis group" in Figure 2.

3. Administrative matters
a. please ensure that we have an ICMJE form (http://www.thelancet.com/pb/assets/raw/Lancet/authors/icmje-coi-form.pdf) for each author. Apologies if I've missed them - as there are many forms repeated online and it was hard to be sure what was and wasn't there - but I couldn't see forms for PG, JI, CaM, LN, MarP, AB, PC, JB, and K-JS.

The forms have been re-uploaded as requested.

b. please ensure that all declarations match the ICMJE forms. For example, the form for Dr Schulz includes declarations that aren't in the paper - in such cases please either update the paper or supply a new ICMJE form that matches the paper.

The modifications have been performed as requested. In addition declarations of Dr Kang have been updated.

c. please supply signed author statement forms (http://www.thelancet.com/pb/assets/raw/Lancet/authors/tln-author-signatures.pdf) for all authors. Again I might have missed them, but I couldn't see forms for PG and K-JS.

The forms have been re-uploaded as requested.

d. please supply a signed statement to confirm that all authors agree with their contribution as listed in the revised paper. Several of the signed author statement forms we do have currently lack the page that lists the contributions (eg, MR, ASo, ASu, AA, AF, SB, but there might be others), and we will need to receive formal confirmation that these authors agree with their contributions as listed.

The forms have been re-uploaded as requested.

e. please supply a new signed author statement form from Dr Brice, as the current one seems to have no signature.

The form has been re-uploaded as requested.

f. please supply signed consent from the people named in your acknowledgments section to confirm that they agree to be mentioned in this way.

The forms have been uploaded as requested.

g. I could not see a response to our comments on data sharing. As a reminder, we encourage authors to share any additional data, preferably translated into English, that would facilitate the replication or further analysis of their work—eg, the raw numbers underlying their analysis or the code for any modelling. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in a section entitled "Data sharing" at the end of the Methods section, ahead of "Role of the funding source". If authors have already deposited their data in another repository, or have made other arrangements for data to be shared (eg, by means of an adjudication process or contacting the authors), they should use this section to elaborate.

The consent obtained from the study participants did not include publishing raw data in a repository. However, we are willing and able to share data upon request provided that the objective of the planned analysis is compatible with the consent given by the participants.

-------Comments from reviewers----

Reviewer #5: statistical reviewer
I would like to thank the authors for addressing my comments. I could not find the information on post-hoc statistical power in the manuscript.

This should be be reported in the statistical analysis section

The information on post-hoc statistical power has been added in the statistical analysis section as follows:

Because the backward selection model heavily relies on statistical significance which in turn depends on statistical power, we computed a posteriori statistical power to highlight an increase in the risk of death of 2 (HR = 2) for any binary variable with a proportion of patient of 50% in each group (para 3, Methods).

and the Results section to support the discussion of the limited statistical power for some analyses.

The information on post-hoc statistical power has been added in the Results section as follows:

A posteriori statistical power to highlight an increase in the risk of death of 2 (HR = 2) for any binary variable with a proportion of patient of 50% in each group was 55%, 58%, 53% and 24% for SCA1, 2, 3 and 6 respectively (para 7, Results).

Figure1

Click here to download Figure: Figure1.pdf

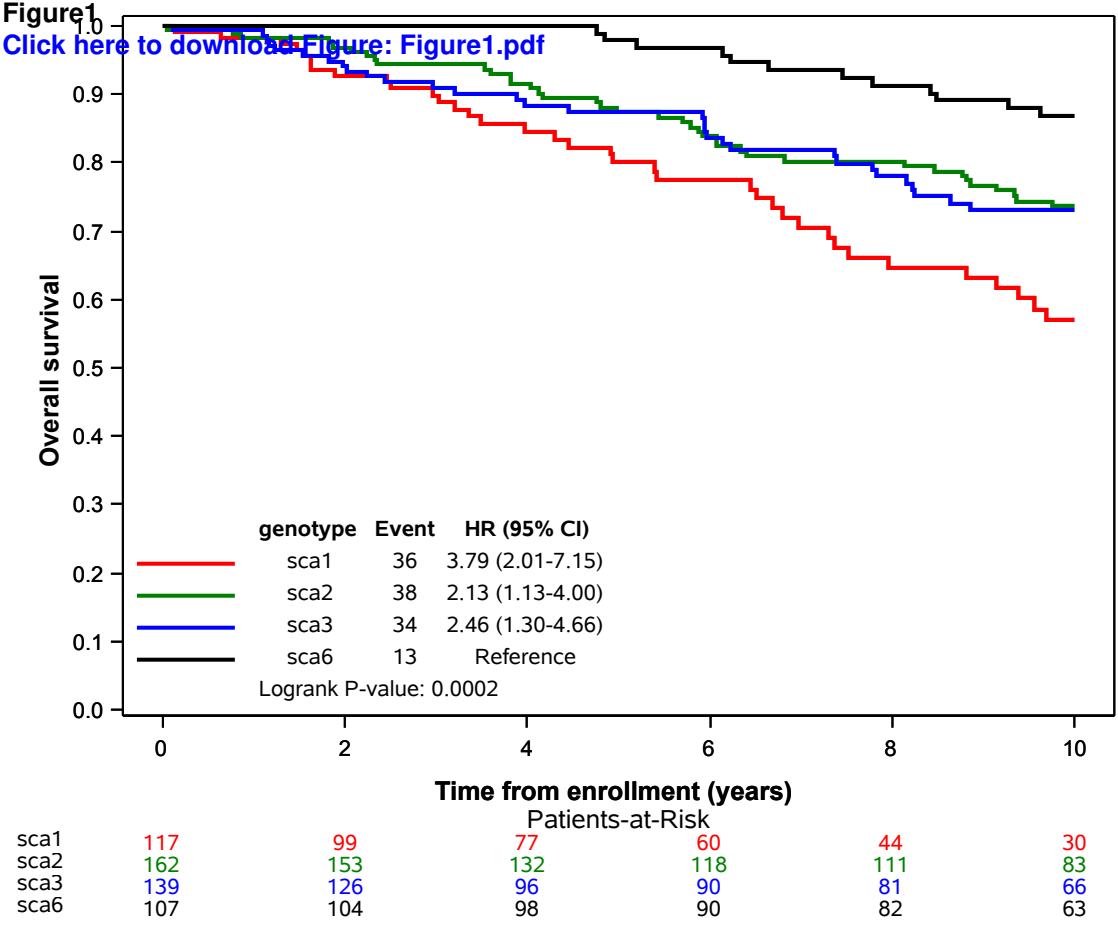

Figure2

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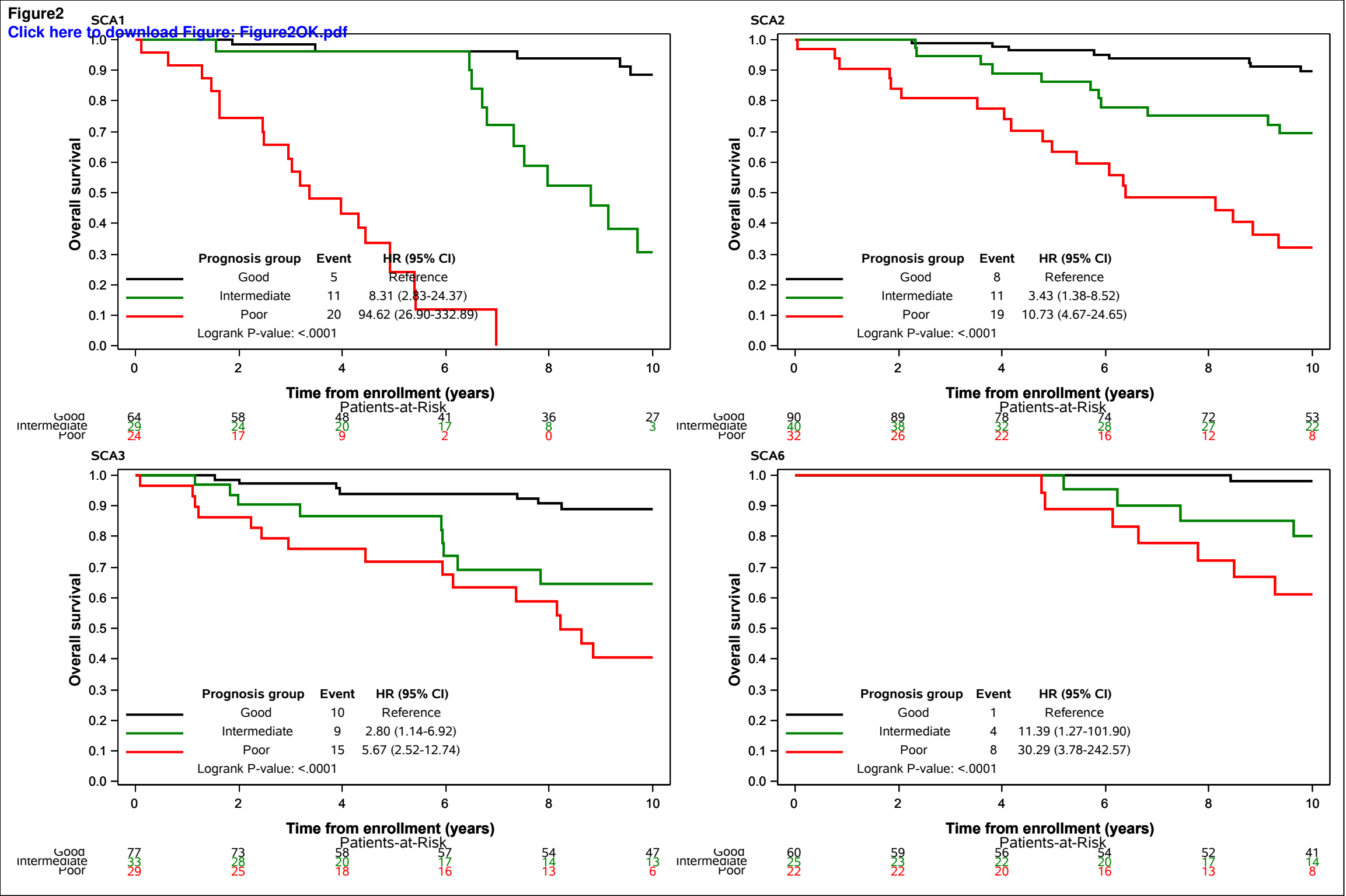

Appendix

Figure 1: Prognostic nomograms to predict the probability of individual overall survival of patients with spinocerebellar ataxia type 1, 2, 3, and 6.

Points are assigned to each risk factor by drawing a line upward from the corresponding value to the 'Points' line. The total sum point for the three factors is plotted on the 'Total points' line. A line is drawn down to read the corresponding predictions of the probability of five- and 10-year survival.

For example, a 50-year-old SCA1 patient (3 points) with dysphagia (17 points) and a SARA score of 20 (50 points) has 70 points (3 + 17 + 50), placing him in the *intermediate* group with a probability of five- (blue line) and 10-year (red line) survival of 80% and 5%, respectively.

Figure 2: Calibration plots for predicting ataxia patient overall survival at each time point by genotype.

The X-axis shows the nomogram predicted probability of survival. Patients were grouped by quartiles of predicted risk. The Y-axis is the actual probability of five- (blue) and 10-year (red) survival estimated by the Kaplan-Meier method. The solid line represents the values from the nomograms with their 95% CI. A plot along a 45-degree line (dotted line) would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes.

Table 1: Univariate Cox model in SCAs of the 28 potential predictors of death

	SCA1	SCA2	SCA3	SCA6
	HR (95 % CI)	**HR (95 % CI)**	**HR (95 % CI)**	**HR (95 % CI)**
Gender (male)	0·80 (0·41 1·56)	1·34 (0·71 2·54)	1·42 (0·72 2·80)	1·61 (0·52 4·94)
Age at onset (years)	**0·84 (0·78 0·90)**	**0·90 (0·86 0·95)**	**0·89 (0·85 0·94)**	0·97 (0·90 1·04)
Disease duration (years)	**1·20 (1·12 1·28)**	**1·11 (1·05 1·16)**	**1·12 (1·06 1·18)**	1·03 (0·96 1·12)
Number of CAG repeats	**1·13 (1·06 1·19)**	**1·27 (1·15 1·40)**	**1·21 (1·08 1·34)**	1·11 (0·36 3·42)
BMI (kg/m^2)	**0·81 (0·74 0·90)**	0·94 (0·86 1·04)	0·94 (0·85 1·03)	1·02 (0·88 1·17)
SARA score	**1·23 (1·17 1·29)**	**1·16 (1·12 1·21)**	**1·16 (1·12 1·20)**	**1·17 (1·08 1·27)**
Number of non-ataxia signs	**1·60 (1·32 1·95)**	**1·42 (1·24 1·63)**	**1·99 (1·62 2·46)**	1·22 (0·94 1·58)
Hyperreflexia (yes)	0·66 (0·34 1·30)	0·74 (0·26 2·10)	1·73 (0·84 3·57)	0·71 (0·15 3·28)
Areflexia (yes)	**2·53 (1·22 5·26)**	1·82 (0·86 3·85)	1·28 (0·58 2·82)	0·75 (0·20 2·89)
Extensar plantar (yes)	2·01 (0·94 4·29)	1·21 (0·60 2·43)	**2·78 (1·34 5·77)**	*
Spasticity (yes)	0·67 (0·34 1·30)	1·59 (0·61 4·10)	**4·14 (1·77 9·67)**	2·34 (0·64 8·59)
Paresis (yes)	**2·90 (1·47 5·74)**	**3·32 (1·60 6·91)**	**4·36 (2·16 8·80)**	3·19 (0·71 14·42)
Muscle atrophy (yes)	**3·96 (2·03 7·73)**	**6·14 (3·14 12·00)**	**2·89 (1·41 5·95)**	0·45 (0·06 3·49)
Fasciculations (yes)	**3·39 (1·67 6·88)**	**1·93 (1·00 3·69)**	**3·04 (1·54 6·02)**	*
Myoclonus (yes)	**3·22 (1·13 9·17)**	**2·80 (1·34 5·87)**	1·84 (0·43 7·86)	*
Rigidity (yes)	2·83 (0·36 22·05)	**5·44 (2·37 12·49)**	**3·19 (1·36 7·46)**	**8·83 (2·64 29·55)**
Chorea/dyskenia (yes)	**3·01 (1·04 8·73)**	**3·83 (1·46 10·02)**	**7·83 (3·57 17·20)**	2·54 (0·31 20·80)
Dystonia (yes)	**3·63 (1·73 7·61)**	**2·31 (1·09 4·90)**	**4·10 (2·08 8·07)**	1·98 (0·25 15·61)
Resting tremor (yes)	**3·08 (1·17 8·07)**	1·27 (0·53 3·04)	2·06 (0·49 8·67)	4·38 (0·56 34·19)
Sensory symptoms (yes)	1·68 (0·74 3·82)	0·63 (0·31 1·26)	1·48 (0·63 3·49)	0·89 (0·29 2·76)
Urinary dysfunction (yes)	**2·01 (1·02 3·96)**	1·25 (0·65 2·38)	1·81 (0·87 3·75)	2·99 (0·96 9·29)
Cognitive impairment (yes)	**3·03 (1·520 6·03)**	**2·63 (1·36 5·08)**	1·03 (0·44 2·40)	3·13 (0·93 10·57)
Brainstem oculomotor signs (yes)	1·63 (0·85 3·14)	1·36 (0·71 2·61)	**3·01 (1·40 6·46)**	2·32 (0·68 7·90)
Dysphagia (yes)	**4·14 (1·81 9·48)**	1·59 (0·82 3·07)	1·93 (0·92 4·06)	0·98 (0·33 2·93)
Double vision (yes)	1·71 (0·77 3·84)	1·22 (0·58 2·60)	1·39 (0·69 2·81)	1·94 (0·65 5·79)
[§]Any physiotherapy use (yes)	1·85 (0·96 3·57)	1·23(0·65 2·34)	0·79 (0·40 1·56)	0·96 (0·32 2·90)
PHQ-9 sum score	**1·05 (1·00 1·10)**	0·99(0·93 1·07)	**1·06 (1·02 1·11)**	1·05 (0·96 1·14)
Disease stage (Independent as reference)	1	1	1	1
Dependent on walking aids	**5·36 (2·07 13·83)**	**2·83 (1·22 6·67)**	**15·33 (1·99 118·21)**	**7·911 (0·88 57·73)**
Dependent on wheelchair	**48·0 (16·16 142·70)**	**10·25 (4·75 22·13)**	**91·76 (12·0 700·7)**	**13·64 (1·30 143·0)**

*The model did not converge due to the absence of an event (death) in one of the modalities, HR: hazard ratio, CI: confidence interval, bold indicates the significance of a predictor of risk of death (HR not included 1);

[§]variable was used as time-dependent covariate in Cox model. All analyses were adjusted on age at inclusion.

Table 2: Various range and threshold prognostic score computed from nomograms

	Observed total score range	Good prognosis	Intermediate prognosis	Poor prognosis	c-index
Our proposed cut-off (55, 25 and 20%)					
SCA1	2·7 – 120·4	<48 (64)[§]	48 – 70 (29)	>70 (24)	**0.905**
SCA2	31·7 – 146·4	<74 (90)	74 – 102 (40)	>102 (32)	**0.822**
SCA3[Ŧ]	39·9 – 131·7	<79 (77)	79 – 92 (33)	>92 (29)	**0.891**
SCA6	3·5 – 112·0	<53 (60)	53 – 68 (25)	>68 (22)	**0.825**
According to tertile (33, 33 and 33%)					
SCA1	2·7 – 120·4	<35 (39)	35 – 56 (39)	>56 (39)	0.823
SCA2	31·7 – 146·4	<62 (53)	62 – 83 (53)	>83 (55)	0.781
SCA3[Ŧ]	39·9 – 131·7	<69 (44)	69 – 84 (44)	>84 (46)	0.715
SCA6	3·5 – 112·0	<42 (35)	42 – 58 (35)	>58 (37)	0.726
Proposed by DR Cox (27, 49.5 and 27%)					
SCA1	2·7 – 120·4	<29 (32)	29 – 45 (57)	>45 (28)	0.825
SCA2	31·7 – 146·4	<59 (44)	59 – 71 (79)	>71 (38)	0.774
SCA3[Ŧ]	39·9 – 131·7	<65 (36)	65 – 91 (66)	>91 (32)	0.712
SCA6	3·5 – 112·0	<39 (29)	39 – 67 (53)	>67 (25)	*

[Ŧ]Interaction between age and CAG repeat length (age x CAG) was divided by 1,000 in the total score computation; *Model did not converged; [§]numbers in brackets are the number of patients in each group.

Table 3: Discrimination measures and β estimates with their SE from the Cox model

	SCA1		SCA2		SCA3		SCA6	
Measures	**Estimate**	**SE**	**Estimate**	**SE**	**Estimate**	**SE**	**Estimate**	**SE**
c-index	0·905	0·027	0·822	0·032	0· 891	0·021	0·825	0·054
β (SE): group 2 versus 1	2·110	0·549	1·233	0·465	1·031	0·461	2·432	1·118
β (SE): group 3 versus 1	4·614	0·640	2·373	0·425	1·735	0·413	3·411	1·062

All values are based on scores from the nomograms. The risk groups were: group 1 (*Good prognosis*), group 2 (*Intermediate prognosis*), and group 3 (*Poor prognosis*). β is the estimate with their SE from the Cox model. Standard error (SE) for the *c*-index was estimated from 1,000 bootstrap samples.

Table 4: Individual non-ataxia signs characteristics at baseline

	SCA1 (n=117)	SCA 2 (n=162)	SCA 3 (n=139)	SCA 6 (n=107)
Hyperreflexia (n, % yes)	79 (68)	21 (13)	53 (39)	23 (22)
Areflexia (n, % yes)	21 (18)	104 (65)	78 (57)	24 (23)
Extensor plantor sign (n, % yes)	54 (51)	45 (31)	57 (42)	2 (2)
Spasticity (n, % yes)	67 (59)	14 (9)	60 (44)	15 (15)
Paresis (n, % yes)	27 (23)	23 (15)	34 (25)	6 (6)
Muscle atrophy (n, % yes)	34 (29)	35 (22)	52 (38)	12 (12)
Fasciculations (n, % yes)	45 (39)	61 (38)	51 (37)	3 (3)
Myoclonus (n, % yes)	5 (4)	22 (14)	6 (4)	0 (0)
Rigidity (n, % yes)	2 (2)	11 (7)	14 (10)	6 (6)
Chorea/dyskenia (n, % yes)	8 (7)	11 (7)	14 (10)	2 (2)
Dystonia (n, % yes)	15 (13)	23 (14)	33 (24)	4 (4)
Resting tremor (n, % yes)	8 (7)	24 (15)	5 (4)	2 (2)
Sensory symptoms (n, % yes)	69 (62)	106 (69)	83 (65)	49 (47)
Urinary dysfunction (n, % yes)	41 (35)	64 (40)	63 (46)	32 (30)
Cognitive impairment (n, % yes)	25 (22)	41 (26)	26 (19)	10 (9)
Brainstem oculomotor signs (n, % yes)	44 (38)	58 (36)	72 (53)	18 (17)
Dysphagia (n, % yes)	70 (60)	85 (53)	83 (60)	58 (54)
Double vision (n, % yes)	18 (15)	32 (20)	78 (56)	45 (42)

Table 5: Predicted probability and actual observed five- and 10-year survival

		Time prediction			
		5-year survival prediction		10-year survival prediction	
Genotype	[§]Groups	Predicted	Observed	Predicted	Observed
SCA1					
	1	0.306	0.302	0.000	0.000
	2	0.885	0.881	0.327	0.315
	3	0.980	1.000	0.831	0.867
	4	0.999	1.000	0.952	0.950
SCA2					
	1	0.640	0.630	0.351	0.335
	2	0.937	0.943	0.828	0.823
	3	0.909	0.918	0.816	0.832
	4	0.995	1.000	0.961	0.971
SCA3					
	1	0.584	0.577	0.167	0.144
	2	0.912	0.926	0.758	0.773
	3	0.991	1.000	0.933	0.966
	4	0.999	1.000	0.997	1.000
SCA6					
	1	0.909	0.910	0.700	0.682
	2	0.999	1.000	0.807	0.815
	3	0.999	1.000	0.934	0.955
	4	0.998	1.000	0.990	1.000

[§]Participants for each genotype were grouped in quartiles based on the risk score from the respective multivariate model.

In each genotype, the predicted probability of five- and 10-year survival was very close to the actual observed survival supporting the statement of a good calibration.

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Table 6: List of the 17 participant centers.

N°	Centers	EUROSCA study group
1	London	Arron Cook, Paola Giunti, Robyn Labrum
2	Paris	Alexandra Durr, Alexis Brice, Perrine Charles, Cecilia Marelli
3	Milan	Caterina Mariotti, Lorenzo Nanetti, Marta Panzeri
4	Warsaw	Maria Rakowicz, Anna Sobanska, Anna Sulek
5	Bonn	Heike Jacobi, Thomas Klockgether, Tanja Schmitz-Hübsch
6	Tubingen	Peter Bauer, Ludger Schöls, Holger Hengel
7	Naples	Alessandro Filla, Antonella Antenora
8	Pécs	Bela Melegh
9	Santander	Jon Infante, José Berciano
10	Nijmegen	Bart P. van de Warrenburg
11	Essen	Dagmar Timmann
12	Bochum	
13	Innsbruck	Sylvia Boesch
14	Frankfurt	Kang Jun-Suk
15	Bruxelles	Massimo Pandolfo
16	GO1	
17	Aachen	Jörg B. Schulz

+ Sophie Tezenas du Montcel and Alhassane Diallo: Biostat Unit (Paris).

Appendix Figure 1 SCA1

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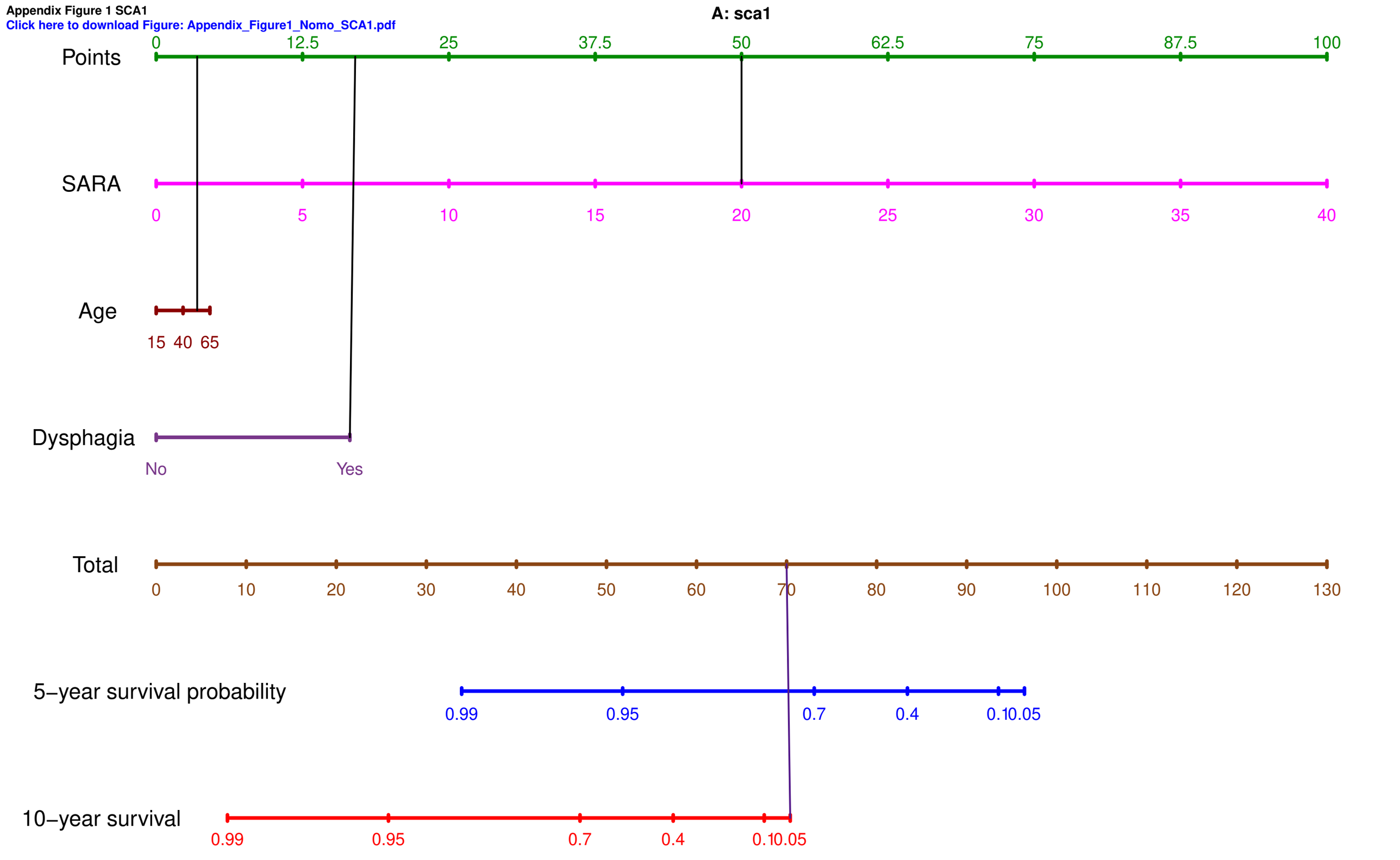

Appendix Figure 1 SCA2

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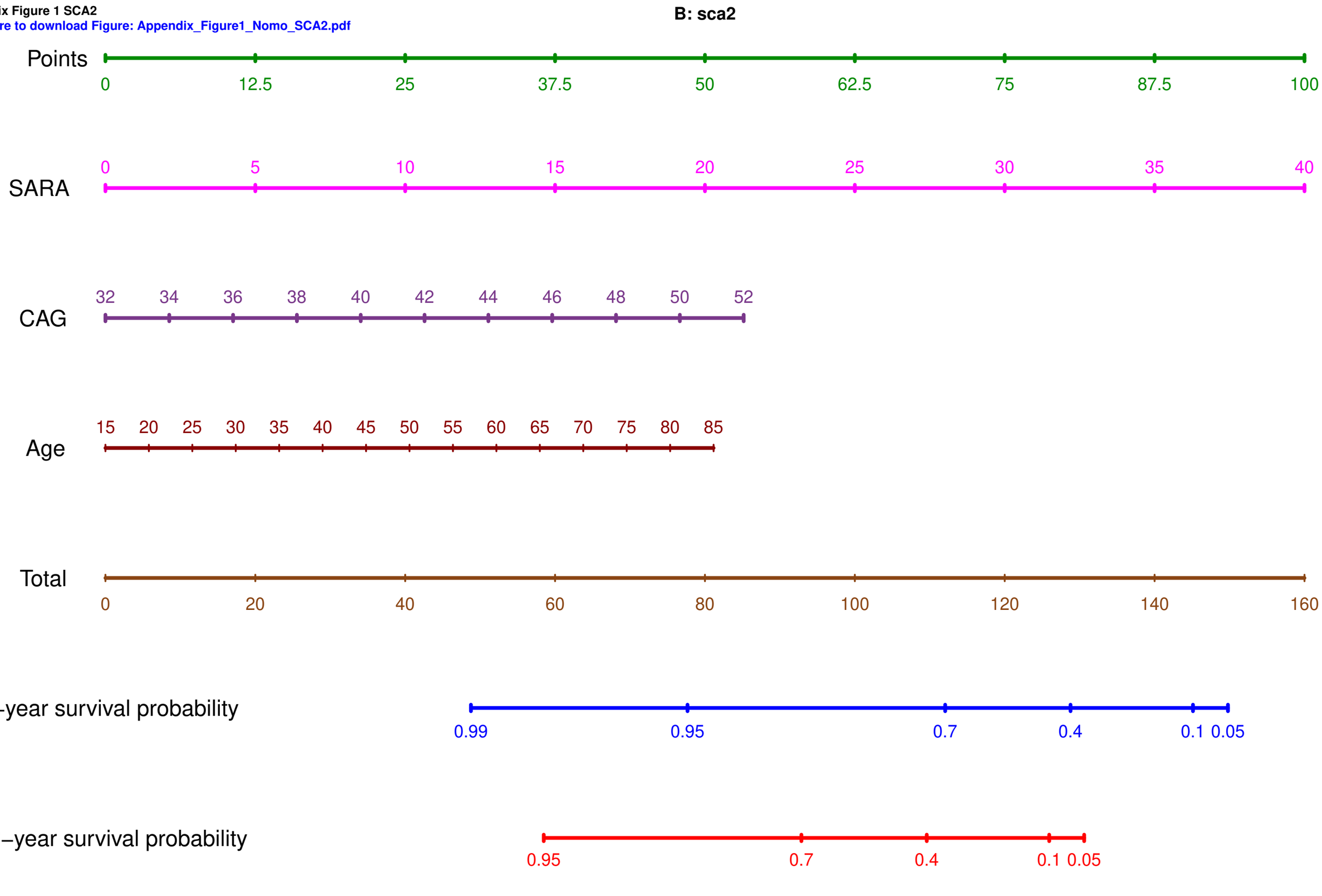

Appendix Figure1 SCA3

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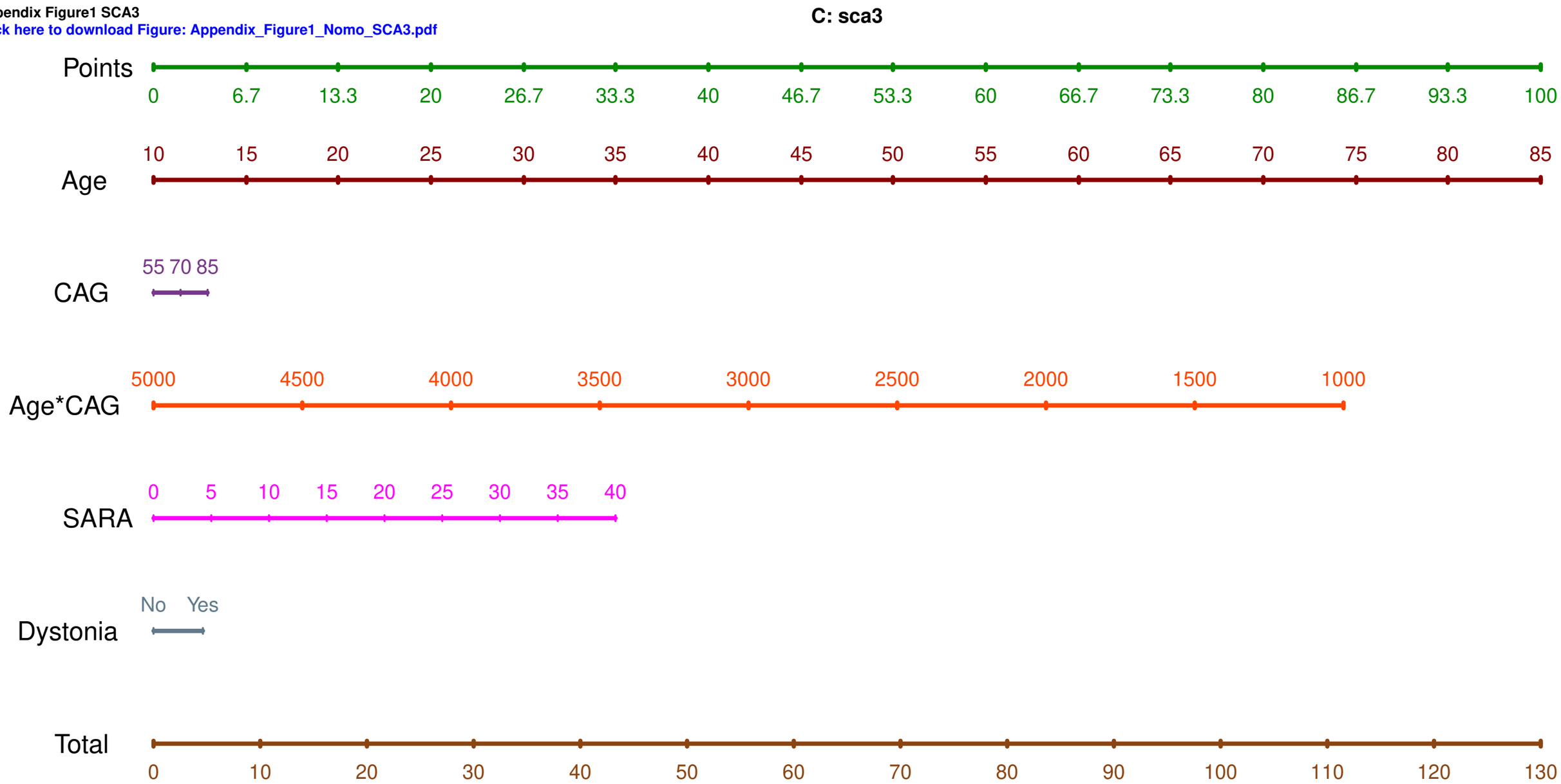

Appendix Figure 1 SCA6

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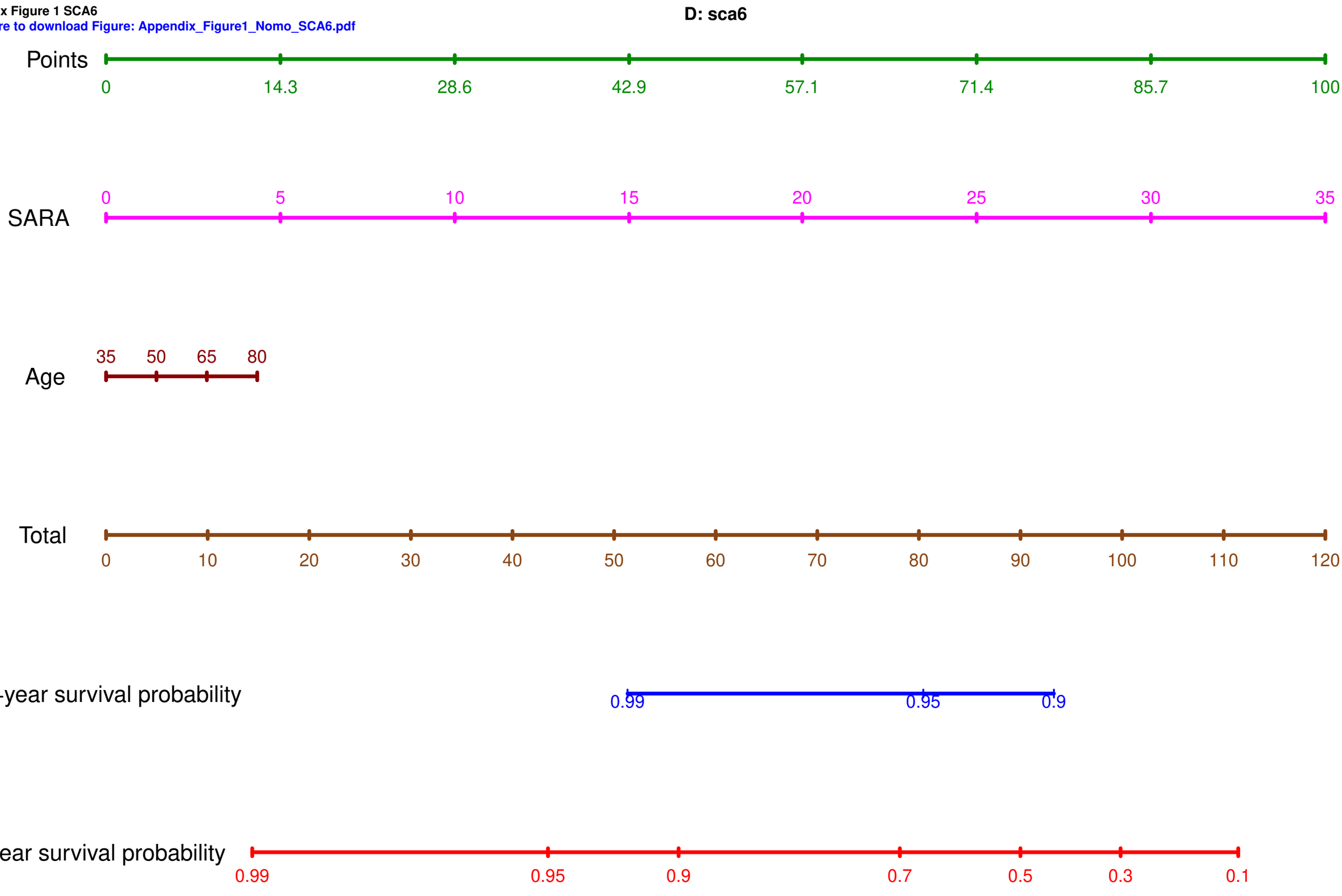

Appendix Figure 2

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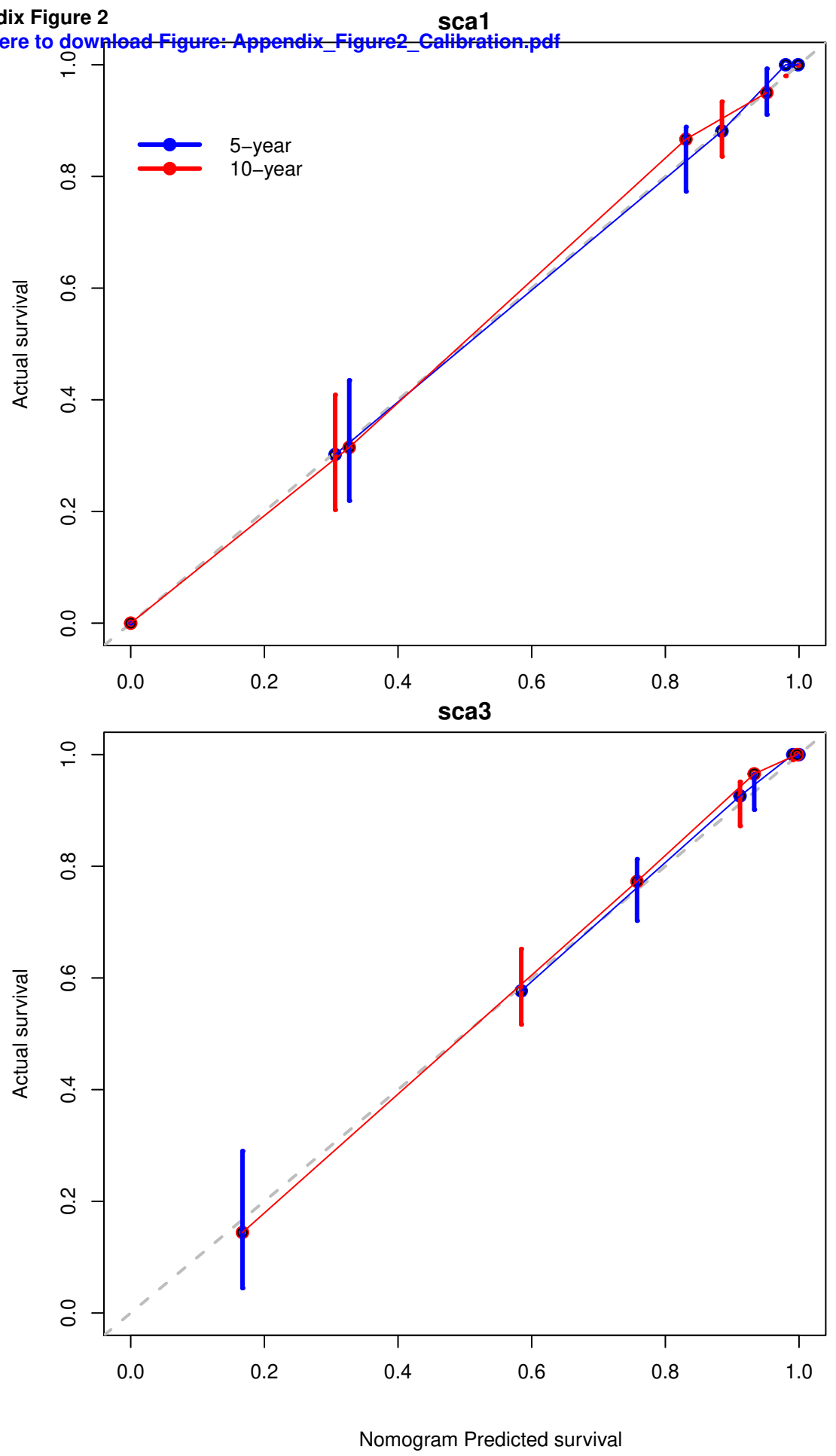

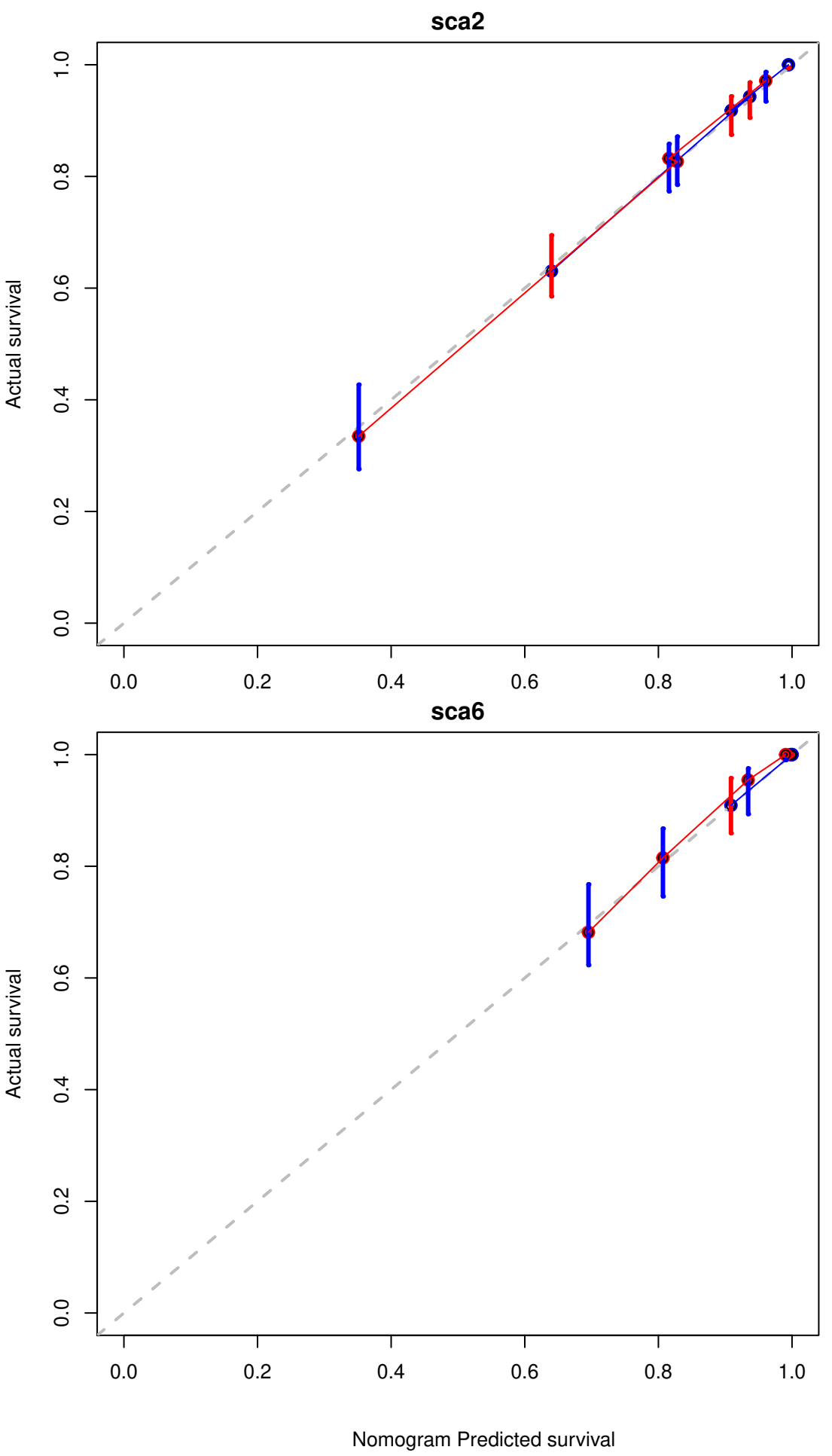

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1, 1st para
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5, 2nd para
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	5, 3th para
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6, 1st para
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6, 1st para
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6, 1st para
	5b	Describe eligibility criteria for participants.	6, 1st para
	5c	Give details of treatments received, if relevant.	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6, 2nd para
	6b	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6, 2nd para
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	Explain how the study size was arrived at.	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6, 3th para
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	6, 3th para
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6, 4th para
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6, 4th para
Risk groups	11	Provide details on how risk groups were created, if done.	6, 4th para
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8, 1st para
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8, 1st para
Model development	14a	Specify the number of participants and outcome events in each analysis.	8, 1st para
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	8, 3th - 6th para
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	8, 3th - 6th para
	15b	Explain how to the use the prediction model.	8, 7th para
Model performance	16	Report performance measures (with CIs) for the prediction model.	9, 2nd para
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	10, 1st, 5th para
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	10, 1st, 3th, 4th para
Implications	20	Discuss the potential clinical use of the model and implications for future research.	10, 5th para

Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	**3, 5th para**

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Authors' contributions

Please insert here the contribution each author made to the manuscript—eg, literature search, figures, study design, data collection, data analysis, data interpretation, writing etc. If all authors contributed equally, please state this. The information provided here must match the contributors' statement in the manuscript.

ADi designed and executed the statistical analysis, and wrote the first draft of the report and reviewed the report; HJ and TS-H contibuted to the conception, organisation,and execution of the research project and reviewed and commanted on the statistical analysis and the report; AC, RL, ADu, AB, PC, CeM, CaM, LN, MarP, MR, ASo, ASu, LS, HH, BM, AF, AA, JI, JB, BPvdW, DT, SB, MP, J-SK, PB, PG and K-JS organised and did the research project and reviewed and commanted on the statistical analysis and the report; TK conceived, organised, and did the research project, and designed, reviewed, and commanted on the statistical analysis and wrote the first draft of the report and reviewed the report; STdM contibuted to the conception of the research project wrote the first draft of the report and reviewed the report.

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Role of the funding source

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The sponsors of the study had no role in the design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest

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Please sign below to confirm that all necessary consents required by applicable law from any relevant patient, research participant, and/or other individual whose information is included in the article have been obtained in writing. **The signed consent form(s) should be retained by the corresponding author and NOT sent to *The Lancet Neurology*.**

I agree with: the plan to submit to *The Lancet Neurology;* the contents of the manuscript; to be an author; and to the conflicts of interest statement as summarised. I have had access to all the data in the study (fc search articles) and accept responsibility for its validity.

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Corresponding author: Tezenas du Montcel

Article type: Original article

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