RESEARCH ARTICLE

Prediction of Survival With Long-Term Disease Progression in Most Common Spinocerebellar Ataxia

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ABSTRACT: Background: Spinocerebellar ataxias are rare dominantly inherited neurodegenerative diseases that lead to severe disability and premature death.
Objective: To quantify the impact of disease progression measured by the Scale for the Assessment and Rating of Ataxia on survival, and to identify different profiles of disease progression and survival.
Methods: Four hundred sixty-two spinocerebellar ataxia patients from the EUROSCA prospective cohort study, suffering from spinocerebellar ataxia type 1, spinocerebellar ataxia type 2, spinocerebellar ataxia type 3, and spinocerebellar ataxia type 6, and who had at least two measurements of Scale for the Assessment and Rating of Ataxia score, were analyzed. Outcomes were change over time in Scale for the Assessment and Rating of Ataxia score and time to death. Joint model was used to analyze disease progression and survival.
Results: Disease progression was the strongest predictor for death in all genotypes: An increase of 1 standard deviation in total Scale for the Assessment and Rating of Ataxia score increased the risk of death by 1.28 times (95% confidence interval: 1.18–1.38) for patients with spinocerebellar ataxia type 1; 1.19 times (1.12–1.26) for spinocerebellar ataxia type 2; 1.30 times (1.19–1.42) for spinocerebellar ataxia type 3; and 1.26 times (1.11–1.43) for spinocerebellar ataxia type 6. Three subgroups of disease progression and survival were identified for patients with spinocerebellar ataxia type 1: "severe" (n = 13; 12%), "intermediate" (n = 31; 29%), and "moderate" (n = 62; 58%). Patients in the severe group were more severely affected at baseline with higher Scale for the Assessment and Rating of Ataxia scores and frequency of nonataxia signs compared to those in the other groups.
Conclusion: Rapid ataxia progression is associated with poor survival of the most common spinocerebellar ataxia. Theses current results have implications for the design of future interventional studies of spinocerebellar ataxia.

Key Words: dynamic predictions; EPOCE; EUROSCA study; longitudinal data; spinocerebellar ataxia

Spinocerebellar ataxias (SCAs) are rare inherited neurological disorders, clinically characterized by progressive balance problems and incoordination, that lead to severe disability and premature death. More than 40 genetically distinct SCAs have been defined, among which the most common are SCA1, SCA2, SCA3, and SCA6.[1] They are caused by abnormal cysteine alanine glycine (CAG) repeat expansions, encoding elongated polyglutamine tracts within the proteins associated with each type.

The European prospective cohort study (EUROSCA) of patients with SCA1, SCA2, SCA3, and SCA6 was initiated in 2005 to study the natural history of ataxia. Longitudinal clinical[2] and survival data[3] from EUROSCA allowed us to establish genotype-specific progression and survival rates and identify factors that influence disease course and survival. These analyses identified SCA1 as the genotype with the fastest disease progression and shortest survival among these SCAs.[2,3] Nevertheless, type I autosomal-dominant cerebellar ataxias are often complex in terms of clinical manifestations, meaning that it is not self-evident that severity of ataxia per se is the best predictor of survival. Simultaneously modeling long-term disease progression and survival would allow the determination of their correlation, a better understanding of their dependence, and identification of common prognostic factors and could advance the design of future clinical trials.

Here, we report data from the EUROSCA study on disease progression in relation to survival with a long-term follow-up. We aimed to (1) quantify the effect of disease progression on the survival of patients with SCA1, SCA2, SCA3, or SCA6; (2) identify distinct subgroups of disease progression and survival, as well as factors that influence these groups; and (3) compute and compare the individual dynamic prediction of survival based on disease progression.

Methods

Standard Protocol Approvals, Registration, and Patients Consents

The ethics committees of the participating centers approved the study. The study is registered with ClinicalTrials.gov, number NCT02440763. At enrollment, a written consent form was obtained from all study participants.

Study Population

A subsample of 462 SCA patients, with at least two visits, were analyzed from the 525 SCA patients enrolled between July 1, 2005 and August 31, 2006 in the multicenter (17 European centers) EUROSCA prospective cohort study.[4] These patients were diagnosed with progressive, otherwise unexplained, ataxia and had a positive molecular genetic test for SCA1 (n = 107), SCA2 (n = 146), SCA3 (n = 122), or SCA6 (n = 87). Assessments were performed according to a written study protocol. Patients were seen at baseline and followed by annual visits for 3 years. Afterward, 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 on November 3, 2016, after a maximum observation period of 11 years.

Clinical Outcomes and Genetics Evaluations

Clinical outcomes were disease progression and overall survival. We avoided survival bias by updating the vital status from the available electronic EUROSCA patient registry, interviews of family members, or querying records from civil registry offices, when feasible, as in the previous survival study.[3] Disease progression was measured by the Scale for the Assessment and Rating of Ataxia (SARA).[4] Briefly, the SARA score consists of eight items that yield a total score of 0 (no ataxia) to 40 (most severe ataxia). All investigators were experienced in the use of the SARA. We selected candidate predictors for joint disease progression and survival modeling, consisting of age at baseline, sex, age at ataxia onset, repeat lengths of the expanded alleles, SARA score at baseline, dysphagia, and dystonia, which have been reported as predictors for survival or disease progression in our previously published studies.[2,3] We selected additional candidates, consisting of the inventory of nonataxia signs (INAS)[5] and its reported abnormalities, such as double vision and cognitive impairment, physical state (body mass index; BMI), and health-related quality of life, assessed by the visual analogical scale (VAS) of the EuroQol five dimensions questionnaire (EQ-5D).[6,7] BMI was calculated using the formula (weight/height ^{2}). 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).

Statistical Analysis

Frequencies (percentages) or means (standard deviation; SD) were used to describe the categorical and continuous variables at baseline. Time from enrollment was used as the time scale. 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. We simultaneously modeled time-to-death and disease progression using the shared random-effects (SRE) model[8] to quantify and capture the best relationship between disease progression and survival, and the joint latent class (JLC) model[9] to identify subgroups of homogeneous patients in terms of survival and disease progression. In each joint model, the survival model consisted of the Weibull proportional regression model, adjusted for age at inclusion, and the longitudinal model consisted of a linear mixed-effects regression model. We explored several structural dependencies (Supporting Information Table S1) to capture the best relationship between disease progression and survival using the SRE model. Thereafter, we selected the strongest contributing predictors for survival from a multivariate regression through a backward procedure based on the lowest Akaike information criterion (AIC).

The proportion of death for SCA2, SCA3, and SCA6 patients was much smaller than that for SCA1 patients. Thus, we performed a search for subgroups of participants sharing the same profiles of disease progression and risk of death using the JLC model for patients with SCA1 only. We selected the best-fitting model with the optimal number of latent classes using a compromise between the lower integrated classification likelihood with Bayesian information criterion approximation[10] and the nonsignificant score test for the conditional independence assumption between longitudinal and survival outcomes.[11] Distributions of the baseline variables across these classes were compared a posteriori using a chi-squared (χ^2) test for categorical variables and an analysis of variance for continuous variables with the honestly significant difference test to account for multiple comparisons.

We assessed the ability of the longitudinal SARA score to predict death by deriving the individual dynamic predictions of death from the best-fitting JLC model and the one-class JLC model, which assumes that the SARA score is independent of the risk of death. The dynamic predictions are usually the predicted probabilities that the death occurs in a window of time $[s, s + t]$ computed using the baseline candidate predictors and the SARA score measure collected before time s. Time t is called the "horizon of prediction" ($t \geq 0$) whereas time s is often called the "time of prediction" or the "landmark time" ($s \geq 0$).[9] These predictions were updated at each new SARA measurement in a 5-year time horizon using all SARA measurements collected until the time of prediction s (before 5 years). The choice of a 5-year prediction horizon was guided by the feasibility and clinical perspective of targeting patients at high risk of disease progression and death who could benefit from future treatment. We compared the predictive accuracy and discriminative capacity of these predictions using the expected prognostic observed cross-entropy (EPOCE)[12] and time-dependent area under curve (AUC),[13] as well as the 95% confidence intervals (CIs) of the differences in EPOCE and AUC: for the EPOCE, the lower the value, the better the accuracy and, conversely for the AUC, the higher the value, the better the prediction.

We randomly selected a new patient, not included in building the model, to illustrate how joint modeling can be used in practice to perform individual dynamic predictions. Subsequent analyses were performed separately for each genotype, given that survival and disease progression differed between genotypes.[2,3] All data analyses were performed using the "*JM*" and "*lcmm*" R packages (R Foundation for Statistical Computing, Vienna, Austria). Values of $P < 0.05$ were considered to be statistically significant, and all tests were two-sided.

Results

Population Characteristics

The 462 patients analyzed here had a total of 2,192 visits, with a median of three visits (interquartile range: 2–4) for each patient. Individual profiles of the SARA evolution show that deceased patients generally had a higher SARA score at baseline (Supporting Information Fig. S1). Demographic and clinical data at baseline are shown in Table 1. During the follow-up, 102 (22%) patients died: 32 (30%) with SCA1, 33 (23%) with SCA2, 26 (21%) with SCA3, and 11 (13%) with SCA6.

Relationship Between Disease Progression and Survival

We applied the SRE model to explore the best relationship between disease progression and survival. For all genotypes, the current value of the SARA score at a particular visit t showed the best relationship with the risk of death at the same visit according to the AIC (Supporting Information Table S1). In SCA1 patients, a predictive model obtained from the multivariate joint model identified higher age at baseline, dysphagia, and current value of the SARA score as the strongest contributing risk factors for death (Table 2). An increase of 1 SD in the total SARA score was associated with a 28% increase in the risk of death. For SCA2, the corresponding risk factors for death were higher age at baseline, longer CAG repeat number, and the current value of the SARA score. Risk of death increased by 19% for an increase of 1 SD in the SARA score (Table 2). For SCA3 and SCA6, the only contributing risk factor for death was the current value of the SARA score. An increase of 1 SD in the SARA score increased the risk of death by 30% for SCA3 patients and 26% for SCA6 patients.

Subgroups of Disease Progression and Survival for SCA1 Patients

We identified patient subgroups that shared the same profiles of disease progression and risk of death by estimating the JLC model with one to four latent classes for patients with SCA1. The model with the optimal number of classes selected by the compromise criterion included three classes (Supporting Information Table S3). Class-specific trajectories and survival function displays showed a small group (severe group), consisting of 12% (n = 13) of patients with the fastest progression of the SARA score (4·67 [standard error {SE}: 2·96]) associated with a higher risk of death than that of the intermediate group (hazard ratio [HR]: 11.28; 95% CI: 3.75, 33.93; $P < 0.0001$; Fig. 1A,B). The other groups, consisting of 29% and 59% of the patients, corresponded to an evolution of the

TABLE 1. Population characteristics at baseline

No.	SCA1 (n = 106*)	SCA2 (n = 146)	SCA3 (n = 122)	SCA6 (n = 87)
Sex (n, %male)	66 (62)	68 (47)	61 (50)	48 (55)
Death (n, %yes)	32 (30)	33 (23)	26 (21)	11 (13)
Age (years)	46 (12)	46 (14)	50 (12)	65 (11)
Age at onset (years)	37 (11)	35 (13)	38 (11)	55 (10)
Disease duration (years)	9 (5)	11 (6)	12 (6)	10 (6)
Repeat length expanded allele	49 (6)	40 (4)	71 (4)	22 (1)
Repeat length normal allele	30 (2)	22 (2)	22 (5)	12 (1)
SARA score	15 (8)	16 (8)	14 (8)	15 (7)
Number of nonataxia signs (INAS)	5 (2)	4 (2)	5 (2)	2 (2)
Median follow-up (years), 95% CI	9.96 (7.2 10.3)	10.25 (10.2 10.3)	10.26 (10.2 10.4)	10.28 (10.2 10.4)

Data are shown as the mean (SD) or number (%).
*One patient (randomly selected) was removed to illustrate how the joint model can be used to provide individual dynamic predictions.

TABLE 2. Multivariate shared random-effect model (survival submodel) from the SARA score according to genotype

Parameter	Estimate	SE	HR (95% CI)	*P* Value
SCA1				
Age at baseline	0.032	0.015	1.03 (1.00, 1.07)	**0.0383**
Dysphagia (yes)	2.071	0.951	7.93 (1.20, 52.27)	**0.0317**
SARA (current value)[a]	0.244	0.039	1.28 (118, 138)	**<0.0001**
SCA2				
Age at baseline	0.066	0.017	1.07 (1.03, 1.11)	**0.0001**
CAG (number repeats)	0.217	0.070	1.24 (1.08, 1.43)	**0.0019**
SARA (current value)[a]	0.156	0.029	1.17 (1.10, 1.24)	**<0.0001**
SCA3				
Age at baseline	0.213	0.249	1.24 (0.76, 2.02)	0.3937
CAG (number repeats)	-0.306	0.221	0.97 (0.63, 1.49)	0.8722
Interaction age and CAG	-0.003	0.004	0.99 (0.98, 1.00)	0.3915
SARA (current value)[a]	0.263	0.046	1.30 (1.19, 1.42)	**<0.0001**
SCA6				
Age at baseline	0.075	0.049	1.08 (0.98, 1.19)	0.1273
SARA (current value)[a]	0.229	0.064	1.26 (1.11, 1.43)	**0.0004**

[a]Progression of the SARA score was linear for all genotypes and was influenced by the expanded repeat CAG for SCA1 patients and age at onset for SCA2 patients. There were no other predictors for SCA3 or SCA6 patients. The corresponding longitudinal submodel is shown in the Appendix. Bolded p values were < 0.05, which means the corresponding factor was significantly associated with death.

SARA score associated with an intermediate and moderate risk of death, respectively. A posteriori classification showed the patients in the severe group to be significantly more severely affected at baseline than those in the intermediate and moderate groups (Table 3). Thus, the severe group was characterized by a lower health-related quality of life, BMI, and CAG repeat length of the normal allele, and a longer duration of disease, a higher SARA score and frequency of number of nonataxia signs, and the following individual nonataxia signs: dystonia, cognitive impairment, and dysphagia.

Dynamic Predictions

We derived the individual dynamic prediction of survival from the one- and three-class JLC model for different times of prediction s (<5 years) in the window $[s, s + 5]$ years and compared them (Fig. 2). According to the 95% CIs of the difference in EPOCE and AUC (zero excluded), the three-class JLC model provided a more accurate estimate (lower EPOCE) and better discriminative capacity to detect patients with a high risk of death (higher time-dependent AUC). This ability of the SARA score to discriminate between subjects with a high-risk of death from those with a lower risk of death exceeded 85% (AUC, 0.852 [SD, 0.062], 0.965 [0.026], 0.974 [0.016], and 0.952 [0.025] for the prediction at the time of visit 1, visit 2, visit 3, and visit 4, respectively). We considered a patient with SCA1 who was randomly selected and not included to build the joint model to illustrate the individual dynamic prediction of survival from the joint model. His

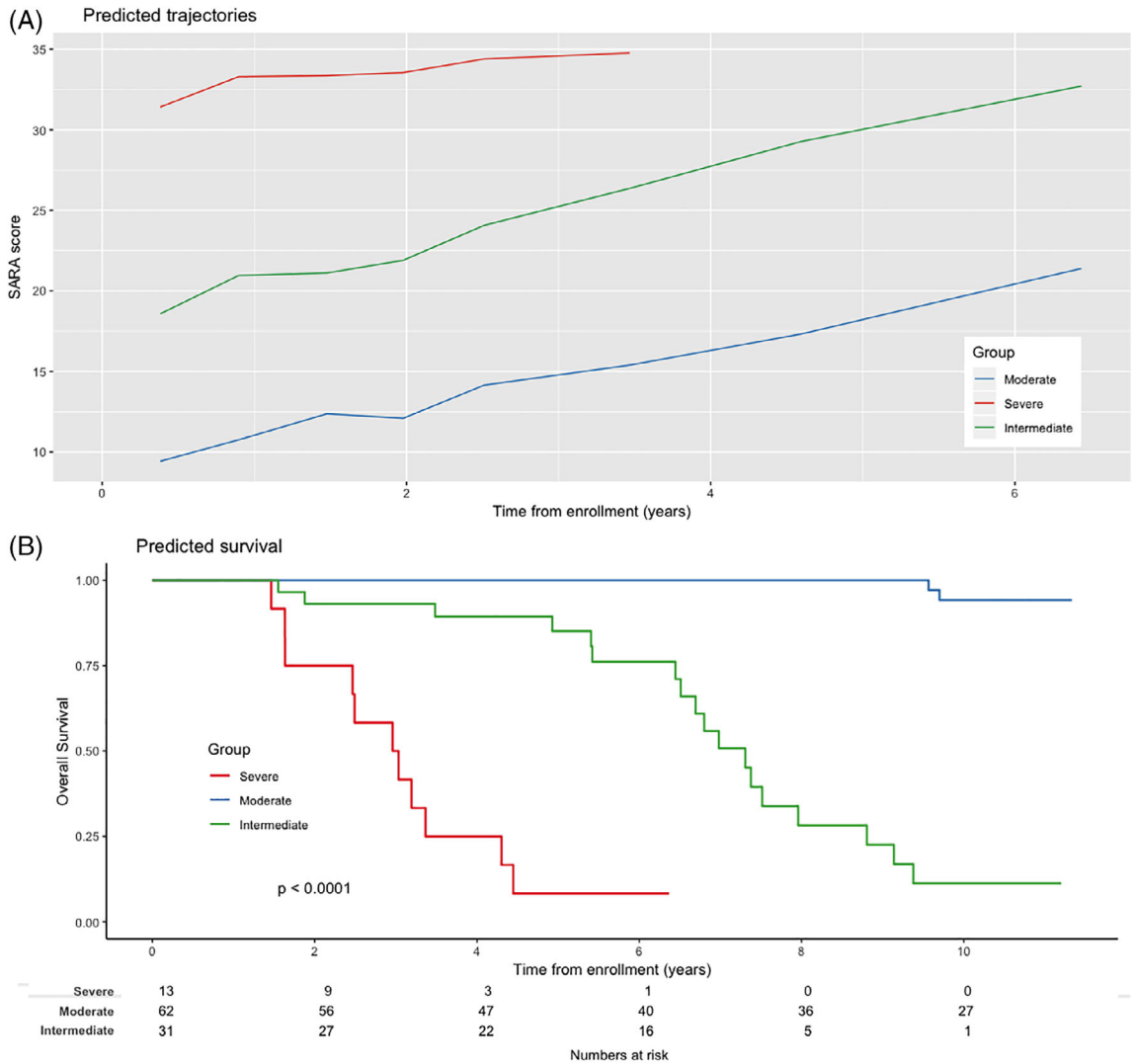

FIG. 1. Class-specific mean trajectories and predicted survival probabilities from the three-class JLC model for longitudinal SARA score in SCA1 patients. (A) Weighted subject-specific predicted SARA trajectories according to the JLC model equation: severe (red line) = 18·5 + 4·7 * time + 0·27 * CAG - 0·07 * interaction between time and repeat CAG; intermediate (green line) = 26·4 – 0·94 * time – 0·16 * CAG + 0·07 * interaction between time and repeat CAG; moderate (blue line) = 9·7 – 1.86 * time – 0·006 * CAG + 0·08 * interaction between time and repeat CAG. (B) Predicted survival according to the Weibull proportional hazard model equation with the intermediate group as reference (green line): severe (red line) = $0{\cdot}27530^2$ * $1{\cdot}76747^2$ * $((0{\cdot}27530^2 * \text{time})^{(1{\cdot}76747^{2-1})})$ * $e^{2.42274}$; moderate (blue line) = $0{\cdot}27530^2$ * $1{\cdot}76747^2$ * $((0{\cdot}27530^2 * \text{time})^{(1{\cdot}76747^{2-1})})$ * $e^{-3.43041}$. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3. Description of the posterior classification from the SARA joint latent class model according to the baseline characteristics for SCA1 patients

Characteristics	Severe (n = 13)	Intermediate (n = 31)	Moderate (n = 62)	*P* Value
Sex (n, %male)	7 (53.8)	20 (66.7)	39 (60.9)	0.7160
Cognitive impairment (n, %yes)	7 (53.8)	7 (23.3)	6 (9.4)	**0.0007**
Urinary dysfunction (n, %yes)	8 (61.5)	11 (36.7)	17 (26.6)	0.0601
Double vision (n, %yes)	4 (30.8)	6 (20.0)	8 (12.5)	0.2371
Dysphagia (n, %yes)	11 (84.6)	22 (73.3)	30 (46.9)	**0.0253**
Dystonia (n, %yes)	4 (30.8)	8 (22.8)	1 (1.6)	**<0.0001**
Death (n, %yes)	10 (83.3)	17 (51.5)	4 (6.6)	**<0.0001**
Age (years)	52.1 (13.7)	46.1 (13.5)	44.8 (10.6)	0.1324
Age at onset (years)	35.3 (11.5)	36.0 (10.7)	37.7 (10.3)	0.7241
Disease duration (years)	16.8 (4.5)	10.1 (4.8)	7.1 (4.1)	**<0.0001**
Expanded CAG	48.3 (7.3)	49.3 (6.6)	46.8 (4.6)	0.3241
Normal CAG	27.6 (1.9)	29.7 (2.1)	29.9 (2.0)	**0.0019**
SARA score	31.8 (0.9)	18.9 (0.7)	9.4 (0.5)	**<0.0001**
EQ-5D VAS	39.0 (28.0)	51.8 (18.5)	67.1 (19.1)	**0.0004**
INAS	7.6 (0.9)	6.0 (0.4)	3.9 (1.8)	**<0.0001**
BMI	22.5 (3.1)	23.6 (3.9)	25.7 (3.9)	**0.0073**

Data are shown as the mean (SD) or number (%). Bolded *p* values were < 0.05, which means the corresponding factor was significantly associated with subgroups latent class.

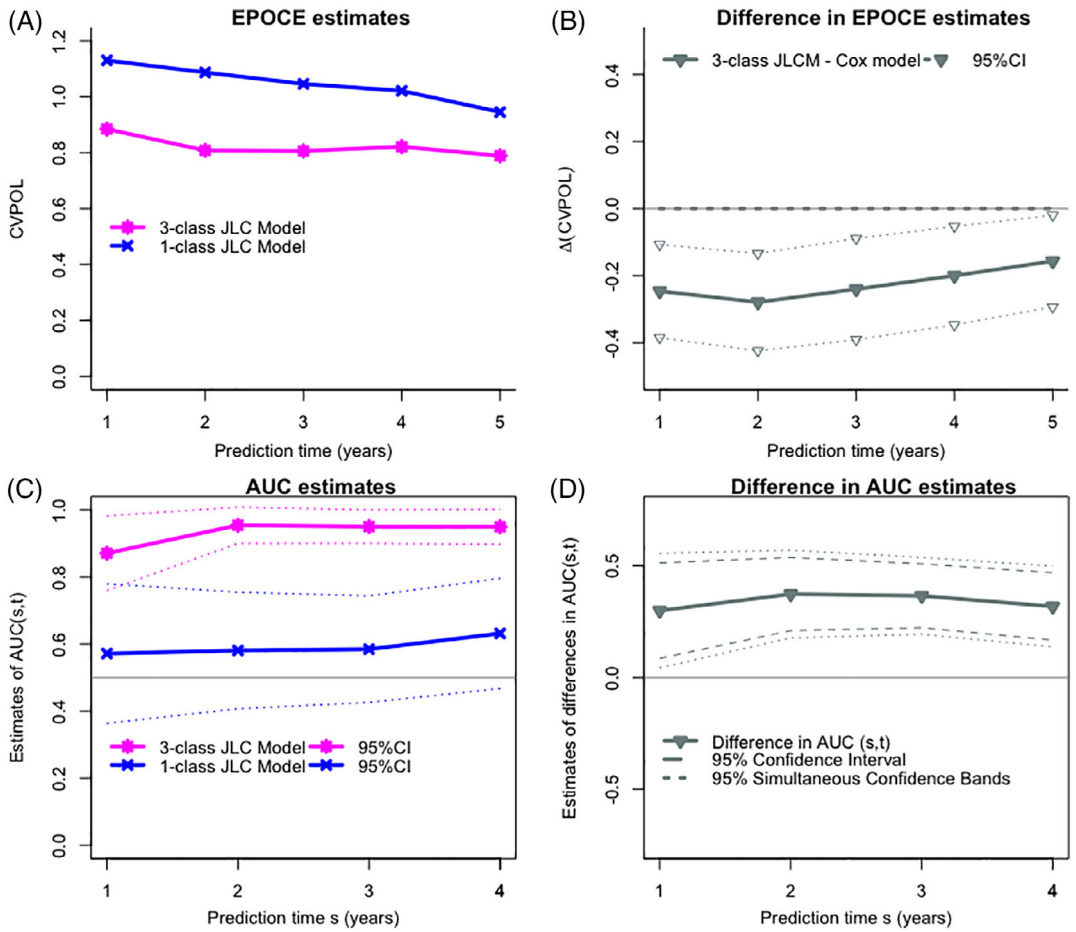

FIG. 2. Comparison of the predictive accuracy of the two predicted risk of death models within the time window (s, s + 1) when s = [visits before 5-year] and t = 5 years from the JLCM estimated from SCA1 patient data: (A) Cross-validated estimate of EPOCE. (B) Difference in EPOCE and 95% tracking interval (top panel). (C) AUC estimate and 95% point-wise CIs (dashed lines). (D) Difference in AUC (solid line), 95% point-wise CIs (dashed lines) and 95% simultaneous confidence bands (dotted lines). CVPOL is the cross-validated estimate of EPOCE. [Color figure can be viewed at wileyonlinelibrary.com]

predicted probability of death within 5 years, for each SARA score collected during the follow-up, is shown in Supporting Information Figure S2. Overall, risk of death predicted by the three-class JLC model increased with increasing SARA score trajectories, whereas predictions from the one-class JLC model remained very low.

Discussion

This is the first longitudinal study to address joint disease progression and survival modeling among patients with SCA. We used this approach to identify subgroups in terms of disease progression and survival for patients with SCA1 and develop an individual dynamic prediction tool of survival.

We assessed the progression of ataxia using the SARA score, which was validated in a rigorous process[4] and is more sensitive to change than the number of nonataxia signs (INAS).[14] Moreover, progression of ataxia was strongly associated with death in all disease subtypes, underlining the clinical relevance and predictive power of the SARA score. Although the INAS score allows the capture of additional information on neurological symptoms and signs other than ataxia, we did not identify a significant effect of INAS score progression on survival for any genotype (data not shown).

We quantified the effect of disease progression on survival by testing several structural dependencies between two outcomes. Survival was more highly influenced by severity of ataxia at a given time point t (current value) than by rate of disease progression for all genotypes. The strongest contributing risk factors of death from the joint model were similar to those previously identified by Cox models, except for SCA3 patients.[3] We failed to replicate the significant negative interaction between age at baseline and number of CAG repeats, probably attributable to the lack of power following restriction of the analysis to patients who had at least two visits, which decreased the number of events from 34 to 26. For SCA2 patients, risk of death increased with longer CAG repeats and higher age at inclusion, in addition to the current value of the SARA score. Similar results were obtained in a recent retrospective analysis of Italian SCA2 patients.[15] However, we did not find a significant effect of CAG on ataxia progression, unlike in the Cuban study, that showed a strong effect of CAG repeat expansion size on saccade peak velocity progression rate in patients with SCA2. Possible reasons of these discrepancies are genetic background and differences between health care systems.[16]

Three profiles for the SCA1 patients homogeneous in terms of disease progression and survival were identified, with the average probability of belonging to the three-class JLC model being higher, ranging from 0.89 to 0.98, suggesting unambiguous classification (Supporting Information Table S4). Patients from these groups shared the same ataxia evolution and risk of death, with 12% of the subjects attributed to the severe group. The most important finding was that the severe group had faster disease progression and a higher risk of death. Moreover, patients from the severe group had a smaller number of CAG repeats of the normal allele, highlighting the modifier effect of the normal *ATXN1* allele in SCA1. A deleterious effect of shorter length of the normal allele in SCA1 has been previously shown for age at onset,[17] but not for disease progression.[2] These patients also had a lower body weight at baseline than the other groups, in accord with the recent reported data on weight loss in relation to disease progression. Investigators showed that patients who lose weight exhibit faster disease progression.[18]

Furthermore, we derived a subject-specific dynamic prediction of survival from the JLC models (one- and thee-class) and showed that the three-class JLC model provides a more precise estimate and better predictive accuracy than the one-class JLC model, which assumes that the SARA score evolution is independent of risk of death conditionally to the latent classes. These findings highlight the importance of subgroup analysis that departs from the hypothesis of homogeneity of the population assumed by the one-class JLC model and confirms the presence of clinical heterogeneity and distinct ataxia progression profiles within the same genotype. Consideration of this heterogeneity will help to improve the design of future clinical trials, particularly in terms of patient selection and stratification.

We previously developed a prognostic nomogram score from the Cox model, from our published survival data for the same cohort, that grouped their prognosis into three risk categories: good, intermediate, or poor.[3] We assessed the agreement between the three-class JLC and Cox models in terms of the classification of SCA1 patients into three groups by computing the kappa coefficient with the 95% tracking CI, using the joint model as the reference. There was an overall good rate of agreement between the two approaches (74% [95% CI: 64–85]). The disagreement concerned 13 patients placed in the good prognosis group in the Cox model that were attributed to the intermediate group in the three-class JLC model or vice versa, and 5 patients in the intermediate prognosis group from the three-class JLC model, classified as having a poor prognosis in the Cox model. However, the agreement for the classification of the poor prognosis group between the two approaches was perfect. Although both approaches show an acceptable agreement rate, the joint model has several advantages. First, the joint model takes into account the repeated measurement of the clinical score (SARA) by correcting the bias induced by random measurement error and the occurrence of the event (death),[19] unlike the Cox model. Second, the joint model provides a better understanding of the link between the repeated clinical scores and the risk of the event. Third, it allows the development of powerful dynamic prognostic tools,[19,20] which

is very useful for the monitoring patients and the decision making during follow-up.

Strengths of our report include the large number of patients and the long-term observational period (up to 10 years). Given the average follow-up of patients of 20 years after ataxia onset, this 10-year observation period might seem short, especially in light of an estimated survival of patients with SCA of 20 to 30 years after onset.[21,22] Information about vital status was incomplete, as in our previous survival analysis.[3] We updated the vital status by the records from the civil registry offices and interviews with family members to reduce the bias attributed to censorship, allowing us to recover 31% (32 of 102) of the deaths. Another strength of our study was the simultaneous disease progression and survival modeling using the joint model methodology, which was robust against a substantial dropout rate, as previously reported, mainly for disease-related reasons during the open extension period.[2] However, limited clinical assessment, the absence of long-term biomarkers and imaging data, and the scarcity of death events, negating the possibility of performing a subgroup analysis for SCA2, SCA3, and SCA6, were limits of this study.

These data extend our knowledge of the biological characteristics of patients with SCA1, SCA2, SCA3, and SCA6. Furthermore, the results provide further information to facilitate the monitoring patients, adaptation of the decision making during follow-up, and selection and stratification of patients for future interventional clinical trials. ■

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Supporting Data

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

A.D.: 2A, 2B, 2C, 3A, 3B
S.T.dM.: 1A, 1B, 1C, 2A, 2C, 3B
H.J.: 1A, 1B, 1C, 2C, 3B
TK: 1A, 1B, 1C, 2A, 2C, 3B
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