RESEARCH ARTICLE

Predictors of Survival in Friedreich's Ataxia: A Prospective Cohort Study

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ABSTRACT: Background: Friedreich's ataxia (FA) is a rare multisystemic disorder which can cause premature death.
Objectives: To investigate predictors of survival in FA.
Methods: Within a prospective registry established by the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS; ClinicalTrials.gov identifier NCT02069509) we enrolled genetically confirmed FA patients at 11 tertiary centers and followed them in yearly intervals. We investigated overall survival applying the Kaplan–Meier method, life tables, and log-rank test. We explored prognostic factors applying Cox proportional hazards regression and subsequently built a risk score which was assessed for discrimination and calibration performance.
Results: Between September 2010 and March 2017, we enrolled 631 FA patients. Median age at inclusion was 31 (range, 6–76) years. Until December 2022, 44 patients

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Relevant conflicts of interest/financial disclosures: The authors declare that there are no conflicts of interest to report related to this work.

Funding agency: European Commission grant (HEALTH-F2-2010-242193).

Received: 15 September 2023; **Revised:** 24 October 2023; **Accepted:** 27 November 2023

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29687

died and 119 terminated the study for other reasons. The 10-year cumulative survival rate was 87%. In a multivariable analysis, the disability stage (hazard ratio [HR] 1.51, 95% CI 1.08–2.12, $P = 0.02$), history of arrhythmic disorder (HR 2.93, 95% CI 1.34–6.39, $P = 0.007$), and diabetes mellitus (HR 2.31, 95% CI 1.05–5.10, $P = 0.04$) were independent predictors of survival. GAA repeat lengths did not improve the survival model. A risk score built on the previously described factors plus the presence of left ventricular systolic dysfunction at echocardiography enabled identification of four trajectories to prognosticate up to 10-year survival (log-rank test $P < 0.001$).

Conclusions: Arrhythmias, progressive neurological disability, and diabetes mellitus influence the overall survival in FA. We built a survival prognostic score which identifies patients meriting closer surveillance and who may benefit from early invasive cardiac monitoring and therapy.

Key Words: Friedreich's ataxia; survival; cardiomyopathy; diabetes mellitus; disability stage

Friedreich's ataxia (FA) (OMIM #229300) is the most frequent inherited ataxia and a devastating multisystemic disease affecting up to 1:20,000 individuals in the Caucasian population.[1]

In around 96% of patients the disease is triggered by biallelic GAA-trinucleotide expansions in the first intron of the frataxin gene.[2] Few patients are compound heterozygous for one GAA expansion and a canonical variant (missense, deletion).[2] Intronic GAA expansions repress the transcription of frataxin gene, resulting in reduced levels of an otherwise normal protein.[3] Frataxin deficiency impairs iron–sulfur cluster synthesis and leads to mitochondrial failure.[4,5] Despite its ubiquitous expression, frataxin deficiency mainly affects the peripheral and central nervous system, the heart, and the endocrine pancreas.[6-10]

FA typically presents with a progressive balance and coordination disorder due to the involvement of dorsal root ganglia, dorsal columns of the spinal cord and, later, of cerebellum.[6] When ataxia is not the inaugural feature, it invariably develops during the disease course.[11] Peripheral neuropathy, spasticity, and muscle weakness may also occur.[6] The neurological presentation is strongly influenced by the genotype.[6,12] Indeed, the length of the shorter GAA repeat displays an inverse correlation with the age at onset of ataxia.[11,13-15] In turn, an earlier age at onset predicts a faster neurological progression.[13,16]

Cardiac disease is an established comorbidity of FA,[7,17] with a prevalence of up to 75%.[6] The most frequent manifestation of cardiac disease are repolarization abnormalities in the electrocardiogram (ECG), typically diffuse T wave inversions.[7,18] Echocardiography usually reveals a mild to moderate left ventricular hypertrophy of a concentric type.[7] Diabetes mellitus is also a recognized feature of FA,[8] which usually occurs later in the disease course and affects up to 8.7% of patients.[19]

The progressive neurological disease leads to severe disability and represents by far the main determinant of morbidity. Hence, two large multicentric consortia addressed the neurological evolution in FA[14,16] providing sample size calculations and outcome measurements for clinical trials.

FA is not only a highly disabling but also a fatal disease, with an average life expectancy of 35–40 years.[20-23] Previous retrospective studies ascribed the shortened survival to cardiac disease.[20,22] This notion justified the early investigation of potential protective drugs, such as idebenone,[24] and the recent development of gene therapy exclusively addressing cardiomyopathy.[25] Nonetheless, cardiac outcome predictors have not been investigated extensively. Moreover, the influence of the other clinical features on survival remains to be defined.

The European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) initiated in 2010 a longitudinal cohort study of genetically confirmed FA patients. Herein, we report the survival data from the EFACTS registry from an observational period of 12 years. Our aims were: (1) to estimate survival rate in FA patients; (2) to identify prognostic factors influencing survival; and (3) to develop a prognostic model for risk stratification in the clinical setting.

Methods

Study Design and Population

The EFACTS registry is a prospective cohort study collecting clinical data from genetically confirmed FA patients in yearly intervals (ClinicalTrials.gov identifier NCT02069509).[13]

The registry was started at 11 centers in seven European countries. For the present study, we considered the first 631 patients consecutively recruited at these centers from September 2010 until March 2017. Longitudinal 2-year and 4-year data from the EFACTS cohort allowed the establishment of subtype specific progression rates which have been published previously.[16,26] Basic clinical and demographic data (age at

onset, sex, length of the GAA repeats) were collected at baseline. Genetic testing was repeated for all study participants at the Laboratory of Experimental Neurology, Université Libre de Bruxelles (Brussels, Belgium). At each yearly visit, neurological outcome measurements, cardiac findings, and the presence of diabetes were collected in a centralized electronic database. The detailed study protocol has been described elsewhere.[13] Each local institutional review board approved the study. Written informed consent was collected by each patient or legal guardian before enrollment.

Clinical Outcome and Predictor Variables

Overall survival was the outcome of interest, which was defined as the time interval elapsing between study enrollment and death of any cause. The observational period spanned from the date of enrollment until December 2022. Candidate predictors were selected based on previous literature[20-23,27] and their clinical relevance.[13,26] As general predictors we included the age at enrollment, the age at onset, sex assigned at birth (from here on referred to as "sex"), and the length of GAA repeats on both alleles. In compound heterozygous patients, the only existent GAA expansion was considered as "shorter allele" (or "GAA1" allele) based on the related literature.[28] We also applied the recently described severity metric "disease burden" (GAA1 repeat length multiplied by the disease duration).[29] As neurological predictor variable we considered the "disability stage". This ranking has been widely used in ataxic disorders[13,30] and conveys the additive effect of multiple neurological deficits in a single score which has a direct functional relevance and is readily transferable to other cohorts. The score ranges from 1 (no functional handicap but signs at examination) to 7 (bedridden) (see also Table S1 in the Supplementary Material).

Due to the prognostic role of cardiac involvement in the literature[20,22,23,27] we explored multiple potential cardiovascular predictors including: (1) cardiac symptoms; (2) findings from transthoracic echocardiography and 12-lead ECG; and (3) present cardiovascular diagnoses (hypertrophic cardiomyopathy, history of arrhythmia, arterial hypertension). Cardiac symptoms (dyspnea, palpitations, chest pain, syncope) were specifically enquired about at each visit. Collected echocardiographic findings included standardized measurements of left ventricular hypertrophy such as the end diastolic left posterior wall thickness (also referred to as "posterior wall thickness"), the end diastolic interventricular septal thickness (also referred to as "septum thickness"), as well as left ventricular ejection fraction and/or fractional shortening. For the present analysis, we translated the two latter parameters in the category "left ventricular systolic dysfunction", which was defined as ejection fraction <50% or fractional shortening <25%. ECG findings were entered into the database as binary variables (present/absent) according to the following categories: repolarization abnormalities, arrhythmia, left ventricular hypertrophy, and conduction abnormalities. As a further predictor, we considered the presence of diabetes mellitus.

Statistical Analysis

We used mean ± standard deviation and median (interquartile range) to describe continuous variables and absolute values/percentages for categorical variables. We applied the Kaplan–Meier method, life tables, and log-rank test to estimate and compare survival rates in the whole cohort and in subgroups. Data for patients who were alive, lost to follow-up, or who terminated the study for reasons other than death were censored. Cox proportional hazards regression was used to study prognostic factors. First, a univariable analysis was run separately for each candidate predictor. We selected variables that showed statistical significance in the univariable model and entered them into a multivariable Cox regression. Missing values in categorical variables were treated as a separate category in these models, missing values in continuous variables were imputed with group medians or means as appropriate. We report hazard ratios (HRs) with their 95% confidence intervals (CIs) and two-sided *P*-values. Clinically relevant predictors selected via the present Cox model and previous literature were inputted into a risk stratification score based on the estimated survival probability after 10 years. The internal validity of the model was assessed by computing the area under the curve (AUC) in the receiver operating characteristic (ROC) analysis for the discriminatory performance and the Hosmer–Lemeshow test for calibration. Statistical analysis was performed with IBM SPSS Statistics, version 28. Statistical significance was set at $P < 0.05$.

Data Sharing

The consent obtained from the study participants did not include publication of raw data in a repository. Data will be made available by the corresponding author upon reasonable request, provided that the objective of the planned analysis is compatible with the consent given by the participants.

Results

Our cohort comprised 631 genetically confirmed FA patients (339 women, 292 men). Seventeen patients (2.7%) were compound heterozygous for one GAA expansion and a canonical mutation (6 missense variants, 2 single nucleotide deletion, 1 splice variant, 1 nonsense variant; for details see also Reetz et al.[13]). The

Table 1 *Clinical data in the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort*

			Univariable Cox regression	
EFACTS cohort – baseline features	**All patients (n = 631)**	**Deceased (n = 44)**	**HR (95% CI)**	***P*-value**
Sex (women), n (%)	339 (54)	18 (40.9)	1.62 (0.98–1.02)	0.12
Age at inclusion (years), median (IQR)	31 (22–43)	30 (23–41)	1.00 (0.98–1.02)	0.91
Age at onset (years), median (IQR)	13 (8–18)	10 (6–13)	0.91 (0.87–0.96)	**<0.001**
Shorter GAA repeat, median (IQR)	650 (423–800)	756 (622–875)	1.28 (1.12–1.46)	**<0.001**
Longer GAA repeat, median (IQR)	912 (812–1050)	980 (883–1127)	1.25 (1.07–1.49)	**0.005**
Disease burden[a], median (IQR)	9350 (4620–15,300)	16,825 (9215–25,795)	1.08 (1.05–1.11)	**<0.001**
Disability stage, median (IQR)	5 (3–6)	6 (6–6)	2.01 (1.42–2.84)	**<0.001**
Diabetes mellitus, n (%) of which insulin-dependent	46 (7.3) 27/46 (59)	9 (21) 4/9 (44)	3.35 (1.61–6.98)	**0.001**
Cardiovascular disease				
Hypertrophic cardiomyopathy, n (%)	228 (36.1)	27 (61)	3.21 (1.69–6.13)	**<0.001**
History of arrhythmia, n (%) of which atrial fibrillation/flutter	52 (8.2) 19/52 (37)	14 (32) 6/14 (43)	6.32 (3.30–12.09)	**<0.001**
Arterial hypertension, n (%)	63 (10)	8 (18.2)	1.35 (0.53–3.45)	0.53
Cardiac symptoms				
Dyspnea, n (%)	142 (22.5)	9 (21)	1.40 (0.67–2.92)	0.37
Palpitations, n (%)	95 (15.1)	9 (21)	1.81 (0.87–3.76)	0.11
Chest pain, n (%)	52 (8.3)	4 (9)	1.65 (0.59–4.62)	0.34
Syncope, n (%)	22 (3.5)	2 (5)	1.90 (0.46–7.87)	0.38
ECG findings	(n = 428)	(n = 31)		
Repolarization abnormalities, n (%)	269 (62.9)	22 (71)	2.29 (0.87–6.06)	0.09
Left ventricular hypertrophy, n (%)	72 (16.8)	7 (23)	2.08 (0.88–4.96)	0.1
Conduction abnormalities, n (%)	27 (6.3)	5 (16)	2.85 (1.07–7.6)	**0.04**
Arrhythmia, n (%)	16 (3.7)	5 (16)	7.29 (2.71–19.65)	**<0.001**
Echocardiographic findings	(n = 429)	(n = 31)		
Left ventricular systolic dysfunction, n (%)	27 (6.3)	6 (18)	3.30 (1.35–8.10)	**0.009**
Septum thickness (mm), median (IQR)	10 (9–12)	12 (10–13)	1.17 (1.03–1.33)	**0.02**
Posterior wall thickness (mm), median (IQR)	10 (9–12)	11 (9–13)	1.08 (0.93–1.24)	0.32
Medications (*n*, %)				
β-Blockers	88 (13.9)	12 (27)	NA	NA
Other anti-arrhythmic drugs[b]	28 (4.4)	1 (2)	NA	NA
ACE inhibitors/angiotensin receptor blockers	70 (11.1)	3 (7)	NA	NA
Diuretics	32 (5.1)	2 (5)	NA	NA
Cardiac glycosides	8 (1.3)	2 (5)	NA	NA
Anticoagulants	28 (4.4)	5 (11)	NA	NA
Antiplatelet drugs	29 (4.6)	2 (5)	NA	NA
Insulin and oral antidiabetics	39 (6.2)	7 (16)	NA	NA

Note: The baseline data for the whole cohort and for the patients who died during the follow-up are reported, along with HRs and *P*-values of the univariable Cox regression analysis. For all continuous variables, HRs are expressed per unit increase except for the GAA repeat (HR per 100 additional repeats) and for the metric "disease burden" (HR per 1000 units increment).Bold type denotes statistical significance.

Abbreviations: HR, hazard ratio; CI, confidence interval; IQR, interquartile range; NA, not applicable; ACE, angiotensin-converting enzyme.

[a]Calculated as number of repeats on the shorter GAA allele multiplied by disease duration, according to Ref. 31.

[b]Including amiodarone, propaphenone, flecainide, and verapamil.

baseline clinical characteristics of the cohort are reported in Table 1. Median (IQR) age at enrollment was 31 (22–43) years (range, 6–76 years; see also eFig. 1 in the Supplementary Material). According to a recent classification,[29] 20.1% of patients had an early onset (0–7 years), 40.7% a typical onset (8–14 years), 23.1% an intermediate onset (15–24 years), and 15.7% a late onset (>24 years) (see also Fig. 1). Almost half of the patients (n = 307, 48.7%) were wheelchair-bound (disability stage = 6).

At the first visit, 240 patients (38%) had a diagnosis of cardiovascular disease, mainly consisting of hypertrophic cardiomyopathy (228/631 cases, 36.1%). Fifty-two patients had a diagnosis of arrhythmic disorder (8.2%), with 19 (3%) suffering from atrial fibrillation/flutter. Sixty-three patients (10%) suffered from arterial hypertension. Two patients had undergone heart transplantation prior to inclusion in the registry. Nine patients carried a cardiac device at baseline (n = 7 implantable cardioverter defibrillator, n = 2 pacemaker). At baseline, dyspnea and palpitations were the most frequent cardiac symptoms, reported by 142 (22.5%) and 95 (15%) patients, respectively. Syncope had occurred previously in 22 patients (4%). Baseline echocardiographic findings were available in 429 patients (Table 1). The median septum and posterior wall thickness were within the normal range and all available measurements were <30 mm. Left ventricular systolic dysfunction was evident in 27 patients (6%). Baseline ECG data were available for 428 patients. Of them, 287 (67%) showed abnormal findings. Repolarization abnormalities, mainly diffuse T wave inversions, were the most common sign (269/428 ECGs, 62.9%). With a far lower frequency, FA ECGs showed positive indexes of left ventricular hypertrophy (72/428, 16.8%), conduction abnormalities (27/428, 6.3%), mostly consisting of right bundle branch block (16/27). Arrhythmias were evident in 3.7% of baseline ECGs (16/428, of whom 7 showed supraventricular tachycardia/ectopic beats, 5 atrial fibrillation, 2 atrial flutter, and 1 ventricular ectopic beats).

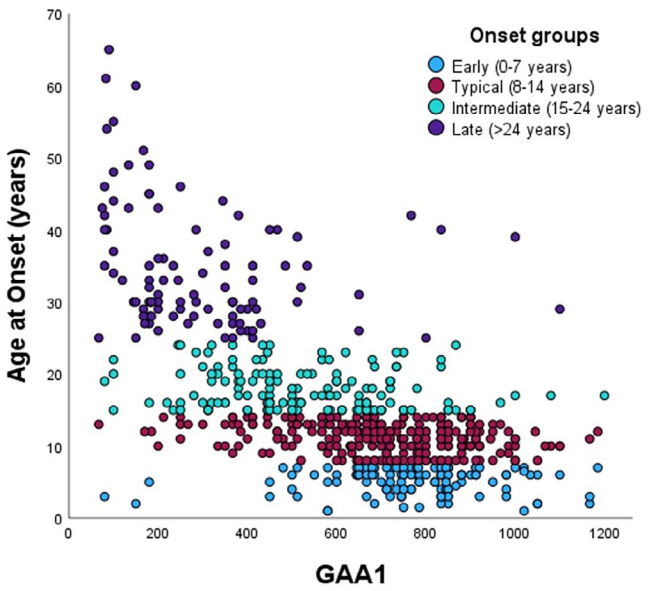


FIG. 1. Age at onset and GAA1 repeat lengths in the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) registry. GAA1, shorter GAA repeat expansion length. According to the reported age at onset, patients are assigned to an early, typical, intermediate, or late onset group (see also Ref. 29). [Color figure can be viewed at wileyonlinelibrary.com]

At baseline, 46 patients (7.3%) had diabetes mellitus, which was insulin-dependent in 27/46 (59%). The use of cardiac and antidiabetic medications at baseline is reported in Table 1.

A total of 3767 visits were finalized from September 2010 to December 2022. The median (IQR) follow-up time was 6 (3–9) years. For 579 patients at least two visits were available.

Survival Analysis

Over a 12-year observation period, 44 patients died and 119 patients terminated the study for other reasons (lost to follow-up, retrieval of consent). The 10-year cumulative survival rate in the whole cohort was 87%. Death occurred at a mean age of 39 ± 14 (range, 13–73) years, after a median (IQR) follow-up of 6 (3–10) years. Thirteen patients died of cardiovascular causes. The underlying event was progressive heart failure in 7/13 cases, three of whom experienced an abrupt worsening of cardiac function upon an intercurrent infection. Arrhythmia was the likely cause of death in 4/13 cases (described as sudden death). Five patients died from pneumonia (3 = aspiration pneumonia, 1 = COVID-19 pneumonia). In 2 patients, death was ascribed to a general, progressive deterioration. Two patients died because of cancer (1 = metastatic bladder cancer, 1 = acute leukemia), 2 by means of euthanasia, 1 patient succumbed to traumatic neck injury, and 1 died following a thrombosis. In the remaining 18 cases the cause of death was unknown. Death of cardiac cause tended to occur earlier than death of other/unknown causes: median age at cardiac death 33 (range, 13–60) years versus 39 (range, 21–73) years ($P = 0.27$). No significant correlation was found between GAA repeat lengths and the age at death. Of the 9 patients carrying an implantable cardioverter/pacemaker, 5 died during follow-up, after a range of 6–28 years after implantation. In this group, death occurred because of heart failure in 4 patients and due to pneumonia in 1 patient. The 2 patients who received a heart transplantation were still alive at the last observation, 12 and 19 years after the transplantation, respectively.

In a univariable analysis, several variables were associated with overall survival, including general features (age at onset, GAA repeats length of both alleles), the

disability stage, diabetes mellitus, and several cardiac predictors (hypertrophic cardiomyopathy, history of arrhythmia, septum thickness, left ventricular systolic dysfunction, arrhythmia at ECG, conduction abnormalities; see also Table 1). Cardiac symptoms showed no significant association with survival. In the multivariable analysis, the disability stage, a history of arrhythmic disorder, and diabetes mellitus remained the only significant, independent predictors of survival (Table 2). Notably, GAA repeat lengths were not an independent predictor of survival in the multivariable model. Also the newly described metric "disease burden",[31] which encompasses both GAA repeat lengths and disease duration, displayed a strong association with survival in the univariable analysis (HR 1.08, 95% CI 1.05–1.11, $P < 0.001$), but not in the multivariable one (HR 1.03, 95% CI 0.99–1.07, $P = 0.1$, when inputted in the model instead of the shorter GAA repeats).

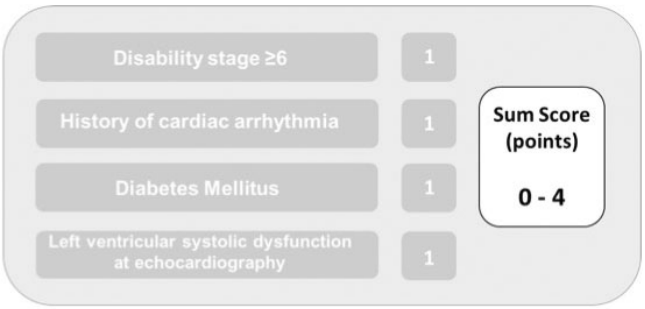
Prognostic Model

Considering the number of events (n = 44), we selected four predictors in a stepwise backward regression and inputted them into a prognostic model (disability stage, history of arrhythmia, diabetes mellitus, and left ventricular systolic dysfunction). Disability stage was transformed in a categorical variable with a ≥6 threshold based on the distribution of events across worsening ranking. We then arbitrarily assigned each predictor one point to calculate a final sum score. While the absence of all four predictors (sum score 0) predicted a 10-year survival rate approaching that of general European population,[32] increasing sum scores enabled discrimination between different prognostic trajectories with stepwise increasing risk, as shown in the Kaplan–Meier curves (log-rank test $P < 0.001$; Figs 2 and 3, and Supplementary Table S2). Cumulative 10-year survival was estimated at 96% with a sum score of 0, 84% with a sum score of 1, 70% with a sum score of 2, and 42% with a sum score ≥3 (Fig. 2). The discriminatory ability of the risk score was confirmed by the ROC analysis (AUC 0.75) and its calibration by the Hosmer–Lemeshow test ($\chi^2 < 0.01$, df = 1, $P = 1$).

TABLE 2 *Candidate predictors of survival in the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort*

	Multivariable Cox proportional hazards regression analysis	
Predictor	**HR (95% CI)**	***P*-value**
Age at onset	0.96 (0.90–1.02)	0.20
Shorter GAA repeat	1.00 (0.81–1.21)	0.91
Longer GAA repeat	1.11 (0.89–1.39)	0.37
Disability stage	1.51 (1.08–2.12)	**0.02**
Diabetes mellitus	2.31 (1.05–5.10)	**0.04**
Systolic dysfunction	1.48 (0.56–3.91)	0.43
Hypertrophic cardiomyopathy	1.75 (0.86–3.58)	0.13
History of arrhythmia	2.93 (1.34–6.39)	**0.007**

Note: For continuous variables HRs are expressed per unit increase (disability stage) or per 100 additional repeats (GAA repeat length).
Bold type denotes statistical significance.
Abbreviations: HR, hazard ratio; CI, confidence interval.



Sum score	10-years cumulative survival rate	95% CI
0	96·4%	93·4%-99·4%
1	84·3%	77·4%-91·3%
2	69·6%	55·4%-83·8%
≥3	42·4%	10·7%-74·1%

FIG. 2. European Friedreich's Ataxia Consortium for Translational Studies Survival Predictive Score (EFACTS-SPS). Depending on the presence of the four predictors individuated by the study a score range from a minimum of 0 to a maximum of 4 is assigned. An increasing score is associated with a significant reduction in the 10-year survival rate (see also Fig. 3).

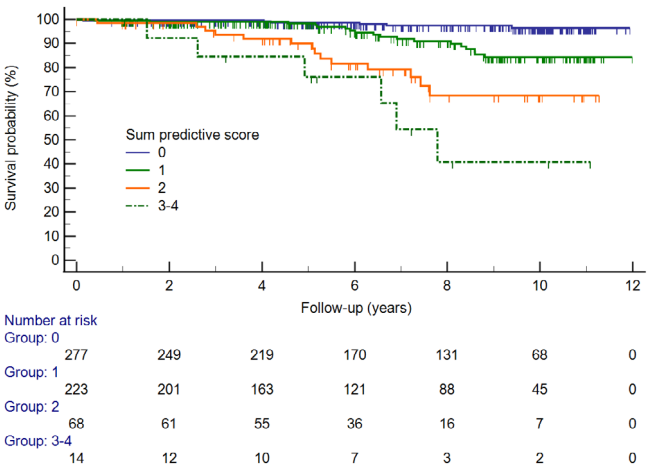


FIG. 3. Survival rates in the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort according to the developed prognostic score. Tick marks indicate censored subjects (patients who were still alive at follow-up and patients lost to follow-up). Number of subjects at risk for each subgroup at follow-up intervals is reported. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

This is the first multicentric, prospective study addressing survival in FA. In the EFACTS registry, death occurred at a mean age of 39 years, similar to reports published after the introduction of genetic testing.[20,23] Cardiovascular etiologies were documented in half of the patients with known death cause, including both progressive heart failure and arrhythmia. In a multivariable analysis, three factors emerged as significant, independent predictors of survival: history of arrhythmias, the disability stage, and diabetes mellitus.

Despite the prognostic role of heart disease in FA, cardiological assessment and early treatment, including invasive therapies, received less attention. In our large, multicentric cohort, the diagnosis of arrhythmic disorder emerged as the solely independent cardiac predictor of survival in the multivariable model. Supraventricular arrhythmias, including atrial fibrillation, are frequently documented in FA.[23,33,34] They might precipitate heart failure and increase mortality related to thromboembolic complications.[23] Ventricular arrhythmias, one major substrate of sudden cardiac death, are supposedly rare in the literature on FA cardiomyopathy.[33-35] Nonetheless, very few observations from ECG monitoring studies are available in FA, preventing firm conclusions being drawn on this issue.[36] Notably, fatal arrhythmias do occur in the setting of cardiomyopathies with preserved systolic function.[37,38] Indeed, microscopic histopathological alterations following interstitial collagen deposition and replacement scarring after myocyte death constitute an unpredictable arrhythmogenic substrate.[38] To date, one prospective, single-center study analyzing 18 death events in FA suggested as predictor of survival a progressive decline in the ejection fraction.[23] We might have missed such an effect due to the shorter observation period of our study (12 vs. 22 years). Conversely, our findings underscore the previous observations that systolic dysfunction is a late event in FA,[27,39] which may abruptly develop shortly before death,[27] as observed in our cohort. Importantly, cardiac symptoms had no role in our prediction model. Due to the neurologically determined limitation in physical activity, FA patients may have little exertional symptoms. This limits the application of the New York Heart Association classification to quantify the progression of heart failure in FA.[17]

GAA repeat lengths, especially of the shorter allele, is the best recognized predictor of both age at onset and progression rate of the ataxic disorder.[11,13-15] Concerning survival, the length of the shorter allele was the best predictor of survival in a monocentric prospective study by Pousset et al.[23] It furthermore significantly correlated with age of death in a retrospective study.[20] In our cohort, the predictive role of GAA repeat lengths in the univariable model was not confirmed in the multivariable analysis and no correlation was found between this parameter and the age of death. These differences are not explained by the clinical characteristics of our cohort, which are indeed comparable with those of the cited studies. Nonetheless, the observation period in these earlier studies started more than a decade before the establishment of EFACTS, and even prior to the availability of a molecular diagnosis. The standard of care of the non-neurological comorbidities improved meanwhile and might have influenced the disease course in the EFACTS cohort. Moreover, the study by Pousset et al. did not include a measure of neurological severity in the survival analysis.[23] Instead, the global neurological burden, as reflected by the disability stage, emerged as an independent predictor of mortality in our study, with a cumulative HR of 4.5 in a wheelchair-bound patient (disability stage = 6) compared to a patient with overt ataxia but independent gait (disability stage = 3). Consistently, causes of death classically associated with increasing neurological disability (eg, aspiration pneumonia) were recurrently reported. These findings suggest that therapeutic strategies targeting the neurological outcome may contribute to influence the survival rate in FA. They furthermore stress the need for regular monitoring and complementary management with rehabilitation programs in all stages of the disease.

The morbidity and mortality risk caused by diabetes mellitus in the general population is well established.[40] Hewer documented ketoacidosis as cause of death in an early study on "fatal cases" of FA.[27] A negative prognostic role of diabetes mellitus was suggested by a retrospective analysis conducted before the advent of genetic diagnosis.[22] This is the first study to clearly show a significant effect of diabetes mellitus on survival in FA, setting the rationale for a systematic investigation of targeted interventions.

In agreement with previous studies on FA and other spinocerebellar ataxias,[23,41] we chose the time-on-study (ie, time from the enrollment) as the timescale, which is more suitable for assessing predictive discrimination. Neither in the present study, nor in an earlier prospective analysis by Pousset and coworkers,[23] did age at inclusion play a role as predictor of survival. This finding is likely related to the age dependency of FA phenotype. Indeed, older patients are more likely to have less severe disease and lower risk of premature death due to FA, thus counterbalancing the inherent mortality risk otherwise connected with advancing age.

Several patients were on medical treatment for heart disease and diabetes or received invasive cardiological therapies before recruitment. These interventions may modify the clinical course of the non-neurological manifestations and possibly influence their weight as predictors in the survival analysis. The non-controlled design of our study precluded an evaluation of their impact on survival.

Consequences for the Current Management of FA

Considering the significant predictors defined by the present study and previous literature,[23] we built an easy-to-apply clinical predictive score, which clearly discriminated between different prognostic trajectories. This score may support clinical management by identifying high-risk patients who merit closer clinical surveillance and might benefit from early invasive therapies aimed at improving survival.

Current recommendations include yearly transthoracic echocardiography and 12-lead ECG to monitor cardiomyopathy in FA. Holter ECG is listed as an optional examination only in symptomatic patients.[42] Our findings support the introduction of systematic prolonged ECG monitoring, independently from symptoms, to tackle intermittent arrhythmias. In the era of digital biomarkers, portable devices may help accomplish this task in a home setting, especially in patients with advanced disease. To date, cardiac studies in FA have mostly been cross-sectional and focused on ultrasound biomarkers. We urgently need longitudinal natural history studies specifically investigating cardiac outcome and integrating both ultrasound and ECG biomarkers.

Limitations

Our study has several limitations. First, the EFACTS cohort comprises mostly adults, while pediatric cases with longer repeats expansions are underrepresented. Moreover, the cohort comprises a large proportion of patients at an advanced disease stage (almost 50% were wheelchair-bound), reflecting the characteristics of European FA patients at the time point of recruiting to EFACTS in 2010 and thus the usual characteristics of a FA cohort captured at a certain time point. The restricted number of early-onset cases with severe cardiac disease might partly explain the limited number of events of interest (n = 44) which occurred in the observation period. To the best of our knowledge, only one retrospective study specifically investigated cardiac disease and survival in a pediatric cohort.[43] Of 79 patients, eight fatalities were reported in a median observation period of 5 years (atrial arrhythmia-related n = 2, heart failure-related n = 1, non-cardiac n = 2, unknown cause n = 3). Surprisingly, this study did not consider the GAA repeats in the survival analysis, nor did it succeed in identifying any clinical predictors of outcome. A global registry study, including both children and adults, together with reliable genetic information on the precise repeat length on both alleles, would certainly be the desirable context for FA research. This unmet need might be fulfilled in the future by the ongoing fusion and harmonization of the North American, Australian, and European FA registries.[44]

Due to the multicentric nature of the present study, cardiological evaluation within EFACTS encompassed only widely assessable parameters. For this reason, and due to the number of missing examinations (n = 13 missing data in the patients who died), we were not able to draw any inferences on the role of specific ECG and echocardiographic biomarkers. Earlier studies identified cardiomyopathy as the main cause of premature death in FA. Cardiac events were also frequently reported in our study. Nevertheless, since the exact circumstances of death were not obtained in several patients, our assumption as to the causes of mortality in FA has limitations.

Conclusions

In conclusion, the present multicentric, prospective study pinpointed: (1) arrhythmias as the most important cardiac predictor of survival and (2) defined for the first time progressive neurological disability and diabetes mellitus as further major contributors to mortality in FA. Consequently, we propose a simple predictive score which allows stratification of prognostic trajectories based on the presence of relevant predictors (disability stage ≥6, history of arrhythmias, systolic dysfunction, and diabetes mellitus). This tool awaits external validation in further prospective FA cohorts. Collectively our findings have relevant implications for disease monitoring, risk stratification, and development of future therapeutic strategies in FA.

Acknowledgments: Several authors of this study are members of the European Reference Network for Rare Neurological Diseases—Project ID No. 739510.

Data Availability Statement

The consent obtained from the study participants did not include publication of raw data in a repository. Data will be made available from the corresponding author upon reasonable request, provided that the objective of the planned analysis is compatible with the consent given by the participants.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Financial Disclosures for the Previous 12 Months

E.I. is supported by the European Joint Programme on Rare Diseases (EJP-RD WP17 Research Mobility Fellowship) and received funding from the Friedreich's Ataxia Research Alliance (FARA), FARA Ireland, and FARA Australia, as well as from the Intramural Funding Program of the Medical University Innsbruck for Young Scientists (MUI-START, Project 2022-1-3).