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ARTICLE CLASS OF EVIDENCE

Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy

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Abstract

Objective

To assess the natural history and treatment effect on survival among patients with transthyretin-associated familial amyloid polyneuropathy (TTR-FAP) stage 1 Val30Met.

Methods

Multi-institutional, hospital-based study of patients with TTR-FAP Val30Met prospectively followed up until December 2016, grouped into untreated (n = 1,771), liver transplant (LTx)-treated (n = 957), or tafamidis-treated (n = 432) cohorts. Standardized mortality ratios, Kaplan-Meier, and Cox methods were used to estimate excess mortality, survival, and adjusted hazard ratios (HRs) for all-cause mortality.

Results

Disease-modifying treatments decreased TTR-FAP excess mortality from 10 to 4 (standardized mortality ratio 3.92, 95% confidence interval [CI] 2.64–5.59). Median overall survival of untreated and LTx-treated cohorts was 11.61 (95% CI 11.14–11.87) and 24.73 years (95% CI 22.90–27.09), respectively, and was not reached in the tafamidis-treated cohort (maximum follow-up, 10 years). Both disease-modifying treatments improved survival. Among early-onset patients (younger than 50 years of age), tafamidis reduced the mortality risk compared with untreated patients by 91% (HR 0.09, 95% CI 0.03–0.25, $p < 0.001$) and with LTx-treated patients by 63% (HR 0.37, 95% CI 0.14–1.00, $p = 0.050$). Previous tafamidis treatment did not affect mortality risk after LTx (HR 0.83, 95% CI 0.25–2.78, $p = 0.763$). Among late-onset patients (50 years and older), tafamidis reduced mortality risk by 82% compared with untreated patients (HR 0.18, 95% CI 0.06–0.49, $p = 0.001$).

Conclusion

LTx and tafamidis convey substantial survival benefits, but TTR-FAP mortality remains higher than in the general population. These results strongly reinforce the importance of timely diagnosis and earlier treatment, boosting the pursuit for an increased life expectancy.

Classification of evidence

This study provides Class III evidence that for patients with stage 1 Val30Met TTR-FAP, LTx and tafamidis increase survival.

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Glossary

CI = confidence interval; **HR** = hazard ratio; **LTx** = liver transplant; **mOS** = median overall survival; **RMST** = restricted mean survival time; **SMR** = standardized mortality ratio; **TTR-FAP** = transthyretin-associated familial amyloid polyneuropathy.

Transthyretin-associated familial amyloid polyneuropathy (TTR-FAP) is an autosomal-dominant, adult-onset, progressive neurodegenerative systemic disease, described in 1952 by Corino de Andrade.[1] TTR-FAP is rare with endemic populations predominantly in Portugal, Sweden, Japan, and Brazil.[2–4] Its symptoms stem from amyloidosis that results from misfolding of the TTR protein tetramer.[2,5–7] More than 120 TTR gene mutations are associated with TTR-FAP, the most common of which is Val30Met.[5] If untreated, the disease progresses rapidly to death, usually within the first decade after symptom onset.[2,8,9]

Orthotopic liver transplantation (LTx) was first implemented in the 1990s as a surgical gene therapy strategy to ameliorate or halt familial TTR amyloidosis.[10,11] In the past decade, the oral disease-modifying treatment tafamidis became available as a treatment option at 20 mg once daily, first in the context of clinical trials (2007) and later as an approved drug (November 2011 in the European Union) for the treatment of adult patients with early-stage TTR-FAP to delay disease progression.[12,13] Other treatment options are being evaluated in phase 3 trials.[14,15]

Although disease-modifying treatments are used worldwide to delay or halt disease progression, challenges in clinical assessment remain because of disease rareness, clinical heterogeneity, incomplete natural history, and uncertain treatment effectiveness. Hence, in this study, we aimed to assess natural history survival, evaluate the effect of LTx and tafamidis on survival, explore prognostic factors, and compare treatment effectiveness in patients with early-onset (younger than 50 years of age) and late-onset (50 years and older) disease.

Methods

The report of this study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[16]

Study design and participants

This was a multi-institutional, hospital-based cohort study of consecutive symptomatic adult patients (18 years and older) with a diagnosis of TTR-Val30Met FAP given prospective longitudinal follow-up since the first patient observation in 1939[1] through the end of the study on December 31, 2016, at either of 2 Portuguese referral centers. Historically, diagnosis of TTR-Val30Met FAP was based on the patient's clinical findings, family history, and pathology. Since 1985, when genetic testing became available,[17] it was possible to link all cases to families in whom the Val30Met mutation was confirmed. Asymptomatic carriers were excluded.

To account for selection bias and to reduce clinical heterogeneity, we predefined different populations for comparative purposes.

For the tafamidis cohort, we included all patients who started treatment, regardless of whether they discontinued tafamidis (intention-to-treat approach), and all those who underwent subsequent LTx because of patient preference or disease progression despite tafamidis treatment.

The intended overall LTx cohort for comparative analysis consisted of patients who underwent transplantation beginning in 1992, the year LTx became a routine treatment option in Portugal. Although clear-cut absolute and relative contraindications for LTx are difficult to establish, the following factors are considered at Portuguese centers for the selection of patients: age (younger than 50 years); disease duration (<7 years); low polyneuropathy disability score (stage 1 disease); modified body mass index ≥600 $kg/m^2 \cdot g/L$; no severe autonomic dysfunction; absence of amyloid cardiomyopathy; and no significant renal dysfunction.[18,19]

Patients who underwent LTx in 2012 or later were excluded (in Portugal, tafamidis became a first-line treatment option in 2012, and selection to treatment biases could have occurred because of physician or patient preference), as were patients who underwent LTx at more advanced stages of the disease[20]—stages 2 and 3, for which tafamidis is not approved. We anticipated that more than 20 years of important changes could have occurred in the LTx setting and could have increased survival because of improvements in surgical techniques, surgeons' learning curves, enhancement of adjuvant pharmacologic treatments (e.g., protocols for lifelong immunosuppressants), and optimization of patient selection criteria for LTx (e.g., selection of patients with better prognosis factors).[21] Therefore, we tested this hypothesis by comparing survival between patients who underwent LTx before 2007 and during or after 2007 (the year tafamidis became available as a treatment option in a clinical trial context). If no significant differences were found, the overall LTx cohort selected for primary comparative analysis encompassed stage 1 patients who underwent LTx between 1992 and 2011 (20-year time interval) to maximize informative cohort follow-up (up to 25 years). Nonetheless, even in this scenario, we conducted an exploratory comparative analysis considering only LTx patients who underwent LTx in 2007 and later to assess the robustness of the findings. If significant differences were detected, the primary comparative analysis included only patients who underwent LTx in more recent years.

The overall untreated cohort was evaluated within 3 disease-onset periods: 1992 onward, 1972–1991 (20-year time interval as for the intended overall LTx cohort), and before 1972. We anticipated survival gains over time, even among untreated patients, as changes occurred in global health care services relating to TTR-FAP. However, patients with disease onset in more recent years who have not received treatment are more likely to have poorer prognoses (for example, patients with late-onset disease), not fulfilling eligibility criteria for available treatment. Therefore, we selected the 1972–1991 untreated cohort for subsequent analysis, prospectively studied since disease onset (stage 1 patients).

Procedures

Data were extracted from clinical records regarding sex, dates of birth, disease onset and death, and treatment-related data (type, date of initiation, and follow-up). Disease onset was defined as the patient's age when TTR-FAP symptoms were first noticed by the patient. Data discrepancies were actively searched by means of database queries and resolved through revision of the patient chart. With the exception of 4% of the patients (n = 121), who were censored at the time of their last visit, date of death was confirmed in the National Health Service User Registry.

Statistical analysis

Pearson χ^2 test was used to compare categorical variables. Continuous variables were checked for normal distribution and analyzed accordingly with parametric or nonparametric tests. The overall effect of TTR-FAP treatment on mortality was assessed through standardized mortality ratios (SMRs) calculated for the years 1991 (before treatment availability) and 2016 (end-of-study year), by sex and age group.[22]

Survival was estimated using the Kaplan-Meier method. All-cause mortality was evaluated from disease onset (index event) except for the analysis of prognostic factors among treated cohorts, in whom overall survival was evaluated since treatment initiation to account for the effect of disease duration before treatment on survival. Patients were monitored until death or end of study. Administrative censoring of data was performed for patients who were alive at the end of the study (n = 1,176), for those enrolled in ongoing clinical trials (n = 34), and for those lost to follow-up (n = 121). For patients in the tafamidis cohort, the primary analysis also censored patients who underwent subsequent LTx (n = 44) with censoring starting at the time of transplantation. Sensitivity analysis was also performed that encompassed all tafamidis-treated patients and included survival follow-up of patients enrolled in clinical trials and of those who underwent subsequent LTx.

Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated through Cox regression models, all of which were stratified by hospital referral center. Within each treatment cohort, exploration of prognostic factors for survival included sex, late-onset status, stage (for LTx only), and disease duration before treatment, all of which were explored together in a Cox proportional hazards model adjusted for decade of onset as a covariate.

Comparisons of treatment effectiveness were made separately for populations with early- and late-onset disease according to a Kaplan-Meier method crediting time before treatment in the LTx and tafamidis cohorts to the untreated cohort. A Cox regression model with treatment as a time-varying covariate was used, with adjustment for age at onset in 5-year categories and for sex.[23,24] The treatment variable used a value of zero until treatment initiation and a value of one from treatment to death or censoring. This allowed follow-up before LTx or tafamidis initiation to be credited to the untreated natural history cohort. To assess the robustness of the findings, we have also compared survival between cohorts using the restricted mean survival time (RMST) as a complementary summary measure to HR,[25] since there is evidence that treatment-effect measures on the basis of RMST are more conservative than HRs[26] and do not rely on hazards proportionality. RMST-based treatment-effect measures were calculated taking the time horizon as the minimum of the largest observed event time among all cohorts.

For the early-onset population, and to address whether previous treatment with tafamidis modified survival after LTx, we conducted an exploratory analysis that compared patients with and without previous tafamidis treatment. To ensure similar follow-up, non–tafamidis-treated patients included only those who underwent LTx from 2007 to 2011. A further exploratory analysis for the early-onset population was performed, comparing LTx and tafamidis-treated cohorts, and evaluating mortality risk since treatment initiation (index event) for a period of 10 years. For the population with late-onset disease, LTx is not a general treatment option; therefore, analysis of treatment effectiveness compared only the tafamidis and untreated cohorts.

Statistical analysis and graphs were performed using Stata Statistical Software: Release 15.0 (StataCorp LLC, College Station, TX). The threshold for statistical significance was set at $\alpha = 0.05$.

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the institutional ethics board committees (Centro Hospitalar do Porto and Centro Hospitalar Lisboa Norte) and by the National Data Protection Committee. Informed consent was obtained from live participants.

Primary research question

Has disease-modifying treatment (LTx and tafamidis) improved survival among patients with Val30Met TTR-FAP? This study provides Class III evidence that for patients with stage 1 Val30Met TTR-FAP, LTx and tafamidis increase survival. This study is rated Class III because of the potential of important confounding differences between groups.

Data availability

Anonymized data generated during the current study are available on reasonable request from individuals affiliated with research or health care institutions located in Portugal, as approved by the National Data Protection Committee. See data available from Dryad (table 1, doi.org/10.5061/dryad.3583v22).

Results

Characteristics of the study cohorts

The study included 3,221 symptomatic patients. Sixty-one patients were excluded because of missing data at disease onset (n = 57) or date of LTx (n = 4). Our sample for analyses thus included 3,160 patients: 1,771 in the untreated, 957 in the LTx-treated, and 432 in the tafamidis-treated cohorts (data available from Dryad, table 1, doi.org/10.5061/dryad.3583v22). Median follow-up was 10.25 years in the untreated cohort, 13.67 years in the LTx cohort, and 5.45 years in the tafamidis-treated cohort. Overall, 1,853 patients (58%) died.

The mean (SD) age at disease onset was 36.7 (12.2) years and 1,697 patients (53.7%) were male (data available from Dryad, table 1, doi.org/10.5061/dryad.3583v22). The cohorts did not differ in sex distribution ($p = 0.321$). The proportion of patients with late-onset disease and their median age at disease onset differed between cohorts ($p < 0.0001$). Both were lower in the LTx-treated cohort than in either other cohort, as expected given that LTx is not routinely recommended for patients with late-onset disease. Median duration of disease before treatment was longer among LTx-treated than tafamidis-treated patients ($p < 0.0001$), also as expected given the additional waiting time for LTx (data available from Dryad, table 1, doi.org/10.5061/dryad.3583v22). Similar results were found for comparisons between the selected cohorts used for analysis of comparative treatment effectiveness (table 1).

Effect of treatment

SMR analysis for year 1991 (before LTx became available) indicated that untreated patients had a 10-fold (SMR 9.79, 95% CI 6.65–13.90) excess mortality rate than did the general population. In 2016, patients with TTR-FAP faced a 4-fold (SMR 3.92, 95% CI 2.64–5.59) excess mortality rate compared with the general population, indicating a decrease of 60% after treatment (LTx or tafamidis) became available. The excess mortality rate was highest in patients 45 to 54 years of age than in other age groups and was higher in women than in men (table 2).

Survival prognostic factors

Untreated cohort (natural history)

The 1972–1991 untreated cohort, which exhibited a median overall survival (mOS) of 11.61 years (95% CI 11.14–11.87 years), showed the highest survival among all untreated cohorts (figure 1). In this cohort, the mortality risk was higher

Table 1 Characteristics of patients with Val30Met TTR-FAP in the selected cohorts

	Untreated (year of onset 1972–1991)		LTx (year of LTx 1992–2011)[a]		Tafamidis (year of treatment initiation 2007–2016)	
	Early	Late	Early	Late	Early	Late
Patients, n	755	116	855	32	347	85
Male, %	53.5	47.4	52.7	46.9	51.9	48.2
Age at onset, y						
Mean ± SD	32.3 ± 6.4	58.3 ± 6.4	31.6 ± 6.1	53.4 ± 4.3	33.8 ± 6.7	61.6 ± 7.8
Median (IQR)	31 (28–36)	57 (53–63)	31 (27–35)	53 (51–57)	33 (29–38)	60 (55–67)
Disease duration from onset to treatment initiation, y						
Mean ± SD	—	—	4.1 ± 2.7[b]	4.0 ± 2.9	2.4 ± 2.0	3.2 ± 2.7
Median (IQR)	—	—	3.5 (2.3–5.2)	3.0 (2.4–4.8)	2.0 (1.0–3.3)	2.7 (1.6–3.8)
Follow-up from onset, y						
Mean ± SD	11.9 ± 4.9	9.4 ± 4.2	14.4 ± 6.2	13.1 ± 4.7	5.9 ± 3.0	6.0 ± 3.6
Median (IQR)	11.4 (8.9–14.4)	8.8 (6.4–11.8)	14.1 (10.0–18.7)	12.8 (9.3–16.3)	5.5 (4.0–7.7)	5.4 (3.8–7.7)

Abbreviations: IQR = interquartile range; LTx = liver transplant; TTR-FAP = transthyretin-associated familial amyloid polyneuropathy.
[a] LTx-treated cohort, excluding patients in disease stages 2 and 3.
[b] Among early-onset patients, disease duration was 1.7 years ($p < 0.0001$) higher in LTx-treated than tafamidis-treated patients.

Table 2 Standardized mortality ratio for TTR-FAP (years 1991 and 2016)

		Observed deaths, n/expected[a] deaths, n			Standardized mortality ratio (95% CI[b])		
Age group, y	Patients at risk, n	Males	Females	All	Males	Females	All
1991							
18–24	10	0/0.02	0/0	0/0.02	—	—	—
25–34	197	5/0.33	0/0.04	5/0.37	15.20 (4.94–35.47)	—	13.51 (4.39–31.53)
35–44	308	5/0.44	5/0.23	10/0.66	11.45 (3.72–26.72)	21.95 (7.13–51.23)	15.05 (7.22–27.67)
45–54	126	3/0.2	6/0.29	9/0.49	15.25 (3.14–44.56)	20.78 (7.63–45.24)	18.54 (8.48–35.20)
55–64	55	2/0.37	1/0.22	3/0.59	5.38 (0.65–19.42)	4.60 (0.12–25.64)	5.09 (1.05–14.88)
65–74	20	2/0.22	1/0.27	3/0.49	9.04 (1.09–32.66)	3.72 (0.09–20.71)	6.12 (1.26–17.88)
≥75	5	0/0.35	1/0.2	1/0.55	—	5.12 (0.13–28.53)	1.82 (0.05–10.13)
Total	721	17/1.93	14/1.24	31/3.17	8.82 (5.14–14.13)	11.29 (6.17–18.95)	9.79 (6.65–13.90)
2016							
18–24	2	0/0.00	—	—	—	—	—
25–34	115	0/0.05	1/0.01	1/0.06	—	151.19 (3.83–842.40)	18.00 (0.46–100.27)
35–44	475	2/0.42	0/0.14	2/0.56	4.76 (0.58–17.18)	—	3.55 (0.43–2.83)
45–54	388	3/0.77	5/0.38	8/1.14	3.90 (0.80–11.40)	13.30 (4.32–31.03)	6.99 (3.02–13.77)
55–64	163	4/0.64	3/0.38	7/1.02	6.21 (1.69–15.90)	7.97 (1.64–23.29)	6.86 (2.76–14.13)
65–74	87	3/0.96	2/0.39	5/1.35	3.12 (0.64–9.10)	5.16 (0.63–18.65)	3.70 (1.20–8.64)
≥75	47	5/1.78	2/1.75	7/3.53	2.81 (0.91–6.57)	1.14 (0.14–4.13)	1.99 (0.80–4.09)
Total	1,277	17/4.62	13/3.04	30/7.66	3.68 (2.14–5.89)	4.28 (2.28–7.32)	3.92 (2.64–5.59)

Abbreviations: CI = confidence interval; TTR-FAP = transthyretin-associated familial amyloid polyneuropathy.
[a] Expected deaths that would occur if patients with TTR-FAP were at the same mortality risk as the general Portuguese population (data from INE, Statistics Portugal), according to sex and age.
[b] The 95% CIs for standardized mortality ratios were computed under the assumption that occurrence of the events followed a Poisson distribution.

in men than women (HR 1.20, 95% CI 1.04–1.38, $p = 0.011$) and in patients with late-onset (mOS 9.21, 95% CI 8.05–10.80) than early-onset (mOS 11.86 years, 95% CI 11.43–12.19) disease (HR 1.98, 95% CI 1.60–2.44, $p < 0.0001$) (figure 2A).

Liver transplantation

In the LTx comparison cohort (stage 1 patients, 1992–2011), mOS since disease onset was 24.73 years (95% CI 22.90–27.09); mOS following LTx was 20.92 (95% CI 18.43–not estimable). LTx resulted in early excess mortality following the surgical procedure; the cumulative mortality rate in the first year after LTx was 14% (95% CI 11%–16%). Patients who underwent LTx in more advanced stages of the disease (stage 2 or 3) experienced higher mortality risk than those in stage 1 (HR 1.58, 95% CI 0.94–2.47, $p = 0.091$). Among patients in stage 1 treated with LTx, the mortality risk was lower in men than in women (HR 0.70, 95% CI 0.55–0.89, $p = 0.003$) and in patients with shorter disease duration before LTx. For each year LTx was delayed, the mortality risk increased by 17% (HR 1.17, 95% CI 1.12–1.23, $p < 0.0001$). We found no differences between patients with late-onset and early-onset disease (HR 1.59, 95% CI 0.90–2.80, $p = 0.112$; figure 2B).

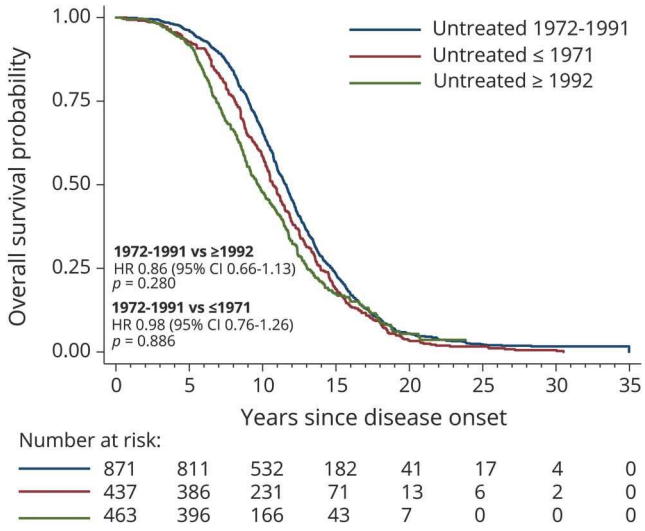
Tafamidis

The mOS for the tafamidis-treated cohort was not reached, though the maximum follow-up was only 10 years. The observed survival rate at 10 years after treatment initiation was 92.9% (95% CI 83.1%–97.2%). Mortality risk was greater among patients with longer disease duration before tafamidis treatment. For each year tafamidis treatment was delayed, the risk of death increased by 39% (HR 1.39, 95% CI 1.05–1.83, $p = 0.022$). No differences were found based on sex (HR 1.29, 95% CI 0.27–6.04, $p = 0.749$) or late-onset vs early-onset disease (HR 3.40, 95% CI 0.80–14.51, $p = 0.098$; figure 2C).

Comparative treatment effectiveness

Although a lower 1-year cumulative mortality rate and a higher 10-year survival rate were observed in patients who underwent LTx during 2007 or later vs those who underwent LTx before 2007 (10% vs 14% and 85% vs 74%, respectively), no overall survival differences were found (HR 0.80, 95% CI 0.51–1.23, $p = 0.309$). Therefore, in accordance with the prespecified criteria, for primary comparative analysis, we considered the overall LTx cohort encompassing stage 1 patients who underwent LTx between 1992 and 2011. Hence,

Figure 1 Untreated cohort (natural history) Val30Met TTR-FAP survival



Kaplan-Meier survival estimates in the Val30Met TTR-FAP untreated cohort (natural history) according to the era of disease onset. CI = confidence interval; HR = hazard ratio; TTR-FAP = transthyretin-associated familial amyloid polyneuropathy.

according to the eligibility criteria (see methods), 871, 887, and 432 patients in the untreated, LTx-treated, and tafamidis-treated cohorts, respectively, were included in the evaluation of comparative treatment effectiveness (table 1).

Early-onset disease

Both treatment cohorts experienced increased survival compared with the untreated 1972–1991 cohort. The 10-year survival probabilities after TTR-FAP onset were 72% (95% CI 69%–75%), 73% (95% CI 68%–78%), and 96% (95% CI 87%–99%) in the untreated, LTx-treated, and tafamidis-treated cohorts, respectively. The 20- and 30-year survival probabilities after disease onset were 7% (95% CI 5%–9%) and 2% (95% CI 1%–4%) in the untreated cohort, and 56% (95% CI 50%–61%) and 29% (95% CI 18%–39%) in the LTx-treated cohort, respectively.

Overall, there was a 75% (HR 0.25, 95% CI 0.22–0.29, $p < 0.0001$) and a 91% (HR 0.09, 95% CI 0.03–0.25, $p < 0.0001$) reduction in mortality risk in the LTx-treated and tafamidis-treated cohorts, respectively. Survival was higher in the tafamidis-treated cohort than in the LTx-treated cohort; mortality risk was reduced by 63% (HR 0.37, 95% CI 0.14–1.00, $p = 0.050$; figure 3A). The crossing of the LTx and untreated survival curves is indicative of nonproportionality in the hazards, and therefore the reported HR should be thought of as an average over time. Similar results, in terms of direction of treatment effect (although of lower magnitude) and statistical significance, were obtained for RMST-based measurements (table 3).

Results of the exploratory analysis considering only the more recent LTx cohort (2007–2011) were of similar magnitude, including comparison between the tafamidis- and LTx-treated cohorts (HR 0.36, 95% CI 0.13–1.02, $p = 0.055$). Similar results were obtained when comparing the more recent LTx cohort with tafamidis since treatment initiation (HR 0.18, 95% CI 0.08–0.40, $p < 0.0001$). Sensitivity analysis that included post-LTx and post-clinical trial follow-up data for all patients initially treated with tafamidis showed an 87% mortality risk reduction compared with the untreated cohort (HR 0.13, 95% CI 0.06–0.27, $p < 0.0001$) and a 50% mortality risk reduction compared with the LTx cohort (HR 0.50, 95% CI 0.24–1.06, $p = 0.072$). When comparing tafamidis-naive LTx patients from 2007 to 2011 (more recent and contemporaneous) with those who underwent transplantation but previously received tafamidis, no difference in posttransplantation survival rate was observed ($p = 0.763$, figure 4).

Late-onset disease

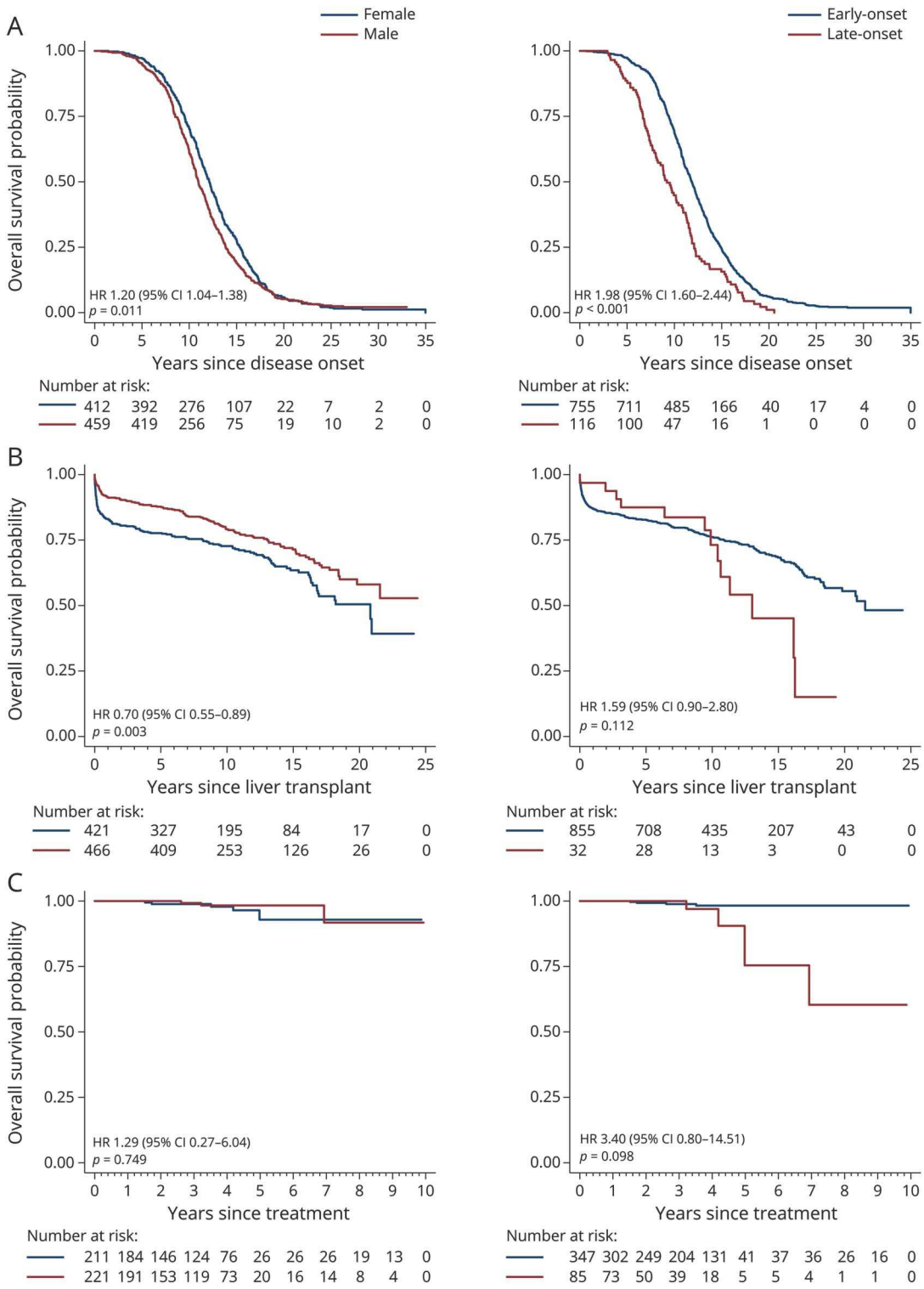
Given that LTx is not generally recommended for patients with late-onset disease and that only a small set of patients (n = 32) with late-onset disease underwent LTx, no comparative analysis was performed for this cohort (mOS since disease onset, 17.04 years, 95% CI 13.31–19.88). Furthermore, this LTx-treated subgroup represented a highly selected set of patients with late-onset disease who still fulfilled eligibility criteria for surgery. The 10-year survival probability after TTR-FAP onset was 49% (95% CI 39%–58%) and 92% (95% CI 71%–98%) in the untreated and tafamidis-treated cohorts, respectively. Overall, among patients with late-onset disease, tafamidis treatment (n = 85) was associated with an 82% reduction in mortality risk compared with the untreated (n = 116) cohort (HR 0.18, 95% CI 0.06–0.49, $p = 0.001$; figure 3B).

Discussion

This research of more than 3,200 Portuguese patients represents the largest cohort study of patients with TTR-FAP to date. Our findings reveal that both sexes are affected and disease onset occurs primarily in young adulthood (28–42 years of age). We found a slight but clinically relevant improvement in survival among the untreated cohorts of almost 1 year, probably because of easier access to better medical care. The reduced survival rate of untreated patients in the era of LTx probably reflects the coexistence of clinical characteristics (such as later disease stage and poor nutritional status) and social conditions (such as health illiteracy and low awareness of disease treatment) that precluded the eligibility and timely access to LTx.

The main clinical relevant finding of our study is that the advent of disease-modifying treatments (in particular LTx) changed dramatically the long-term prognosis for patients with TTR-FAP in the past 25 years, from a progressive, devastating, fatal disease to a more chronic condition with treatment leading to delayed disease progression. The beneficial effect of treatment as a whole on mortality was demonstrated by the 60% SMR reduction from 1991 to 2016; in 2016, however,

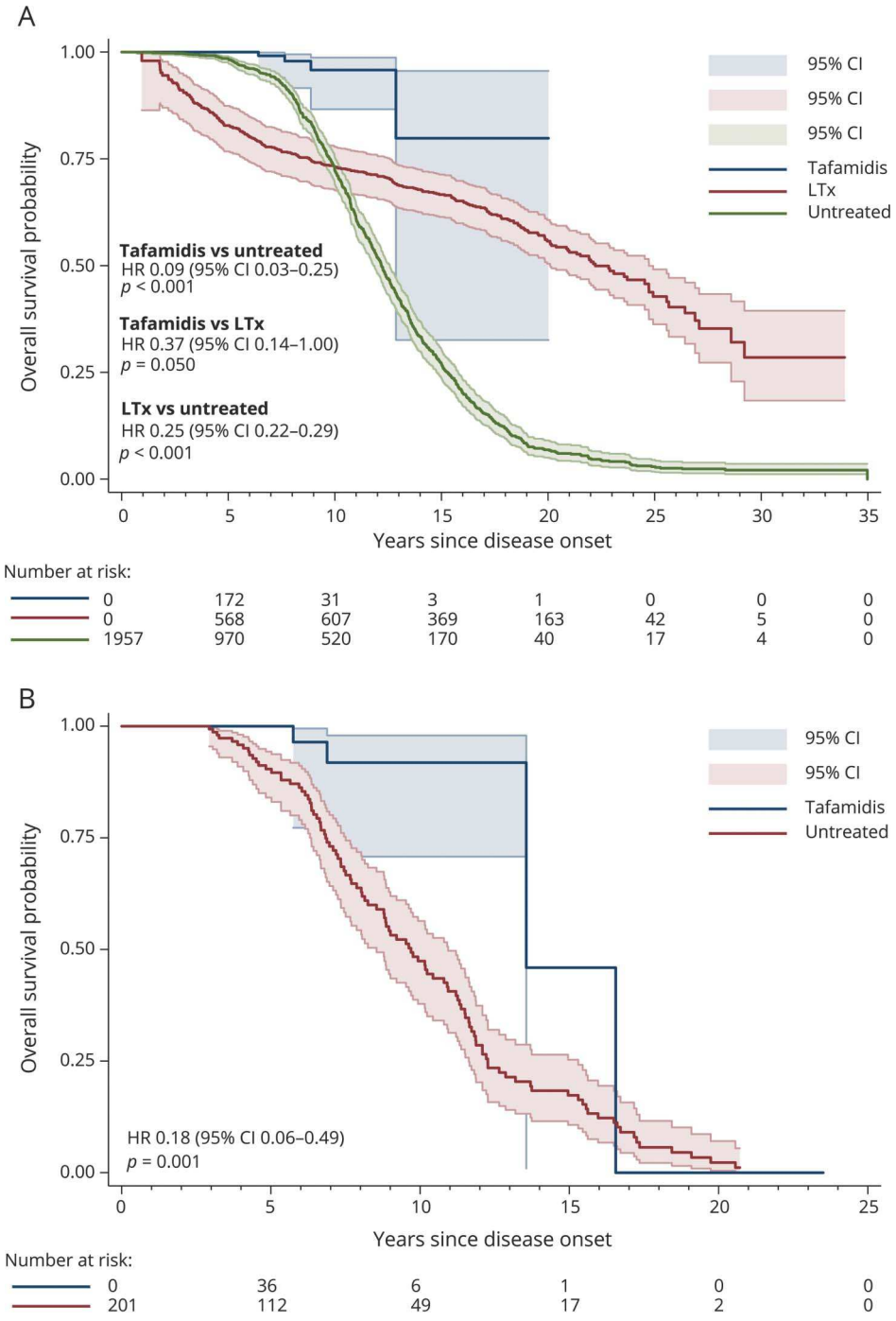
Figure 2 Untreated, LTx-treated, and tafamidis-treated Val30Met TTR-FAP survival



Kaplan-Meier survival estimates by sex and age at disease onset (early/late onset) according to Val30Met TTR-FAP cohort: untreated (A), LTx-treated (B), and tafamidis-treated (C) patients. CI = confidence interval; HR = hazard ratio; LTx = liver transplant; TTR-FAP = transthyretin-associated familial amyloid polyneuropathy.

mortality rates remain 4-fold greater than in the general population. In our study, the prognosis for treated patients was poorer for those with longer disease duration before treatment, which is consistent with the published literature on LTx[21,27,28] and with the benefits of earlier tafamidis treatment on neurologic progression and nutritional status.[29–31] This result strongly reinforces the need to start treatment (either LTx or tafamidis) at an early stage of the disease.

Figure 3 Comparative survival estimates in patients with early- and late-onset Val30Met TTR-FAP



Kaplan-Meier survival estimates since disease onset (with 95% CI) in Val30Met TTR-FAP selected cohorts with comparative treatment effectiveness among early-onset (A) and late-onset (B) patients. CI = confidence interval; HR = hazard ratio; LTx = liver transplant; TTR-FAP = transthyretin-associated familial amyloid polyneuropathy.

The results from the comparative effectiveness analysis raise several further findings for discussion. First, among patients with early-onset disease, tafamidis treatment may result in improved overall survival compared with LTx, attributable perhaps in part to the absence of early operative risks. Caution is required, however, when interpreting this finding because median tafamidis follow-up was relatively short as compared with LTx median follow-up, and mOS has not yet been reached. Moreover, within the first years after the introduction of LTx, and in contrast to tafamidis, LTx resulted in higher mortality rates than no treatment. Although this is an expected finding, the proportional hazard assumption of the Cox regression analysis is violated, which means that, with longer follow-up, treatment effect is likely to change. Nonetheless, the robustness of this finding is supported by the similar results found in the analysis that made use of different statistical methods (RMST), as well as in the exploratory analysis that included only the more recent LTx cohort (2007–2011). This

Table 3 Post hoc RMST estimates (with 95% CI) among TTR-FAP Val30Met early- and late-onset patients (20 years since disease onset)

	Early-onset cohorts			Late-onset cohorts	
	Untreated	LTx	Tafamidis	Untreated	Tafamidis
Patients, n	755	855	347	116	85
RMST, y (95% CI)	12.57 (12.29–12.85)	15.08 (14.40–15.77)	18.36 (15.95–20.77)	10.35 (9.54–11.16)	14.35 (11.48–17.22)
LED, y (95% CI)					
LTx vs untreated		2.51 (1.77–3.25)		—	
Tafamidis vs untreated		5.79 (3.36–8.21)		4.00 (1.02–6.98)	
LTx vs tafamidis		−3.28 (−5.78 to −0.77)		—	
LER, ratio (95% CI)					
LTx vs untreated		1.20 (1.14–1.26)		—	
Tafamidis vs untreated		1.46 (1.28–1.67)		1.39 (1.12–1.72)	
LTx vs tafamidis		0.82 (0.72–0.94)		—	

Abbreviations: CI = confidence interval; LED = life expectancy difference; LER = life expectancy ratio; LTx = liver transplant; RMST = restricted mean survival time; TTR-FAP = transthyretin-associated familial amyloid polyneuropathy.

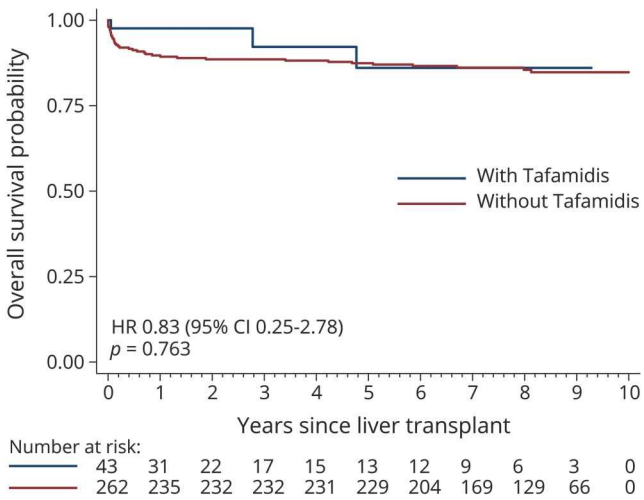
more recent LTx cohort experienced an overall higher survival rate than the former LTx cohort, was contemporaneous with the tafamidis-treated cohort, and had comparable follow-up.

Second, among patients with early-onset disease and up to 10 years of follow-up, no differences in survival were found between LTx-treated patients who did and those who did not previously receive tafamidis treatment, though other possible benefits of tafamidis beyond survival—such as improvement in nutritional and overall health status[13]—were not analyzed in this study.

Third, among patients with late-onset disease, a subgroup with poorer prognosis and shorter median survival,[32,33] and for whom LTx is not generally recommended,[34] tafamidis treatment resulted in a clinically relevant survival benefit.

From a study of the largest LTx cohort of patients with TTR-FAP (Familial Amyloidosis Polyneuropathy World Transplant Registry, encompassing 2,171 patients from 81 centers and 21 countries), researchers retrospectively reported[21] a 20-year survival rate of 55.3%, a noteworthy improvement in overall survival compared with reports on the natural history of the disease. In the study, higher modified body mass index, early onset of disease (younger than 50 years), shorter disease duration before LTx, and TTR Val30Met rather than non–TTR Val30Met mutations were found to be independent, favorable, significant factors for survival. The overall highest transplantation activity contributing to this registry originates from Portugal, which contributed more than 45% of the data. Our research shows that TTR-FAP overall median survival after LTx is 21 years. Limitations of LTx include waiting times for a compatible donor organ[35] and relevant intraoperative mortality and postoperative complications as evidenced by the high cumulative first-year mortality rate, which is similar to what others have found.[21] One interesting finding from our study was the higher mortality risk among LTx-treated women in comparison to men. Although the overall LTx literature is supportive of this finding,[36,37] the reasons in Val30Met TTR-FAP remain unclear. The difference in mortality risk occurs early after LTx. Therefore, this difference is probably attributable to imbalanced unobserved baseline prognostic factors (including systematic epidemiologic bias

Figure 4 LTx (with and without previous tafamidis) Val30Met TTR-FAP survival since LTx



Kaplan-Meier survival estimates since LTx according to previous tafamidis treatment in Val30Met TTR-FAP LTx patients with early-onset stage 1 disease. CI = confidence interval; HR = hazard ratio; LTx = liver transplant; TTR-FAP = transthyretin-associated familial amyloid polyneuropathy.

against women and a poorer metabolic status) and/or higher rate of early LTx fatal complications.

Previous studies evaluating the survival of patients with TTR-FAP enrolled either a small number of patients[27,28] or lacked comparison groups.[21] Furthermore, some assumptions and conclusions from previous studies may be questionable, such as reporting a 100% survival rate at 10 years among LTx-treated patients by excluding deaths considered not related to amyloidosis.[27]

An important limitation of our study is its observational design. We have attempted to deal with selection bias objectively by using explicit criteria to define clinically comparable cohorts and by adjusting for sex, age at onset, and disease duration before treatment when modeling. However, because of the unavailability of data, we were unable to include other possible determinants of outcomes, such as nutritional status[21] and other clinical characteristics.[38] In addition, using historical data for comparison has the disadvantage that cohorts may differ in unmeasured prognostic factors for survival. In our study, all patients had Val30Met mutation conferring genetic homogeneity to the population evaluated. Although this may be considered a strength of this study, it is also a further limitation, because results are not generalizable to other TTR mutations and other disease presentations, including sporadic cases and later-stage disease, which are more common in other geographies with higher genetic and clinical heterogeneity.[32,33]

Our findings suggest that potential improvements may be made in the prognosis of patients with TTR-FAP and strongly reinforce the importance of timely diagnosis and early treatment initiation. Treatment with LTx or tafamidis dramatically changed the clinical course of TTR-FAP. However, these treatments have not proven to reverse established damage. In fact, mortality rates remain higher than in the general population, which should stimulate further basic and clinical research, targeting the development of biomarkers of early-stage and subclinical disease, as well as new disease-specific drugs.

We report a comprehensive treatment effectiveness study comparing natural history, LTx, and tafamidis treatment in patients with TTR-FAP. It is unrealistic to expect that randomized controlled trials will address the questions investigated here. This evidence can be a valuable source of effectiveness, particularly in a rare-disease setting, and may inform regulatory agencies, health technology assessment bodies, and clinical treatment guidelines and recommendations. Therefore, we suggest setting up properly designed prospective, clinical registries as longer follow-up data may facilitate understanding of how clinical practice can reconcile different treatment options, especially as new drugs emerge from phase 3 clinical trials.[39,40]

Author contributions

T. Coelho: study concept/design, data collection, interpretation, critical review, study supervision. M. Inês: study concept/design, statistical analysis, interpretation, manuscript drafting, and critical review. I. Conceição: data collection, interpretation, critical review. M. Soares: statistical analysis, interpretation, critical review. M. de Carvalho: interpretation, critical review. J. Costa: study concept/design, interpretation, manuscript drafting, critical review, study supervision.

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Disclosure

T. Coelho received financial support from Alnylam, Ionis, and Pfizer to attend scientific meetings and personal fees from Alnylam and Pfizer to provide scientific lectures. M. Inês is a full-time employee of Pfizer and holds stock and/or stock options. I. Conceição acknowledges financial support as primary investigator of clinical studies from FoldRx Pharmaceuticals/Pfizer Inc., Alnylam Pharmaceuticals, and Ionis Pharmaceuticals. She also received research support from Pfizer and serves on the THAOS scientific advisory board, financially supported from Pfizer. I. Conceição also participates in medical advisory boards promoted by Alnylam and Pfizer. M. Soares, M. de Carvalho, and J. Costa report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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