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Natural history, hospitalizations and mortality causes in ATTRv V30M amyloidosis in an endemic European cohort

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Original article

Natural history, hospitalizations and mortality causes in ATTRv V30M amyloidosis in an endemic European cohort

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ABSTRACT

Variant transthyretin amyloidosis (A-ATTRv) caused by the p.Val50Met mutation is a multisystemic disease with marked geographic variability. Mallorca represents one of the main endemic foci in Europe. Although disease-modifying therapies have improved prognosis, real-world data on hospitalization patterns and causes of death remain limited.

We conducted a retrospective observational study including deceased patients with A-ATTRv V30M from Mallorca up to November 2024. Demographic characteristics, comorbidity burden, neurological stage, hospital admissions and causes of death were analyzed using clinical records.

Fifty-five patients (60% male) were included, with a median age at diagnosis of 68.5 years (IQR 59–75). Most patients (78.2%) presented a mixed neurological and cardiac phenotype. During follow-up, 41.8% experienced five or more emergency department visits or hospital admissions. Infectious complications, particularly urinary tract infections, were the most frequent cause of hospitalization, followed by cardiovascular events, mainly heart failure. Cardiovascular causes accounted for the largest proportion of deaths (29.1%), predominantly heart failure and sudden death. Median overall from diagnosis to death was 70 months (IQR 37–108).

In this endemic A-ATTRv V30M cohort, cardiovascular complications—especially heart failure—were the main causes of mortality and a major driver of hospitalization, highlighting the importance of early multidisciplinary management.

Keywords: transthyretin amyloidosis; ATTRv; heart failure; mortality; hospital admissions.

INTRODUCTION

Variant transthyretin amyloidosis (A-ATTRv) is a hereditary systemic disease caused by pathogenic mutations in the transthyretin (*TTR*) gene, leading to extracellular deposition of misfolded transthyretin amyloid fibrils in multiple organs. The p.Val50Met mutation (V30M) represents one of the most extensively studied variants worldwide, characterized by notable variability in age of onset, penetrance, and clinical expression by geographic area [1]. Mallorca is one of the main European endemic sites, reaching an estimated prevalence of 1 case per 2,900 inhabitants [2]. This high morbidity burden, combined with the extensive clinical experience accumulated in the region, provides an optimal scenario for characterizing the natural history, causes of hospitalization, and determinants of mortality in this population.

Although historically considered a familial amyloid neuropathy, it is currently recognized that A-ATTRv is a multisystemic disease in which cardiac involvement plays a critical role in clinical evolution and prognosis, especially in late-onset forms [3–5]. Data from the THAOS international registry have shown that the presence of amyloid cardiomyopathy is a determining factor in mortality and is associated with a higher rate of hospitalization, even in patients with predominantly neurological phenotype [6]. In systemic amyloidosis cohorts, heart failure and sudden death represent common causes of death; however, the specific representation of patients with A-ATTRv V30M in these analyses remains limited, particularly with respect to mortality data and hospitalization patterns in homogeneous endemic cohorts [5,7].

In recent decades, the natural history of A-ATTRv has been modified by the introduction of disease-modifying therapies. Liver transplantation was the first strategy capable of altering disease progression in selected patients, with better outcomes in carriers of the V30M mutation of early onset, although with important limitations related to the progression of cardiac, ocular, or leptomeningeal involvement [8–10].

More recently, pharmacological therapies including transthyretin stabilizers—tafamidis 20 mg [11] and 61 mg [12], and more recently acoramidis [13,14]—and gene silencing therapies—patisiran [15], inotersen [16], vutrisiran [17,18] and eplontersen [19]—have shown to slow neurological progression and, in ATTR cardiomyopathy, reduce cardiovascular hospitalizations and mortality in controlled clinical trials.

However, much of the current evidence comes from clinical trials with strict selection criteria and heterogeneous populations including both hereditary and wild-type transthyretin amyloidosis. Extrapolation of such results to real-world clinical cohorts can be complex, especially in populations with high comorbidity, older age, or more heterogeneous clinical phenotypes.

In endemic areas with prolonged longitudinal follow-up, detailed analysis of hospitalization patterns and causes of death is particularly relevant to understand the current impact of the disease in the era of modifying therapies and to identify potential underestimated prognostic determinants. Despite the availability of disease-modifying therapies, significant mortality and progressive deterioration in quality of life persist, underscoring the need to better characterize contemporary natural history in specific populations [5,20].

The aim of this study is to describe the clinical course, comorbidity burden, causes of hospitalization and causes of death in a cohort of deceased patients with A-ATTRv V30M from the endemic focus of Mallorca, providing real-world information on the contemporary natural history of this disease.

MATERIALS AND METHODS

- **Study Design and Population:**

A retrospective observational study was conducted from a cohort of Mallorcan patients with A-ATTR-V30M. Patients diagnosed from January 1988 and who died until November 2024 were included.

- **Data Collection and Clinical Variables**:

Those deceased patients from the island of Mallorca who were affected by A-ATTRv with a genetic study positive for the V30M mutation were included. Patients with A-ATTRv with a mutation other than V30M and those with other types of amyloidosis (AA, AL...) were excluded.

Demographic and clinical data were collected from the medical records of these patients. Neurological performance status was assessed using the Polyneuropathy Disability Scale (PND), divided into five stages (0: No deficit; I: Sensory deficit without gait disturbance; II: difficulty walking, but no cane needed; IIIa: Requires a cane; IIIb: Requires two canes; IV: wheelchair bound) (1), and the Family Amyloid Polyneuropathy (FAP or Coutinho Scale), assessing functional capacity at three stages ((stage 1 denotes independent ambulation, stage 2 indicates ambulation with support (e.g., cane or walker), and stage 3 describes patients who are wheelchair-dependent or bedridden)) [3,10]. Both scales were recorded at baseline and at the time closest to the patients' date of death.

The Neuropathy Impairment Score (NIS), a quantitative scale that assesses motor, sensory, and osteotendinous reflex function, was also documented, with scores ranging from 0 (no involvement) to 244 points (maximum involvement) [21].

Comorbidity burden was quantified by the Charlson Comorbidity Index, which predicts 10-year mortality based on the patient's age and comorbidities. This index was calculated from comorbidities recorded in the medical record at the end of follow-up to reflect the cumulative comorbidity burden [4,22].

The date of diagnosis of the disease was established as the time when the patient with a V30M mutation presented symptoms of sensory-motor polyneuropathy or fine/autonomic fiber neuropathy and specific alterations in the electroneurographic studies. Specifically, disease onset required evidence of thick fiber involvement or at least three pathological tests of fine fiber involvement or dysautonomy (Sudoscan, Thermotest [QST], R-R interval variability, sympathetic-cutaneous response). This criterion was defined according to local experience and based on the clinical expertise available to date [23,24].

- **Hospitalizations and Causes of Death**:

From the time of diagnosis, the number of admissions and/or emergency room visits presented by the patients was recorded, as well as the reason for them as recorded in the discharge reports. Likewise, the cause of death recorded in the patient's medical record when it was available was established.

- **Specific treatments:**

Regarding the treatment, it was indicated whether or not the patient was transplanted and the date thereof, as well as whether he received any disease-specific treatment with stabilizers (tafamidis, diflunisal) and/or RNA silencers (patisiran, inotersen) and the treatment period. From this data, the average time in months from the start of treatment until death was obtained.

STATISTICAL ANALYSIS:

This study was designed as a descriptive analysis of a retrospective cohort of deceased patients. Continuous variables are presented as median and interquartile range (IQR), and categorical variables as absolute frequencies and percentages. Time intervals, including time from diagnosis to death, time from liver transplantation to death, and time from initiation of disease-modifying treatment to death, were summarized descriptively using median and IQR. No time-to-event modeling was performed. All analyses were descriptive and exploratory in nature.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS:

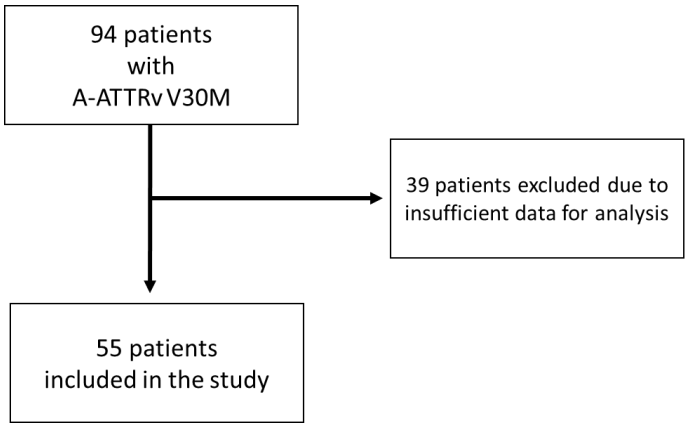
During the preparation of this work, the authors used GPT-4/ ChatGPT to improve readability. After using this service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Julius AI (Julius AI Inc.) was used as a computational assistant to support data processing, consistency checks, and descriptive statistical analysis. All outputs were reviewed, verified, and validated by the authors, who take full responsibility for the final content of the manuscript.

RESULTS:

Ninety-four deceased carriers of the Val30Met mutation were initially identified. Of these, 39 patients were excluded because of incomplete clinical information, resulting in a final cohort of 55 patients included in the analysis (**Figure 1**).

Figure 1. Flow chart of patients included in the study.

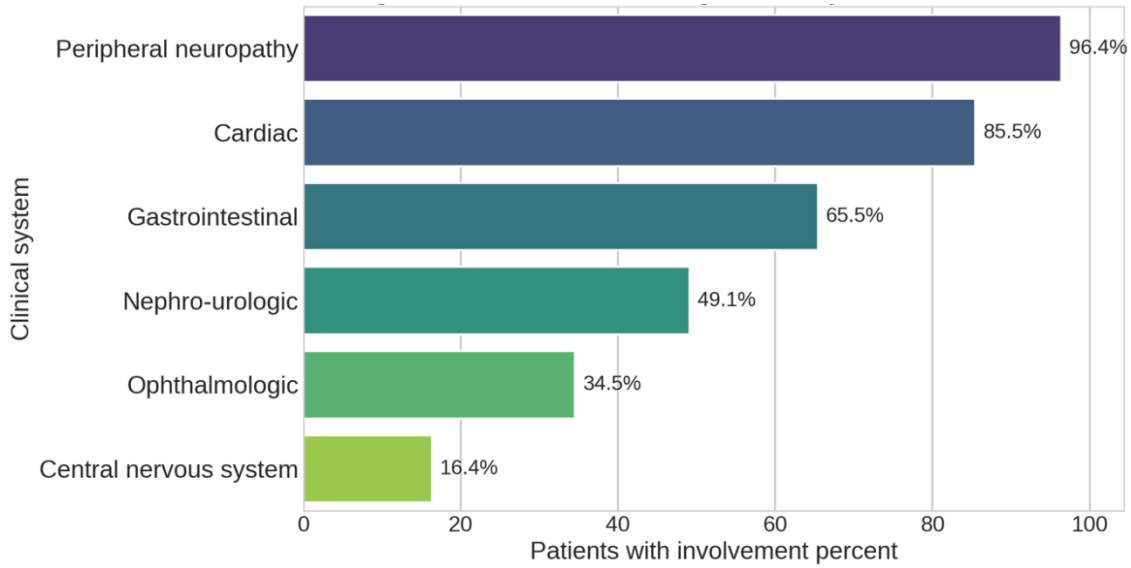


The primary characteristics of the population are described in **Table 1**. Sixty percent (n=33) of patients were male, with a median age of 68.5 years (IQR 59-75) at diagnosis. Most patients (n=43, 78.2%) presented with clinical symptoms of polyneuropathy together with cardiological manifestations, consistent with a mixed phenotype. In addition, a relevant proportion presented with involvement of other organs during the course of the disease, including gastrointestinal manifestations (n=36, 65.5%), nephro-urological manifestations (n=27, 49.1%), ophthalmological manifestations (n=19, 34.5%) and the central nervous system (n=9, 16.4%), reflecting the multisystemic nature of this disease (**Figure 2**).

Table 1. Descriptive analysis of patients. Absolute and relative frequencies were used to describe the qualitative variables (n, %). Quantitative variables were expressed as median (MD) and interquartile range (IQR).

Variables χ	Patients
Age at diagnosis, Median (IQR), (n=55)	68,5 (59-75)
Gender, n(%), (n=55)	
Male	33 (60,0)
Female	22 (40,0)
Inheritance, n(%), (n=55)	
Index case	15 (27,3)
Paternal	9 (16,4)
Maternal	7 (12,7)
Unknown	24 (43,6)
Clinical involvement, n(%)	
Cardiological	47 (85,5)
Polyneuropathy	53 (96,4)
Cardiology + Polyneuropathy	43 (78,2)
Gastrointestinal	36 (65,5)
Ophthalmology	19 (34,5)
Central nervous system (SNC)	9 (16,4)
Nephro-urological	27 (49,1)
FAP at diagnosis, n(%), (n=47)	
I	33 (60,0)
II	13 (23,6)
III	1 (1,8)
PND at diagnosis, n(%), (n=47)	
I	32 (58,2)
II	2 (3,6)
IIIa	7 (12,7)
IIIb	5 (9,1)
IV	1 (1,8)
NIS at diagnosis, Median (IQR), (n=8)	18 (8-20)
Final FAP, n(%), (n=42)	
I	7 (12,7)
II	17 (30,9)
III	18 (32,7)
Final PND, n(%), (n=42)	
I	6 (10,9)
II	3 (5,5)
IIIa	6 (10,9)
IIIb	9 (16,4)
IV	18 (32,7)
Final NIS, Median (IQR), (n=8)	62,5 (25-110)
Charlson, Median (IQR), (n=54)	6,1 (4-8)
Treatment, n(%)	
Transplant	21 (38,2)
Stabilizer/Silencers	15 (27,3)
No treatment	19 (34,5)
Nº emergency room visits +/- admissions, n(%)	
1	6 (10,9)
2	6 (10,9)
3	10 (18,2)
4	7 (12,7)
≥ 5	23 (41,8)
Unknown	3(5,5)
Age at exitus, Md (IQR, years), (n=55)	75 (65-81)
Time to death, Md (IQR, months)	
From diagnosis to death (overall survival) (n=49)	70 (37-108)
From transplant to death (n=21)	90 (45-188)
From start of treatment to death (n=15)	56 (27-78)

Figure 2. Prevalence of clinical involvement by systems: cardiac, polyneuropathic, gastrointestinal, nephron-urological, ophthalmological and central nervous system.



The majority of patients (n=33, 60%) presented with stage I of Coutinho at the time of diagnosis. Neurological progression was observed during the course of the disease, so that at the end of follow-up (median follow-up of 70 months until death), 32.7% (n=18) of patients were in stage III of Coutinho, followed by stage II in 30.9% (n=17). The median Charlson Comorbidity Index score at the end of follow-up was 6.1 (IQR 4-8), indicating high comorbidity.

Regarding the treatment, 38.2% of patients (n=21) underwent liver transplantation and 27.27% (n=15) received specific treatment for amyloidosis with stabilizers and/or silencers.

The mean number of visits to the emergency room (ER)/admissions was 3.7 in the total number of patients, presenting 41.8% (n=23) of cases with 5 or more visits to the emergency room (**Table 1**). Infectious (n=32, 61,5%) and cardiovascular (n=27, 51,9%) causes were the most common reasons for admission/ER visits (**Table 2**). Among cardiovascular etiologies, heart failure was the most common reason in 62.9% of cases (n=17). Other common causes of consultation and/or admission were syncope (n=7; 25.9%), arrhythmias (n=5, 18.5%), or cerebrovascular disease (n=5, 18.5%). Among the infectious etiologies, urinary (n=17, 53.1%) and respiratory (n=10, 31.2%) infections were mainly noted (**Table 2**).

Table 2. Reason for admissions/emergency room visits and number of patients. Absolute and relative frequencies were used to describe the qualitative variables (n, %).

Reason for consultation n, (percentage of the total visits)	**Etiology**	**Number of patients (percentage by etiology)**
Cardiovascular (n=27; 51,9%)	Heart failure	17 (62,9%)
	Syncope	7 (25,9%)
	Arrhythmia	5 (18,5%)
	Cerebrovascular	5 (18,5%)

	Acute Myocardial Infarction	3 (11,1%)
Infectious (n=32; 61,5%)	Urinary	17 (53,1%)
	Respiratory	10 (31,2%)
	Skin / Soft tissue	6 (18,7%)
Traumatology (n=17; 32,7%)	Fractures	9 (52,9%)

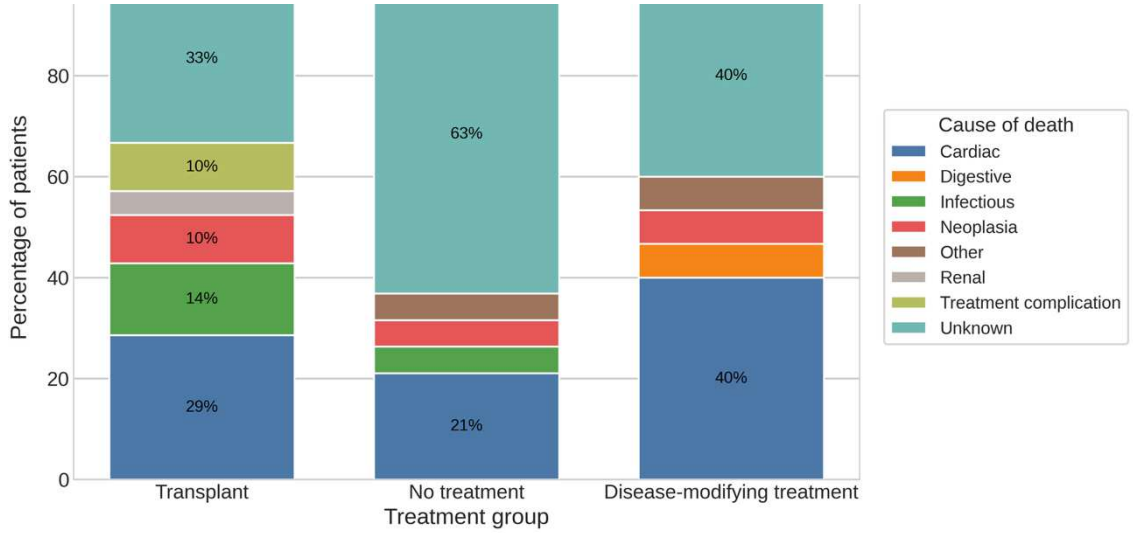
The most common cause of death recorded was cardiovascular (n=16, 29.1%) followed by infectious (n=4, 7.3%) and neoplastic (n=4, 7.3%) etiologies. In 25 patients (45.4%) the cause of death could not be determined from medical records mainly due to community deaths, death in another autonomous community, or lack of documentation in historical medical records (**Table 3).** Likewise, the percentage distribution of the cause of death within each treatment group was established (**Figure 3**). Cardiac death was a major cause, especially among transplant recipients and patients receiving disease-modifying treatment. The transplant group showed a more heterogeneous distribution of causes of death, including infectious and treatment-related causes. In a considerable percentage of cases, the cause of death was unknown in all three categories.

Table 3. Exitus etiology. Absolute and relative frequencies were used to describe the qualitative variables (n, %).

Cause of death n, (percentage of the total)	**Etiology**	**Nº. of patients (percentage by etiology)**
Cardiovascular (n=16; 29,1%)	Heart failure	6 (37,5%)
	Acute myocardial infarction	4 (25%)
	Arrhythmia	1 (6,25%)
	Sudden death	3 (18,75%)
	Cerebrovascular	2 (12,5%)
Infectious (n=4; 7,3%)	Urinary	2 (50%)
	Biliary	1 (25%)
	Skin	1 (25%)
Neoplasm (n=4; 7,3%)	Lung	2 (50%)
	Digestive	2 (50%)
Post-transplant complication (n=2; 3,6%)	Hepatitis plasma cells	1 (50%)
	Postoperative complication	1 (50%)
Renal (n=1; 1,8%)	Renal failure	1 (100%)

Digestive (n=1; 1,8%)	Pancreatitis	1
Other (n=2; 3,6%)	Choking	2
Unknown (n=25; 45,4%)		25

Figure 3. Cause of death by treatment group. Percentage distribution of cause of death within each treatment group. Percentages are calculated within each group; n is indicated per group.



When available (n=49), the average number of months from diagnosis to death was estimated (70 months), with a median age at death of 75 years (IQR 65-81) (**Table 1**). In the subgroup of patients undergoing liver transplantation, the average of months from transplantation to death was 90 months (IQR 45–188). In patients treated with specific drug therapy, the average of months from the start of treatment to death was 56 months (IQR 27–78). Notably, disease-specific pharmacological therapies have only been available in recent years; therefore, patients in this group had a shorter potential follow-up period, and those with favorable treatment responses may still be alive and thus not captured in this deceased-only cohort.

When therapeutic strategy was categorized into three groups (no treatment vs. patients who received transplant vs medical treatment), mean time from diagnosis to death was 49.73 ± 44.39 months among untreated patients, 67.80 ± 37.96 months among those receiving pharmacological therapy, and 122.89 ± 93.66 months among patients who underwent transplantation. Overall differences across groups were significant by one-way ANOVA ($p = 0.0065$) **(Table 4)**.

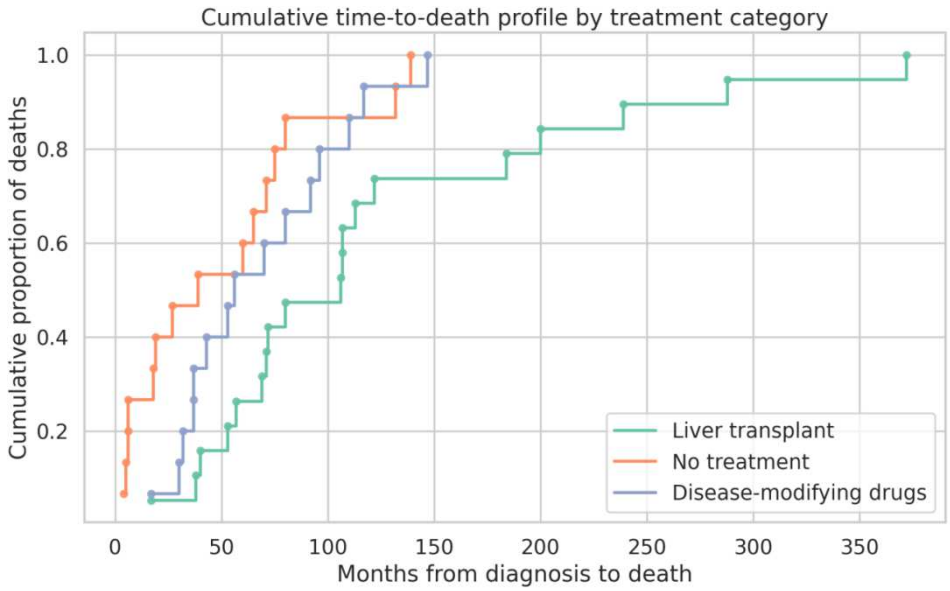
Table 4. Time from diagnosis to death according to therapeutic strategy.

Variable	N analyzable	Mean (SD), months	95% CI, months
No treatment	15	49.73 (44.39)	25.15 to 74.31

Pharmacological therapy	15	67.80 (37.96)	46.78 to 88.82
Transplantation	19	122.89 (93.66)	77.75 to 168.03

Figure 4 shows the cumulative distribution of time from diagnosis to death according to treatment category among deceased patients. Overall, deaths accumulated earlier in the untreated group. The liver transplant group showed a right-shifted curve consistent with longer time to death. Patients receiving disease-modifying drugs showed an intermediate pattern. These findings suggest differences in time-to-death across treatment categories, although interpretation is limited by the restriction of the analysis to deceased patients only and by the potential influence of baseline clinical differences between groups.

Figure 4. Cumulative distribution of time from diagnosis to death according to treatment category among deceased patients.



DISCUSSION:

This study analyzes the causes of hospitalization and mortality in deceased patients with A-ATTRv carrying the V30M mutation from Mallorca, considered one of the main endemic foci of this pathology in Spain and also one of the most important foci worldwide [25,26].

In our study, the fact that cardiovascular disease was the main identifiable cause of death and one of the most frequent causes of hospital admission or emergency room visits stands out. This reinforces the idea that A-ATTRv should be addressed as a systemic disorder whose prognosis depends not only on neurological progression, but also on cardiac involvement, as well as the associated comorbidities in this pathology.

A-ATTRv is characterized by marked clinical heterogeneity, with wide variability in age of onset, clinical phenotype, and disease progression, even among patients carrying the same mutation [1,27].

The median age at diagnosis in this selected cohort of patients was 68.5 years. It should be noted that our cohort includes only patients with A-ATTRv who have died, so the age of onset is higher than that described in the Majorcan focus, with a mean age at diagnosis of approximately 49.8

years [26]. In contrast, the Portuguese and Japanese populations usually show clinical symptoms before age 50, often starting in their thirties [1,28,29]. These findings reflect the influence of the geographic area on the clinical expression of the disease [1,27,30,31].

Moreover, older age at diagnosis is associated with lower time from diagnosis to death. This inverse relationship is clinically relevant. A late diagnosis may reflect delayed recognition, but it may also identify a subgroup with more advanced disease biology, greater comorbidity, or less access to certain therapies. Therefore, age at diagnosis can act not only as a chronological variable, but also as an indicator of treatment suitability and accumulated vulnerability. Thus, the lower survival observed among older individuals therefore fits with the general pattern of therapeutic stratification seen in daily practice.

In our cohort, although a discrete prevalence of the disease is observed in males (60%), recent studies conducted in Mallorca, such as that of *Cisneros-Barroso et al*., found no significant differences in the risk of disease by sex with the V30M mutation for this population [32]. In contrast, greater penetrance in males has been described in the Swedish endemic focus, suggesting that genetic, epigenetic or environmental factors could modulate the clinical expression of the mutation based on geographic area [33].

In our series, the majority of patients presented with a mixed phenotype, characterized by the simultaneous presence of neurological and cardiological manifestations, a clinical pattern described as predominant in non-classically endemic areas or in patients with late onset of the disease [34,35]. Although peripheral neuropathy remained highly prevalent, cardiac involvement was also present in a considerable proportion of patients and appears to decisively influence clinical course. Our data suggest that in a real-world population of deceased patients, cardiac manifestations are not only a frequent cause of hospitalization but also have a clear impact on patient outcomes.

The distribution of disease stages at diagnosis showed that many patients were identified in early phases, likely due to heightened awareness in endemic regions and family screening. However, a significant fraction presented with advanced disease. The neurological progression observed in our cohort (at diagnosis: FAP stage I 60%, PND stage I 58.2%; at end of follow-up: FAP III 32.7%, PND IV 32.7%) demonstrates the progressive course of A-ATTRv without complete disease control [36,37]. This represents a major challenge, as treatment options are more limited and expected benefit is lower once severe neurologic disability or advanced cardiomyopathy are established. These results support the need for earlier detection, particularly in at-risk relatives and patients with suggestive multisystem features who remain undiagnosed.

Regarding the treatment received, 38.2% of patients underwent liver transplantation and 27.3% received specific treatment for amyloidosis with stabilizers and/or silencers. Of note, the high percentage of patients (34.5%) who did not receive any treatment, which would be justified by the advanced stage of the disease they were in, as well as by the time they were diagnosed (enrollment of patients since 1988), with much more limited therapeutic options at that time [38]. All of this, combined with the high comorbidity of the patients included in our sample (mean Charlson Comorbidity Index of 6.1), would result in a lower-than-expected time to death, with a median overall of 70 months from diagnosis to death.

Survival is largely dependent on treatment, as demonstrated by *Coelho et al*. [39]. When therapeutic strategy was categorized into three groups, mean time from diagnosis to death was shortest in untreated patients, intermediate in those receiving drug therapy, and longest in transplanted patients, with an overall significant difference between groups. However, these findings should be interpreted with caution due to a possible epoch effect in this cohort. Patients who underwent transplantation were predominantly treated before the availability of disease-

specific drug therapy, whereas pharmacological treatment was concentrated in more recent years. Consequently, treatment modality was closely confounded by calendar period, limiting direct comparison between transplantation and pharmacological therapy. Although drug therapy was associated with longer time to death compared to no treatment, this difference was not statistically significant in the present analysis, and no causal inference regarding treatment benefit can be made from these retrospective data alone.

Hospital admissions provide additional insight into disease burden beyond mortality alone. More than 40% of patients had five or more emergency room visits or hospital admissions, consistent with recent studies showing a significant increase in healthcare resource utilization in patients with A-ATTRv compared to the general population [5,40,41]. From the perspective of healthcare systems, this trend shows that the consequences of A-ATTRv are not limited to mortality endpoints. Recurrent hospitalization, emergency care utilization, and progressive dependence are also central dimensions of disease burden and should be considered when evaluating the benefit of earlier diagnosis and treatment [26].

The mortality findings are especially noteworthy. Despite proportion of missing data, cardiovascular causes were the most frequent identifiable cause of death in the cohort, exceeding infectious and neoplastic causes. This observation is consistent with prior studies demonstrating the adverse prognostic impact of cardiac involvement in systemic amyloidosis. Cardiac involvement has been increasingly recognized as a major determinant of clinical outcomes in A-ATTRv, including in patients harboring the V30M mutation, historically considered a predominantly neurological variant [1,20,42].

At the same time, the presence of infectious deaths and frequent infection-related admissions likely reflects the cumulative vulnerability of an elderly and medically complex population with repeated hospital contact, nutritional deterioration, impaired mobility, and advanced systemic disease. Thus, mortality in A-ATTRv appears not to be explained by a single pathway, but rather by the interaction between direct organ amyloid damage and the broader consequences of frailty and comorbidity.

A notable limitation of the existing literature is the predominance of heterogeneous cohorts in which A-ATTRv patients, and specifically those with the V30M variant, remain underrepresented [4,5,43,44]. This heterogeneity constrains the generalizability of findings to specific genotypic populations. Our study addresses this gap by examining a well-characterized cohort of deceased patients with A-ATTRv V30M, thereby providing focused insights into the patterns of hospitalization and mortality specific to this population.

Our study has several limitations. First, this is a retrospective study with the inherent limitations of this type of design. Second, missing data affected some variables, most notably the cause of death, which was unknown in a substantial proportion of patients. This may have led to underestimation or misclassification of specific mortality categories. Third, treatment groups were not comparable at baseline, and confounding by indication is likely. As a result, outcome differences between treated and untreated patients should not be interpreted as proof of treatment effect. Fourth, the long observational period may have introduced temporal heterogeneity, as diagnostic pathways, supportive care, and availability of disease-modifying therapies have changed over time. Finally, because the study focused on deceased patients or mortality-related follow-up, selection bias may also influence the observed patterns.

Despite these limitations, our study has relevant clinical implications. It reinforces the need for a comprehensive approach to A-ATTRv, with multidisciplinary management involving specialties such as internal medicine, neurology and neurophysiology, cardiology, genetics, rehabilitation, and palliative care when appropriate. It also underscores the prognostic weight of cardiac

involvement and the importance of identifying and treating the disease before frailty and end-organ dysfunction become predominant. In endemic regions in particular, proactive family screening and early detection of subtle neurological or cardiac signs may enhance access to disease-modifying therapies and ultimately delay death and improve quality of life.

Future studies with larger sample size and prospective design will be needed to more accurately characterize the determinants of hospitalization, mortality and survival, as well as to assess the real impact of new disease-modifying therapies on the natural history of A-ATTRv.

CONCLUSIONS:

Our findings indicate that this cohort of V30M A-ATTRv patients has frequent cardiovascular complications, and a mortality profile dominated by cardiac causes among identifiable events. Time to death appears longer in patients receiving transplantation and/or specific treatment, although these associations are likely influenced by baseline clinical differences. Earlier diagnosis, systematic cardiovascular assessment, and timely access to disease-modifying therapies may be key to improving outcomes in this population.

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of the Balearic Islands (Comité de Ética de la Investigación de las Illes Balears, CEIm-IB) and the Research Commission of Hospital Universitario Son Llàtzer (decision number: IB 5291/23 PI and IB 4641/21 PI). Informed consent was obtained from participants whenever possible. In cases where patients were deceased and obtaining informed consent was not feasible, the requirement for informed consent was waived by the Ethics Committee of the Balearic Islands in accordance with applicable regulations and institutional guidelines.

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AUTHOR CONTRIBUTIONS

P.H.-S, I.L.-L, J.G.-M contributed to patient recruitment and clinical data acquisition.

P.H.-S, I.L.-L, J.G.-M and E.C.-B conceived the study, designed the research strategy, and supervised the analytical process. M.V.-G, D.H.-S Ll. S.-R contributed to data management, processing, and verification, and provided analytical support.

P.H.-S, I.L.-L, J.G.-M and E.C.-B drafted the manuscript. All authors reviewed the manuscript critically for important intellectual content, contributed to revisions, and approved the final submitted version.

CONFLICTS OF INTEREST

J.G.-M, I.L.-L, and E.C.-B have received support for conference attendance and/or honoraria for advisory or speaking activities from Alnylam Pharmaceuticals, Pfizer, Astrazeneca, and Sobi. P.H.-S have received support for conference attendance and/or honoraria for advisory or speaking activities from AstraZeneca. M.V.-G, D.H.-S and Ll. S.-R do not declare any conflicts of interest.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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