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Tafamidis Therapy in Transthyretin Cardiac Amyloidosis: Insights from a Single Center

Transtiretin Kardiyak Amiloidoz'da Tafamidis Tedavisi: Tek Merkez Deneyimi

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Abstract: Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, life-threatening disease characterized by extracellular deposition of amyloid fibrils. Tafamidis is currently the only approved pharmacologic therapy for ATTR-CM, with proven efficacy in clinical trials. However, real-world data, particularly from Türkiye, remain limited. This study aimed to assess the clinical characteristics, treatment responses, and outcomes of patients with ATTR-CM receiving tafamidis in real-world single-center Turkish patients. This was a retrospective, single center, observational study including 13 patients diagnosed with ATTR-CM. Demographic, clinical, echocardiographic, laboratory, and follow-up data were collected. Tafamidis usage, tolerance, and long-term outcomes including mortality, heart failure hospitalization, and biomarker trends were analyzed. Among 13 patients (mean age: 71.4 ±12.2 years; 53.8% male), 8 had ATTRwt and 5 had ATTRv. At baseline, 69.2% were NYHA Class III. The mean treatment duration was 21.6 ±10.4 months. At one year, 92.3% of patients remained on therapy; by year three, five patients had died (38.5%), mostly due to heart failure. Patients who died were older (79 ±6.4 vs. 66.6 ±12.0 years, p=0.035), had worse baseline NYHA class (p=0.033), higher sPAP (p=0.045), and reduced LA reservoir strain (p=0.046). NT-proBNP decreased in 23.1% of patients during the first year, predominantly in those with ATTRv. Tafamidis was generally well tolerated. This single-center real-world study from Türkiye offers valuable insights into tafamidis use in ATTR-CM, highlighting the prognostic relevance of early diagnosis and baseline functional status, and supporting its feasibility, tolerability, and potential clinical benefit in routine care despite the small sample size.

Keywords: Cardiac amyloidosis, real-world data, tafamidis, transthyretin, treatment

Ethics Committee Approval: The study was approved by Eskişehir University Noninterventional Clinical Research Ethical Committee (61, dated 27.03..2025).

Informed Consent: Informed consent was not obtained because of the retrospective design of the study. All procedures were conducted in accordance with the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT07048041).

Authorship Contributions: Concept – S.M., Y.C.; Design – S.M., Y.C.; Supervision – Y.C.; Resource – S.M., Y.C., H.E.Y.; Materials – S.M., H.E.Y., R.O.; Data Collection and/or Processing - S.M., Y.C., H.E.Y., R.O.; Analysis and/or Interpretation - S.M., H.E.Y.; Literature Review – S.M., Y.C., H.E.Y., R.O.; Writing – S.M., Y.C., H.E.Y., R.O.; Critical Review – S.M., Y.C.

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Özet: Transtiretin amiloid kardiyomiyopatisi (ATTR-KM), amiloid fibrillerinin ekstrasellüler birikimi ile karakterize yaşamı tehdit eden bir hastalıktır. Tafamidis, ATTR-KM için etkinliği klinik çalışmalarda kanıtlanmış ve onaylanmış tek farmakolojik tedavidir. Ancak, gerçek yaşam verileri, özellikle Türkiye'den elde edilen veriler oldukça sınırlıdır. Bu çalışma, gerçek yaşam koşullarında tafamidis tedavisi alan ATTR-KM'li Türk hastaların klinik özelliklerini, tedavi yanıtlarını ve uzun dönem sonuçlarını değerlendirmeyi amaçlamaktadır. Bu retrospektif, tek merkezli, gözlemsel çalışmaya ATTR-KM tanısı konmuş 13 hasta dahil edildi. Demografik, klinik, ekokardiyografik, laboratuvar ve takip verileri takip dosyalarından elde edildi. Tafamidis kullanım süresi, ilaca tolerans ve uzun dönem sonuçlar (mortalite, kalp yetersizliği nedeniyle hastaneye yatış ve biyobelirteç değişimleri) değerlendirildi. Çalışmaya dahil edilen 13 hastanın ortalama yaşı 71,4 ±12,2 yıl olup, %53,8'i erkekti. Sekiz hastada ATTRwt (vahşi tip), beş hastada ise ATTRv (herediter tip) mevcuttu. Başlangıçta hastaların %69,2'si NYHA Sınıf III'teydi. Ortalama tedavi süresi 21,6 ±10,4 ay idi. Birinci yıl sonunda hastaların %92,3'ü tedaviye devam ederken, üçüncü yıl sonunda beş hasta (%38,5) yaşamını yitirmişti; ölümlerin çoğu kalp yetersizliğine bağlıydı. Kaybedilen hastalar daha ileri yaşta (79 ±6,4 vs. 66,6 ±12,0 yıl; p=0,035), başlangıçta daha ileri NYHA sınıfında (p=0,033), daha yüksek sPAP değerine sahipti (p=0,045) ve sol atriyum rezervuar strain değerleri daha düşüktü (p=0,046). İlk yıl içerisinde hastaların %23,1'inde NT-proBNP düzeylerinde azalma saptandı ve bu azalma daha çok ATTRv grubunda gözlendi. Tafamidis genel olarak iyi tolere edildi. Türkiye'den elde edilen bu tek merkezli gerçek yaşam verileri, tafamidis kullanımına ilişkin önemli bilgiler sunmakta; erken tanı ve başlangıçtaki fonksiyonel durumun prognostik önemine işaret etmektedir. Küçük örneklem büyüklüğüne rağmen, tafamidis tedavisinin uygulanabilirliğini, tolere edilebilirliğini ve potansiyel klinik faydasını desteklemektedir.

Anahtar Kelimeler: Kardiyak amiloidoz, gerçek yaşam verisi, tafamidis, transtiretin, tedavi.

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1. Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a rare but increasingly recognized disease characterized by the extracellular deposition of amyloid fibrils, leading to progressive heart failure (1-3). The most common forms include transthyretin (ATTR) amyloidosis and immunoglobulin light chain (AL) amyloidosis. ATTR-CM can be further classified into wild-type (ATTRwt) and variant (ATTRv) forms. ATTRwt is primarily associated with aging, whereas ATTRv results from specific genetic mutations (1). In recent years, advancements in the understanding of ATTR-CM pathophysiology and improvements in non-invasive diagnostic techniques have facilitated earlier diagnosis (1-5). However, therapeutic options to slow or halt disease progression remain limited. Tafamidis, a selective transthyretin stabilizer, is the first and currently the only pharmacologic agent approved for the treatment of ATTR-CM (6). The ATTR-ACT trial demonstrated that tafamidis reduces mortality and cardiovascular hospitalizations in ATTR-CM patients, leading to its recognition as the standard therapy for ATTR-CM in both European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines (6-8). While clinical trials have established the efficacy of tafamidis in ATTR-CM, real-world data remain limited. Randomized controlled trials (RCTs) focus on selected patient populations under controlled conditions, whereas real-world studies provide insights into tafamidis treatment outcomes, effectiveness, safety, and tolerability in broader and more diverse patient groups.

Tafamidis was approved by the U.S. Food and Drug Administration (FDA) in 2019 for the treatment of ATTR-CM. In Türkiye, tafamidis initially became accessible through the Turkish Medicines and Medical Devices Agency (TİTCK) via the Off-Label Drug List, allowing its use under reimbursement prior to national marketing authorization, which was granted at the end of 2021. Subsequently, tafamidis meglumine 61 mg received formal regulatory approval and reimbursement in March 2023, enabling broader clinical use. However, during this period, real-world data on tafamidis use in Türkiye have remained limited. This study aims to address this gap by systematically evaluating the clinical characteristics, clinical effectiveness, safety profile, and long-term patient outcomes of patients with ATTR-CM receiving tafamidis therapy in real-world Turkish patients. Although derived from a single center, the real-world experience provided by this study may still offer valuable insights into the clinical application of tafamidis and contribute to refining current treatment strategies.

2. Materials and Metod

1.1. Study Design and Population

This study was conducted in accordance with the Declaration of Helsinki and received approval from the Eskisehir University Non-Interventional Clinical Trials Ethics Committee (Approval Number:61, Date: 27.03.2025). Artificial intelligence-assisted technologies were not used in the production of this study. This study is a retrospective, observational, single-center study evaluating real-world data of patients diagnosed with ATTR-CM between 2021 and 2025. Informed consent was not obtained because of the retrospective design of the study. The study population includes patients who were followed up at Eskisehir Osmangazi University with a confirmed diagnosis of ATTRwt and ATTRv based on clinical and imaging criteria.

1.2. Inclusion Criteria

Patients included in this study must meet the following criteria:

1-Diagnosis of ATTR-CM (ATTRwt and ATTRv) confirmed by:

2- 99m Technetium–Pyrophosphate (99mTc-PYP) (or equivalent) scintigraphy with a Perugini score ≥ 2 and absence of monoclonal protein,

3-Genetic testing confirming a pathogenic TTR mutation in ATTRv cases.

4-Availability of baseline and follow-up clinical and laboratory data.

1.3. Diagnostic Algorithm

ATTR-CM diagnosis was established in accordance with current consensus criteria (1). All patients underwent 99mTc-PYP scintigraphy, and a Perugini score ≥2 in the absence of detectable monoclonal protein was considered diagnostic of ATTR-CM without biopsy. To exclude immunoglobulin light-chain (AL) amyloidosis, serum and urine immunofixation electrophoresis and serum free light-chain assays were systematically performed. Patients with a confirmed pathogenic TTR mutation were categorized as ATTRv, while those without mutations were classified as ATTRwt (1).

Genetic testing was performed using whole-exome sequencing (WES) at our institutional molecular genetics laboratory. Variants in the TTR gene were analyzed and classified as pathogenic or likely pathogenic according to American College of Medical Genetics and Genomics (ACMG) standards. Two pathogenic mutations were identified in the cohort: p.Phe53Leu and p.Val114Ala. Patients carrying a confirmed pathogenic TTR variant were categorized as ATTRv, while those without mutations were classified as ATTRwt.

1.4. Data Collection

Data for this study were retrospectively extracted from electronic medical records. Baseline demographic information, including age, sex, body mass index (BMI), and comorbidities such as hypertension, atrial fibrillation (AF), diabetes, and chronic kidney disease, were recorded. The ATTR subtype and family history of amyloidosis were also documented. Diagnostic assessments included electrocardiographic findings such as low voltage criteria, pseudo-infarct patterns, and AF, as well as echocardiographic parameters, including left ventricular (LV) wall thickness, diastolic dysfunction, and global longitudinal strain (GLS). Cardiac amyloidosis red flags, such as unexplained LV hypertrophy, low voltage on ECG, and bilateral carpal tunnel syndrome were noted. Additionally, the presence of peripheral neuropathy was recorded for each patient. 99mTc-PYP scintigraphy results were collected, with Perugini scoring used to stratify patients.

Laboratory parameters such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T levels were recorded at baseline and during follow-up. Renal function markers, including serum creatinine and estimated glomerular filtration rate (eGFR), as well as liver function tests, and albumin levels were recorded. In ATTRv cases, genetic testing results were documented to identify pathogenic TTR mutations.

Follow-up data included treatment strategies and disease progression, with specific attention to the use of tafamidis as the primary disease-modifying therapy. The duration of tafamidis use (in months) was recorded for each patient, along with data on treatment discontinuation if applicable. For patients who discontinued tafamidis, the reason for stopping treatment was documented, including adverse effects, disease progression, or physician recommendation. Additionally, guideline-directed heart failure medications, including diuretics, beta-blockers, and mineralocorticoid receptor antagonists, were recorded. Device therapy, including implantable cardioverter defibrillators and pacemakers, was also documented. Clinical outcomes such as hospitalization rates due to heart failure exacerbations, all-cause mortality, arrhythmia and cardiovascular mortality were systematically collected. Data were collected at diagnosis and during routine follow-up visits to assess the progression of cardiac amyloidosis and response to tafamidis treatment.

1.5. Statistical analyses

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 23 (IBM, Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables were presented as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. For comparison of continuous variables between groups, the independent samples t-test was used for normally distributed data and the Mann-Whitney U test for non-normally distributed data. The chi-square test or Fisher's exact test was applied

for categorical variables, as appropriate. Changes in NT-proBNP levels during follow-up were analyzed using the Wilcoxon signed-rank test. A p value <0.05 was considered statistically significant.

2. Result

2.1. Baseline Patient Characteristics

A total of 13 patients diagnosed with ATTR-CM were included in the study. Among them, 7 patients (53.8%) were male, and the mean age of the study population was 71.4 ± 12.2 years. Regarding the ATTR subtype, 8 patients (61.5%) had ATTRwt, while 5 patients (38.5%) had ATTRv (Table 1). Among the study cohort, three patients (23.1%) were aged ≤65 years, and all of them were diagnosed with ATTRv. At baseline, 9 patient (69.2%) was New York Heart Association (NYHA) Class III, 4 patients (30.8%) were NYHA Class II and also, the median 6-minute walk test (6MWT) distance **was** 220 meters (IQR: 145-295)**.**

Among the 13 patients included in the study, hypertension was the most common comorbidity, present in 7 patients (53.8%). Coronary artery disease (CAD) was identified in 2 patients (15.4%), while diabetes mellitus was diagnosed in 4 patients (30.8%). Regarding renal function, no patients required dialysis at baseline; however, 4 patients (30.8%) had chronic kidney disease (CKD).

Compared with ATTRwt, patients with ATTRv were significantly younger (58.7 ± 10.9 vs. 77.7 ± 6.8 years, p = 0.004) and more likely to present with peripheral neuropathy (100% vs. 0%, p = 0.001) and autonomic dysfunction (80% vs. 12.5%, p = 0.032), consistent with the hereditary phenotype of ATTRv. Interventricular septal thickness was also greater in the ATTRv group (17.7 ± 1.7 mm vs. 13.8 ± 1.8 mm, p = 0.005), whereas NT-proBNP levels were comparable between groups (2364.5 vs. 1215 pg/mL, p = 0.681). A comparative summary of demographic, clinical, and echocardiographic characteristics between ATTRwt and ATTRv patients is presented in Table 2.

2.2. Red Flags Features

In the study cohort, several red flags suggestive of ATTR-CM were identified. Bilateral carpal tunnel syndrome was present in 2 patients (15.4%). Peripheral neuropathy was noted in 5 patients (38.5%), while autonomic dysfunction, including orthostatic hypotension and gastrointestinal symptoms, was observed in 5 patients (38.5%).

Electrocardiographic abnormalities were prevalent, with low voltage ECG despite increased LV wall thickness detected in 6 patients (46.2%). A pseudo-infarct pattern was documented in 3 patients (23.1%), and conduction disturbances, including atrioventricular block or bundle branch block, were present in 4 patients (30.8%). Atrial fibrillation was observed in 4 patients (30.8 %) at baseline.

Echocardiographic findings revealed LV hypertrophy (mean LV wall thickness: 15.5 mm±2.9 SD). The mean ejection fraction (EF) was 59.6% (±4.0 SD), while the mean left ventricular GLS (LV-GLS) was -10.8% (± 3.0 SD). Apical sparing pattern was observed in 4 patients (30.8%).

On 99mTc-PYP scintigraphy, 5 patients (38.5%) had a Perugini score of 2, while 8 patients (61.5%) had a Perugini score of 3. The heart-to-contralateral lung (H/CL) ratio was 2.1 (±0.64 SD).

2.3. Laboratory results

The median baseline NT-proBNP level was 1215 pg/mL (IQR:775-3208.7), and the median baseline troponin T level was 0.038 ng/mL (IQR:0.013-0.059) in the study cohort at diagnosis. Additionally, the mean baseline serum creatinine level was 0.94 mg/dL (±0.38 SD), and the median eGFR was 80 mL/min/1.73m² (IQR: 49.5-90), the mean serum albumin level was 4.0 g/dL (±0.56 SD), and the mean hemoglobin level was 13.2 g/dL (±1.1 SD).

2.4. Tafamidis treatment data

At presentation, diuretics were the most commonly received medications (61.5%, n=8), followed by beta-blockers and renin-angiotensin system inhibitors (each 38.5%, n=5), and sodium-glucose co-transporter 2 (SGLT2) inhibitors (30.8%, n=4).

In Türkiye, the national health system implemented regulatory approval and reimbursement for tafamidis

meglumine 61 mg in March 2023. Therefore, between 2021 and March 2023, patients who were prescribed tafamidis obtained the medication through an application to the TITCK. During this period, tafamidis was provided as 20 mg tablets, administered as 4 tablets per day (80 mg total daily dose). After this date, patients continued treatment with tafamidis meglumine 61 mg daily, in accordance with the national health system's reimbursement and regulatory approval.

The mean duration of tafamidis use during the follow-up period was 21.6 months (±10.4 SD)**.** At one-year follow-up**,** 12 patients (92.3 %) continued tafamidis therapy**,** while 1 patient (7.7 %) discontinued treatment due to death.

During the second year, an additional 2 patients died. In 1 patient, chronic kidney disease emerged, and the medication was discontinued due to a decrease in GFR to below 30 mL/min/1.73 m². Additionally, one patient did not use the treatment regularly due to experiencing gastrointestinal intolerance during tafamidis treatment, including nausea and abdominal discomfort. During follow-up, patients generally tolerated the treatment well, and no other adverse effects were observed. At the three-year follow-up, 2 additional patients died.

2.5. Follow-up Data of the Patients

A total of five patients (38.5%) died during the follow-up period (Figure 1). One patient died due to ischemic stroke, whereas the remaining four deaths were attributed to heart failure-related complications. In the first year, heart failure-related hospitalizations occurred in four patients (30.8%). Atrial fibrillation was newly diagnosed in one patient and one patient experienced an ischemic stroke. Furthermore, one patient was diagnosed with acute kidney disease, with eGFR declining below 30 mL/min/1.73 m², leading to discontinuation of the treatment. Clinical outcomes and follow-up data of the study population presented in Table 3.

2.6. NT-proBNP Trend and Associated Clinical Characteristics

During the first year of follow-up, a reduction in NT-proBNP levels was observed in three patients (23.1%) who continued tafamidis therapy (Figure 2). All three patients were diagnosed with ATTRv and two of these patients were in NYHA Class II and one in NYHA Class III at baseline. Notably, only one of these patients required hospitalization for heart failure during the first year of the follow-up period, while the other two remained event-free. All three demonstrated improved functional capacities, with an increase in their 6MWT distance compared to baseline assessments. Additionally, all three patients had preserved renal function (eGFR > 60 mL/min/1.73 m²) and lacked significant comorbidities such as diabetes mellitus or AF.

2.7. Comparison Between Deceased and Surviving Patients

Comparison of patients who died during the follow-up period (n=5) with those who survived (n=8) revealed some clinical differences (Table 4). The patients who died were statistically significantly older than those who survived (79 ±6.4 vs. 66.6± 12.0 years, p= 0.035) Moreover, all patients who died during the follow-up period were over 65 years of age. Additionally, the deceased group presented with a more advanced NYHA functional class at baseline (3.0±0.0 vs.2.5±0.5, p= 0.033). Baseline eGFR was lower in patients who died during the follow-up period compared to those who survived (59.4± 19.2 vs. 79.8±13.0, p=0.042) There was no statistically significant difference between the deceased and surviving groups in terms of EF, NT-proBNP levels, or LV-GLS (respectively, p=0.127, p=0.138, p=0.823). In the deceased group, baseline systolic pulmonary artery pressure (sPAP) was higher (48.2 ±6.0 vs. 35.2 ±14.0, p=0.045) and left atrial reservoir strain (LASr) was lower (10±4.2 vs. 17.7±8.0 p=0.046) compared to the surviving group.

Table 1. Baseline Demographic and Clinical Characteristics of Patients

Parameters	**Number of patients (%) N =13**
ATTRwt, n (%)	8(61.5%)
ATTRv, n (%)	5 (38.5%)
Gender; male, n(%)	7 (53.8%)
Age (years ±SD)	71.4 ±12.2
NYHA	
Class II, n(%)	4 (30.8%)
Class III, n(%)	9 (69.2%)
Polyneuropathy, n(%)	5 (38.5%)
Carpal Tunnel Syndrome, n(%)	2 (15.4%)
Atrial fibrillation, n(%)	4 (30.8%)
PYP Grade 2, n (%)	5 (38.5%)
PYP Grade 3, n (%)	8 (61.5%)
PYP Scintigraphy Concordance	13 (100%)
Genetic test positive	5 (38.5%)
Type of mutations (n=5)	
p.Phe53Leu, n (%)	3 (60 %)
p.Val114Ala, n (%)	2 (40%)

Note: *Each patient is represented by a different color line. Bold lines indicate greater reductions in NT-proBNP over time. The grey point represents a patient with missing follow-up data. NT-proBNP values are plotted on a logarithmic scale to improve visualization of trends.*

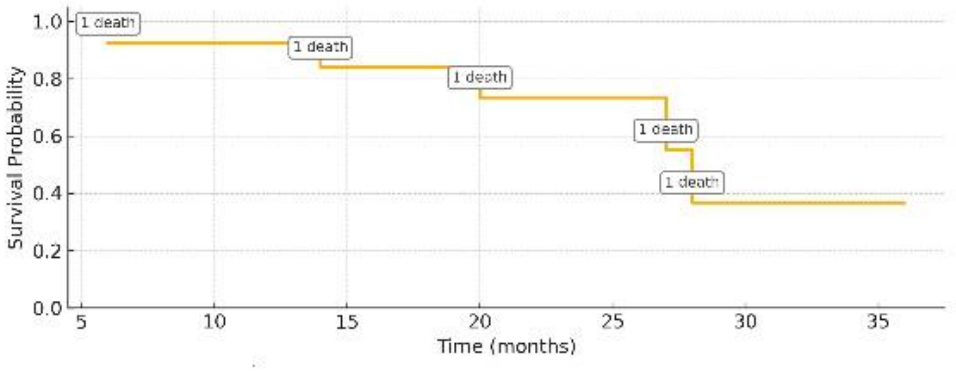


Figure 1. *Survival curve with death events*

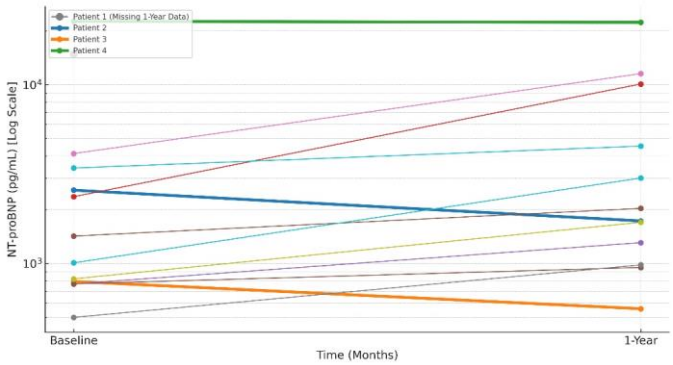


Figure 2. *Longitudinal Change in NT-proBNP from Baseline to 1-Year*

3. Discussion

This real-world, single-center study provides insight into the clinical characteristics, treatment patterns, and outcomes of patients with ATTR-CM who were treated with tafamidis in routine clinical practice. The ATTR-ACT trial clearly demonstrated the efficacy of tafamidis in reducing mortality and cardiovascular hospitalizations in ATTR-CM patients (6). However, real-world evidence remains limited, particularly in unselected patient populations and in regions lacking multicenter data.

To the best of our knowledge, this is also the first study to systematically report real-world data on tafamidis treatment and clinical outcomes in patients with ATTR-CM in Türkiye. To date, real-world data on ATTR-CM from Türkiye remain extremely limited, with most international registries and clinical studies lacking representation from this region. In fact, there is currently no national registry for ATTR-CM in Türkiye, and published data are largely restricted to case reports or single-center experiences. Our study represents the first systematic attempt to characterize the tafamidis treatment data, and outcomes of patients with ATTR-CM in the Turkish population. These findings help address a significant data gap and provide locally relevant evidence that may inform clinical awareness, diagnosis, and management strategies in Türkiye, where delayed recognition and underdiagnosis of the disease remain important challenges.

In Türkiye, limited access to 99mTc-PYP scintigraphy and genetic testing until recent years has likely contributed to delayed diagnosis and incomplete subtype identification. Expanding diagnostic capacity, enhancing clinician awareness, and developing national ATTR-CM registries could significantly improve early recognition, accurate subtyping, and overall management of ATTR-CM. The most frequent TTR variants identified in our cohort were p.Phe53Leu and p.Val114Ala. The p.Val114Ala mutation has been previously reported in Mediterranean populations, particularly in Greece, where it has been associated with a predominantly cardiomyopathy phenotype (9). In contrast, p.Phe53Leu has been described in a limited number of unrelated families across different regions, including Europe and the Middle East, though data remain scarce (10). This mutation pattern may reflect regional genetic diversity and underscores the need for further population-based genetic studies in Türkiye.

Our findings indicate that tafamidis was generally well tolerated, with a high rate of treatment continuation at one year. A minority of patients discontinued therapy due to adverse effects or clinical progression, emphasizing the importance of individualized monitoring. These results are consistent with those of the Long-Term Extension Study of ATTR-ACT, which also demonstrated sustained tolerability and benefit over time (11). While the age distribution in our cohort was comparable to that of RCT populations, a higher proportion of patients in our study presented with advanced heart failure symptoms (NYHA Class III), which may reflect later diagnosis or delayed referral in routine clinical practice. This underscores the challenges of disease recognition and timely treatment initiation in real-world settings.

A recent large-scale study on the impact of earlier diagnosis in cardiac ATTR amyloidosis over the past 20 years highlights a substantial improvement in survival outcomes (12). In this cohort, 36.7% of patients died over a median follow-up period of 30.6 months. When analyzed by 5-year intervals, mortality declined markedly from 73.5% in 2002–2006 to 14.9% in 2017–2021 accompanied by a significant increase in median survival from 34.9 months to over 60 months, underscoring the prognostic benefit of earlier recognition and diagnosis. In comparison, the overall mortality rate in our cohort was 38.5% over a median follow-up of 36 months. While this figure is somewhat higher than the most recent data from broader populations, it may reflect differences in disease stage at diagnosis, patient comorbidities, or healthcare system-related factors. Nevertheless, our findings align with the growing body of evidence supporting the importance of timely diagnosis and suggest that further improvement in survival may be achievable with earlier detection and optimized management strategies.

In addition to early diagnosis, baseline functional status may also play a significant role in prognosis. Recent data also highlight the prognostic importance of functional capacity in ATTR-CM (13). A large single-center cohort study showed that NYHA functional class at the time of diagnosis is an independent predictor of all-cause mortality and provides significant incremental value when incorporated into existing risk scores, such as the Mayo and UK staging systems (14). Consistent with this, in our cohort, most patients who died were in NYHA Class III at diagnosis, underscoring the strong association between advanced functional limitation and adverse outcomes in this population. These results reinforce the notion that functional status readily assessed through clinical evaluation remains a powerful and accessible tool for risk stratification in ATTR-CM. Incorporating NYHA class into patient assessment may help guide therapeutic decision-making and identify individuals who may benefit from earlier and more intensive management.

Beyond functional capacity, structural and hemodynamic abnormalities involving the right heart have also gained increasing recognition as important prognostic markers in ATTRwt (15-17). A recent study demonstrated that moderate-to-severe tricuspid regurgitation (TR) is an independent predictor of mortality in patients with ATTRwt, emphasizing the prognostic significance of TR severity in this population (18). Consistently, in our cohort, all patients who died during follow-up had moderate-to-severe TR, and their baseline sPAP was significantly higher compared to survivors. These findings underscore the importance of evaluating right-sided cardiac function as part of comprehensive risk stratification in ATTRwt.

Furthermore, a recent retrospective study involving 93 patients with ATTR-CM found that those with significant TR had substantially worse outcomes, including a higher incidence of death or heart failure hospitalization over a two-year period (19). In multivariate analysis, both significant TR and elevated NT-proBNP levels emerged as independent predictors of this composite outcome. Collectively, these findings highlight the prognostic relevance of TR severity and cardiac stress markers, reinforcing their role in guiding clinical management and risk assessment in patients with ATTR-CM.

More recently, attention has shifted toward echocardiographic markers such as left atrial (LA) strain, which offer a refined assessment of atrial function and prognostic value in ATTR-CM. A retrospective study comparing patients with ATTR-CM, hypertrophic cardiomyopathy, and healthy controls demonstrated significantly impaired LA function in the cardiac amyloidosis group—even among those with preserved ejection fraction (20). Similarly, in our cohort, baseline LASr (LASr; 13.3% ± 6.9%) were markedly reduced, consistent with atrial involvement in ATTR-CM. In a recent prospective study, tafamidis treatment led to a modest improvement in LASr after one year in patients with sinus rhythm, but not in those with AF (21) Consistent with these findings, in our study, among patients who received tafamidis for at least one year and had follow-up echocardiographic assessment, LASr significantly improved—from 10.8 ± 4.9**%** at baseline to 13.2 ± 5.5% at one year ($p = 0.04$). This further supports the utility of LA strain not only as a prognostic marker but also as an indicator of therapeutic response in ATTR-CM, particularly in patients with sinus rhythm.

4. Conclusion

This single-center, real-world study provides important insights into the clinical profile, treatment patterns, and outcomes of patients with ATTR-CM treated with tafamidis. Our findings support the growing body of evidence emphasizing the prognostic importance of early diagnosis and functional status at baseline. Moreover, we highlight the added value of right-sided cardiac assessment including SPAP and LA strain as critical prognostic markers in ATTR-CM. By addressing a significant data gap in Türkiye and presenting systematic real-world data on tafamidis use, this study contributes to enhancing clinical awareness and guiding patient-specific strategies for risk stratification and long-term management in ATTR-CM.

Limitations

The main limitations of this study are the small sample size and its single-center design. These factors may limit the generalizability of the findings. Larger, multicenter studies are needed to validate

our results and to better understand the real-world effectiveness and outcomes of tafamidis treatment in patients with ATTR-CM in Türkiye.

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