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Unravelling ATTR Cardiac Amyloidosis in Iceland: A Nationwide Epidemiological Study

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Abstract
Introduction: Cardiac amyloidosis (CA) arises from the deposition of misfolded amyloid proteins in the heart's extracellular matrix, leading to significant cardiac disease. Recent data suggest that CA is under-recognised, and advances in treatment have increased focus on this condition with the intention of implementing treatment earlier to improve prognosis. There is limited knowledge regarding the prevalence of transthyretin CA (ATTR-CA) on a national level, particularly in Iceland. Therefore, this study represents the first nationwide effort to evaluate the baseline characteristics, diagnostics, and treatment of ATTR-CA in Iceland. ***Methods:*** A retrospective study of all patients diagnosed with ATTR-CA in Iceland from 6 May 2013 to 11 March 2024 was identified in the Icelandic Cardiac Amyloid Registry (ICE-CAR) created in 2023 by heart failure (HF) specialists at Landspitali University Hospital in Reykjavik, Iceland. Diagnosis was based on different combinations of transthoracic echocardiography, an elevated Perugini score on bone scintigraphy and heart biopsies, as well measurements of free light chains, M-component measurements in blood and urine. Patients were grouped according to the National Amyloidosis Centre (NAC) prognostic staging system for ATTR-CA. ***Results:*** In total, 65 patients with ATTR-CA were identified (males $n = 60$, females $n = 5$, median age 81.4 years [IQR 75.5–85.5 years]), all wild-type and no mutant variant. Diagnosis was made with myocardial biopsy in 7 cases. Upon diagnosis, 83% of the patients had an interventricular septum thickness of ≥15 mm and 92% showed a posterior wall thickness of ≥12 mm. Approximately 57% of patients belonged to New York Heart Association (NYHA) functional class I–II. The HF phenotypes according to left ventricular ejection fraction (LVEF) were distributed as follows: reduced (HFrEF) $n = 24$ (37%), mildly reduced (HFmrEF) $n = 9$ (14%), preserved (HFpEF) $n = 29$ (44.5%), and unknown LVEF $n = 3$ (4.5%). A total of 54 patients had reported NAC stage: stage I 23 (35.4%), stage II 20 (30.8%), stage III 11

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(16.9%). Around 32% received disease-modifying treatment. ***Conclusion:*** Despite the low NYHA class observed in the study population, our findings in Iceland's nationwide assessment of ATTR-CA indicate more advanced age and lower LVEF at diagnosis compared to other studies. This highlights the critical need for early detection and appropriate therapeutic interventions in managing ATTR-CA.

Introduction

Amyloidosis is a group of systemic diseases in which unstable misfolded proteins aggregate and precipitate as amyloid fibrils in the tissues of the body. Accumulation of amyloid fibrils in the heart causes thickening of the atrial and ventricular walls and increased stiffness of the heart. This causes less compliance in diastole (diastolic dysfunction) and can eventually develop into restrictive cardiomyopathy and heart failure (HF) [1]. The two most common types of cardiac amyloidosis (CA) are immunoglobulin light chain cardiac amyloidosis (AL-CA) and transthyretin cardiac amyloidosis (ATTR-CA). Other very rare subtypes of amyloidosis exist, including AapoAI, AApoAII, AApoAIV, A2M, Afib, and Agel [2].

ATTR-CA occurs when the transthyretin (TTR) protein, a tetramer synthesised in the liver, breaks down into monomers that are deposited in the myocardium and other tissues [3]. Two main types of ATTR-CA exist: ATTRv, a hereditary form caused by a faulty or mutated gene, and wild-type ATTRwt, which develops with age and is not inherited. Cardiac involvement is seen in 70% of AL-CA cases, 100% of ATTRwt, and 30–100% of ATTRv cases [2]. Over 90% of ATTRwt occurs in males; the mean age of onset is approximately 75 years, and the median survival after diagnosis is 3.5 years without treatment [4]. The median age of onset of ATTRv amyloidosis, which is also predominant in males, is 39 years [5], and the median survival without treatment is approximately 2.5 years [4]. The reason for male dominance is unknown [4] and may to some extent be implicated by underdiagnosis in women.

The Icelandic Cardiac Amyloidosis Registry (ICE-CAR), founded in December 2023, is the first nationwide effort to map amyloidosis in Iceland. The registry is directly connected to the Icelandic nationwide electronic health record IT system, which includes clinical data on all Icelandic amyloidosis patients diagnosed by or referred to cardiologists from 6 May 2013 onwards.

Methods

This is a retrospective descriptive observational study of all patients in Iceland (population 383,726 on 1 January 2024 [6]) diagnosed with ATTR-CA from 6 May 2013 to 11 March 2024 and registered in the ICE-CAR. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [7]. This study included all patients diagnosed with CA in Iceland during the study period. As this represented a nationwide cohort study, no formal sample size calculation was performed. The sample size was determined by the number of eligible patients identified in the ICE-CAR registry during the specified time period.

The ICE-CAR is electronic and was created in the national IT health system Heilsugátt in December 2023 by HF specialists working at Landspitali University Hospital in the capital, Reykjavík, and in Akureyri Hospital, in Northern Iceland. The set-up of variables was determined in consultation with fellow experts in the field in neighbouring countries. Since 2022, a consensus board of HF specialists and HF nurses at Landspitali University Hospital has been operational that discusses referred patients suspected of having CA and whether they are candidates for disease-modifying therapy. Work-up is completed (where needed), and if a CA diagnosis is confirmed, these individuals are manually added to the ICE-CAR.

Access to the ICE-CAR registry is controlled by Ingimarsdóttir, Úlfarsson, and Hrafnkelsdóttir. Currently, only HF physicians and nurses in the HF outpatient clinic at Landspitali University Hospital have access to it. Patients can opt out if they do not want to answer quality-of-life (QoL) questionnaires, but all clinical variables are recorded as a part of quality assurance and patients do not sign an informed consent form because the data are pseudonymised and cannot be traced back to individuals. Only aggregated data are reported in analyses, and patient privacy and data security are managed by the strict rules that apply to electronic health records in the National Heilsugátt Health IT System. Only with approval of the Scientific Research Committee for Health Research of Landspitali University Hospital, specified health care professionals are given access to the data. The research was conducted ethically in accordance with the World Medical Declaration of Helsinki [8].

The diagnosis of ATTR-CA was based on clinical judgement by the abovementioned consensus board and was based on echocardiography, radionuclide bone scintigraphy, serum and/or urine protein electrophoresis with immunofixation, serum free light chain assay, and

endomyocardial biopsy. The date of diagnosis was set to the date of the bone scintigraphy, where applicable.

General demographic data included in the ICE-CAR are date of amyloidosis diagnosis, date of birth, sex, ethnicity, height (cm), weight (kg), body mass index, body surface area, smoking status, and weekly alcohol consumption. Comorbidities, such as heart valve disease and operation, tendon rupture, carpal tunnel syndrome diagnosis and operation, spinal stenosis, and hip or knee replacement, are registered. Symptoms are registered according to New York Heart Association (NYHA) class, angina pectoris class, and 6-min walking test score. Signs of HF are registered with the grade of peripheral oedema and the presence of ascites and/or elevated jugular venous pressure.

N-terminal pro-b-type natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR) measurements are also registered, and the National Amyloidosis Centre (NAC) disease stages are determined based on these results [9]. Various measurements on the echocardiography results are registered, e.g., left ventricular ejection fraction (LVEF), presence of apical sparing, left atrial volume index, details of aortic stenosis (if present), other valve abnormalities, diastolic dysfunction parameters, and the tricuspid regurgitation pressure gradient. Radionuclide bone scintigraphy with phosphate-based technetium tracers can be used to diagnose ATTR amyloidosis, and Perugini scores 0–3, which are used to grade cardiac uptake compared to rib uptake, are also registered [10]. The medical therapy prescribed for each patient after diagnosis is registered, including both ATTR and HF medications.

The NAC score has previously been used to classify CA into three disease stages based on cutoff points in two serum biomarkers, NT-proBNP and eGFR [9]. We chose to use the modified NAC classification system proposed by Law et al. [11]. This modification further classifies NAC disease stage I into stages Ia and Ib. A patient is classified into stage Ia if NT-proBNP <500 ng/L (<1,000 ng/L with atrial fibrillation), eGFR >45 mL/min/1.73 m^2, and the patient is on no or a low amount of diuretics (<0.75 mg/kg furosemide). A patient is classified into stage Ib if NT-proBNP is 500–3,000 ng/L (1,000 ng/L–3,000 ng/L with atrial fibrillation), eGFR >45 mL/min/1.73 m^2, and furosemide >0.75 mg/kg.

Statistical analysis of the data was conducted with RStudio, using R version 4.3.3 (29 February 2024). Descriptive statistics were employed to illustrate the characteristics of the population. Missing values were excluded from the calculation of descriptive statistics, including means, standard deviations, and medians. Survival analysis was performed using the Kaplan-Meier method. The time-to-event was calculated as the duration from the date of amyloidosis diagnosis to the date of death for deceased patients, or to the date of last follow-up for patients still alive (censored at 14 March 2024). The duration was converted from days to months for easier interpretation. The median survival time was calculated as the time at which the survival probability dropped to 0.5 or below. The median follow-up time was calculated as the median of the time from diagnosis to the last follow-up date for all patients.

Results

Table 1 shows that 78 patients in Iceland were diagnosed with CA over the study period. Of those, 65 had ATTR-CA, 6 had AL-CA, 1 had apolipoprotein A-IV (AApoA4) amyloidosis, and 6 had an unknown type of CA. Overall, 91.0% of the patients were male. Of those with ATTR-CA, 92.3% were male, and of those with AL-CA, 66.7% were male.

Analysis of age at diagnosis showed a mean age of 80.1 years (SD 8.25) and a median age of 81.4 years. When analysing the age at diagnosis separately for different types of amyloidosis, there was an apparent difference in the mean and median ages between groups. Patients with AL-CA had the lowest age at diagnosis, with a mean age of 69.6 years (SD 16.6) and a median age of 67.8 years. Patients with ATTR-CA had the highest age at diagnosis, with a mean age of 80.6 years (SD 6.98) and a median age of 81.4 years. Patients with an unknown type had a mean age at diagnosis of 85.4 years (SD 6.72) and a median age of 88.3 years, significantly older than those diagnosed with a specific type. Of the 65 ATTR-CA patients, 19 (29.2%) underwent genetic testing for known TTR mutations, but all yielded a negative result and were therefore assigned ATTRwt. Diagnosis was made with myocardial biopsy in 7 cases.

Table 2 shows the clinical presentation and assessment at the time of diagnosis with NYHA class, angina pectoris (Canadian Cardiovascular Society [CCS] class), eGFR, and NT-proBNP. More than half (52.3%) of the ATTR patients were in NYHA class II at diagnosis, and 4.6% were in NYHA class I. At diagnosis, 32.3% of ATTR patients were in NYHA class III, and 9.2% were in NYHA class IV. The median eGFR was 56.0 mL/min/1.73 m^2 (IQR 41.75–61.75). The median NT-proBNP level was 3,247 ng/L (IQR 1,435.5–5,594.8). Most patients were either in NAC disease stage Ib (30.8%) or II (30.8%), and a few were in stage Ia (4.6%) or III (16.9%); see Figure 1.

None of the patients who underwent bone scintigraphy were classified as Perugini grade 0 or 1. The highest proportion of patients were classified as Perugini grade 3

Table 1. Baseline patient characteristics of the study population

	TTR (*N* = 65)	AL-amyloidosis (*N* = 6)	Other (*N* = 1)	Unknown (*N* = 6)	Overall (*N* = 78)
Sex, *n* (%)					
Female	5 (7.7%)	2 (33.3%)	0 (0%)	0 (0%)	7 (9.0%)
Male	60 (92.3%)	4 (66.7%)	1 (100%)	6 (100%)	71 (91.0%)
Age at diagnosis, years					
Mean (SD)	80.6 (6.98)	69.6 (16.6)	81.5 (NA)	85.4 (6.72)	80.1 (8.25)
Median [min, max]	81.4 [64.9, 93.8]	67.8 [49.9, 93.1]	81.5 [81.5, 81.5]	88.3 [75.5, 89.7]	81.4 [49.9, 93.8]
Missing	0 (0%)	1 (16.7%)	0 (0%)	2 (33.3%)	3 (3.8%)
Ethnicity, *n* (%)					
Caucasian	65 (100%)	6 (100%)	1 (100%)	4 (66.7%)	76 (97.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	2 (33.3%)	2 (2.6%)
Height, cm					
Mean (SD)	177 (8.38)	177 (9.42)	178 (NA)	174 (0.577)	177 (8.18)
Median [min, max]	178 [158, 197]	180 [164, 188]	178 [178, 178]	174 [173, 174]	178 [158, 197]
Missing	6 (9.2%)	0 (0%)	0 (0%)	3 (50.0%)	9 (11.5%)
Weight, kg					
Mean (SD)	84.6 (15.8)	80.9 (17.6)	69.6 (NA)	88.8 (17.6)	84.2 (15.8)
Median [min, max]	81.1 [49.0, 124]	83.3 [56.0, 99.0]	69.6 [69.6, 69.6]	79.2 [78.0, 109]	81.0 [49.0, 124]
Missing	8 (12.3%)	0 (0%)	0 (0%)	3 (50.0%)	11 (14.1%)
BMI					
Mean (SD)	25.6 (7.26)	25.9 (5.16)	22.0 (NA)	29.4 (5.70)	25.8 (6.98)
Median [min, max]	25.6 [0, 36.8]	25.6 [20.6, 33.2]	22.0 [22.0, 22.0]	26.5 [25.8, 36.0]	25.6 [0, 36.8]
Missing	6 (9.2%)	0 (0%)	0 (0%)	3 (50.0%)	9 (11.5%)

Table 2. Clinical presentation and serum biomarkers of ATTR patients

	Overall (*N* = 65)
NYHA class	
I	3 (4.6%)
II	34 (52.3%)
III	21 (32.3%)
IV	6 (9.2%)
Unknown	1 (1.5%)
Angina pectoris CCS class	
0	52 (80.0%)
I	2 (3.1%)
II	4 (6.2%)
IV	1 (1.5%)
Unknown	6 (9.2%)
eGFR	
Mean (SD)	54.1 (17.0)
Median [min, max]	56.0 [12.0, 90.0]
Missing	5 (7.7%)
NT-proBNP	
Mean (SD)	5,010 (5,620)
Median [min, max]	3,250 [181, 29,800]
Missing	11 (16.9%)

(43.1%), followed by Perugini grade 2 (33.8%) (Fig. 1). However, 23.1% of patients did not undergo bone scintigraphy and therefore had an unknown Perugini grade. Their diagnosis was based on symptomatic HF, ventricular hypertrophy, and an apical sparing pattern on transthoracic echocardiography (TTE).

Figure 1 shows a horizontal bar chart of the distribution of Perugini grades and NAC disease stages for ATT-CA patients. The highest proportion of patients are in Perugini grade 3 and NAC disease stages Ib and II.

Table 3 shows the occurrence of specific health conditions associated with amyloidosis in ATTR-CA patients, where 6.2% had a history of tendon rupture and 27.7% had a history of spinal stenosis. Of the 65 ATTR-CA patients, 17 (26.2%) had been diagnosed with carpal tunnel syndrome, and 12 of those (70.6%) had undergone a carpal tunnel operation. Approximately 35% had undergone hip or knee replacement, and 6.1% had moderate or severe aortic stenosis on an echocardiography.

Table 4 shows the results of the echocardiograms closest to the time of diagnosis. The LVEF had a mean of 46.1% (SD 13.7) and a median of 45.0%. The HF phenotypes according to LVEF were distributed as follows:

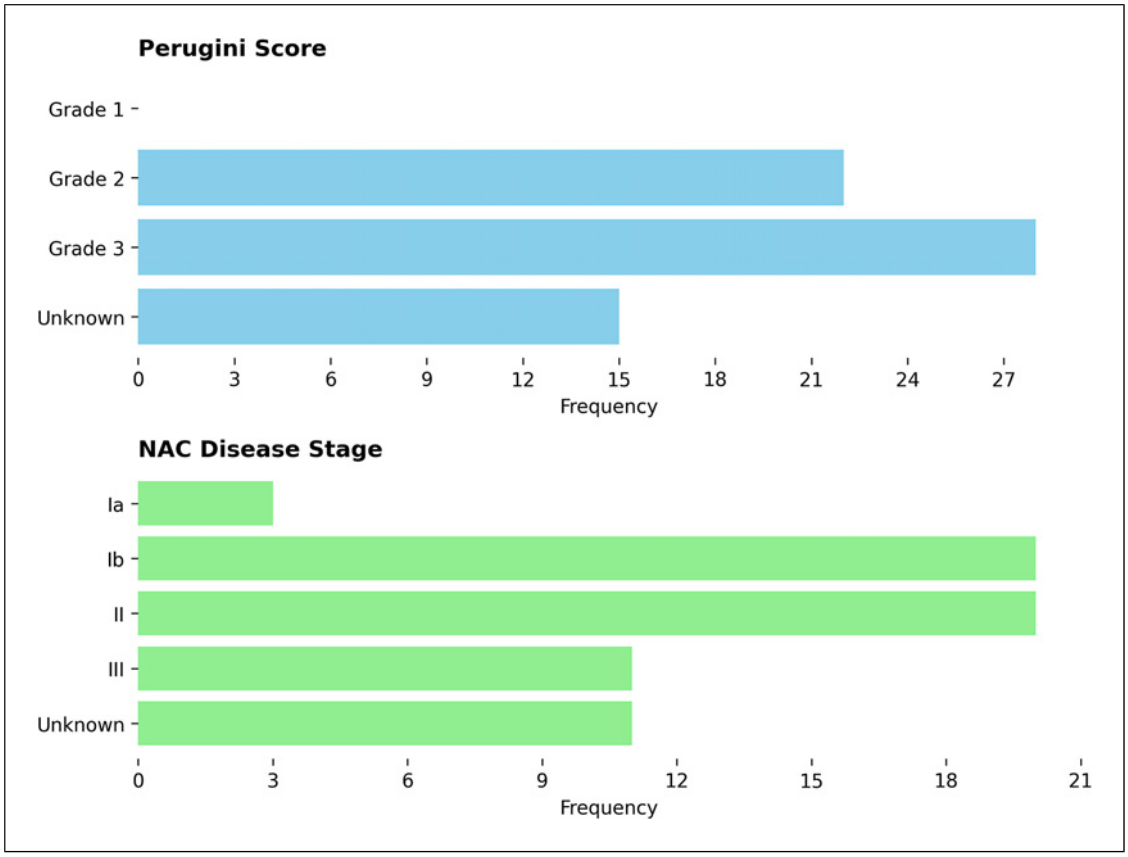

Fig. 1. Perugini score and NAC disease stage in ATTR patients.

reduced (HFrEF) *n* = 24 (37%), mildly reduced (HFmrEF) *n* = 9 (14%), preserved (HFpEF) *n* = 29 (44.5%), and unknown LVEF *n* = 3 (4.5%). The mean interventricular septum thickness was 19.0 mm (SD 4.64), and the median thickness was also 19.0 mm. The posterior wall thickness was on average less than the septum thickness, with a mean of 17.5 mm (SD 3.93) and a median thickness of 17.0 mm. Apical sparing was present on 75.4% of the echocardiograms but not reported in 4.6% of cases; the rest were unknown (image quality too poor for accurate strain imaging or strain not performed). Nearly half of the patients (49.2%) had atrial fibrillation during the echocardiography procedure.

Table 5 shows the number of ATTR-CA patients, alive, deceased, and overall, who received the disease-modifying treatment with ATTR medication tafamidis (Vyndaqel® 61 mg once daily). Of the 38 patients still alive, 50% received ATTR medication, and of the 27 deceased patients, 7.4% had received ATTR medication. Overall, 32.3% of ATTR-CA patients received ATTR medication.

Figure 2 presents a survival analysis of patients with ATTR-CA. A total of 65 patients were included in the analysis, with 27 deaths observed during the study period. The median follow-up time was 29.7 months. The median overall survival for the entire cohort was 34.8 months (95% CI: 29.7–59.9 months). The estimated 1-year survival rate was 90.2% (95% CI: 79.4%–95.5%), and the 3-year survival rate was 45.0% (95% CI: 27.7%–60.9%).

Discussion

This study is the first scientific review of all patients diagnosed with ATTR-CA in Iceland, including their clinical presentation, symptoms, work-up, treatment, and predicted outcome. Our analysis of amyloid demographics in Iceland shows some similarities and some disparities in comparison with other countries, although direct comparison is often biased as limited data exist on nationwide status of ATTR-CA worldwide.

Table 3. Health conditions associated with ATTR

	Overall (*N* = 65)
Tendon rupture	
Yes	4 (6.2%)
No	50 (76.9%)
Unknown	11 (16.9%)
Carpal tunnel diagnosis	
Yes	17 (26.2%)
No	39 (60.0%)
Unknown	9 (13.8%)
Carpal tunnel operation	
Yes	12 (18.5%)
No	48 (73.8%)
Unknown	5 (7.7%)
Spinal stenosis	
Yes	18 (27.7%)
No	43 (66.2%)
Unknown	4 (6.2%)
Hip or knee replacement	
Yes	23 (35.4%)
No	41 (63.1%)
Unknown	1 (1.5%)
Aortic stenosis	
No/mild	54 (83.1%)
Yes, moderate	1 (1.5%)
Yes, severe	3 (4.6%)
Unknown	7 (10.8%)

Table 4. Echocardiography findings of ATTR patients

	Overall (*N* = 65)
LVEF, %	
Mean (SD)	46.1 (13.7)
Median [min, max]	45.0 [10.0, 76.0]
Unknown	3 (4.6%)
Intraventricular septum thickness, mm	
Mean (SD)	19.0 (4.64)
Median [min, max]	19.0 [11.0, 32.0]
Unknown	1 (1.5%)
Posterior wall thickness, mm	
Mean (SD)	17.5 (3.93)
Median [min, max]	17.0 [10.0, 30.0]
Unknown	4 (6.2%)
Apical sparing, *n* (%)	
Yes	49 (75.4%)
No	3 (4.6%)
Unknown	13 (20.0%)
Atrial fibrillation on echocardiography, *n* (%)	
Yes	32 (49.2%)
No	24 (36.9%)
Unknown	9 (13.8%)

Table 5. ATTR-CA patients who have received ATTR medication (tafamidis)

	Alive (*N* = 38)	Deceased (*N* = 27)	Overall (*N* = 65)
ATTR medication			
Yes	19 (50.0%)	2 (7.4%)	21 (32.3%)
No	19 (50.0%)	25 (92.6%)	44 (67.7%)

Baseline Patient Characteristics

Analysis of patient characteristics showed a gender distribution similar to a Swedish study in which 88% of ATTR-CA patients were male [12]. When gender distribution of ATTR-CA in Sweden was assessed on a national level, the percentage of Swedish males fell to 70.1% [13]. The overall ATTR-CA gender distribution in the other Nordic countries (Denmark, Norway, Sweden, and Finland) was 69% for males (ranging from 50.5% in Finland to 79.7% in Denmark) [13]. This may implicate considerable underdiagnosis of women with ATTR-CA in Iceland. Women may be detected later as the sizes of women's hearts and wall thickness are generally lower than in men, therefore being at risk for potential underdiagnosis because they are less likely to meet the threshold in diagnostic algorithms [14]. HFpEF is more prevalent in older women, and physicians treating them may be less suspicious of an ATTR-CA aetiology [13, 14].

Icelandic ATTR-CA patients were, on average, significantly older with mean age of 80.6 years (95% CI: 78.9–82.2), as opposed to 73.1 years overall in the other Nordic countries, ranging from 71.5 years in Denmark to 74.2 years in Norway [13]. The older age at diagnosis in the Icelandic cohort may reflect several factors: (1) delayed diagnosis with more advanced disease, due to less awareness, differences in health care practices, and a different access to diagnostic tools such as bone scintigraphy outside the capital area; (2) population demographics, where Iceland's population structure or genetic factors might contribute to a later onset or diagnosis of ATTR-CA; (3) referral patterns and diagnostic criteria for specialist evaluation may have led to later diagnosis in Iceland compared to other Nordic countries; (4) survival bias; given that the Icelandic cohort is diagnosed later in the disease course, our cohort might represent a group of longer-surviving patients, potentially impacting Icelandic survival estimates.

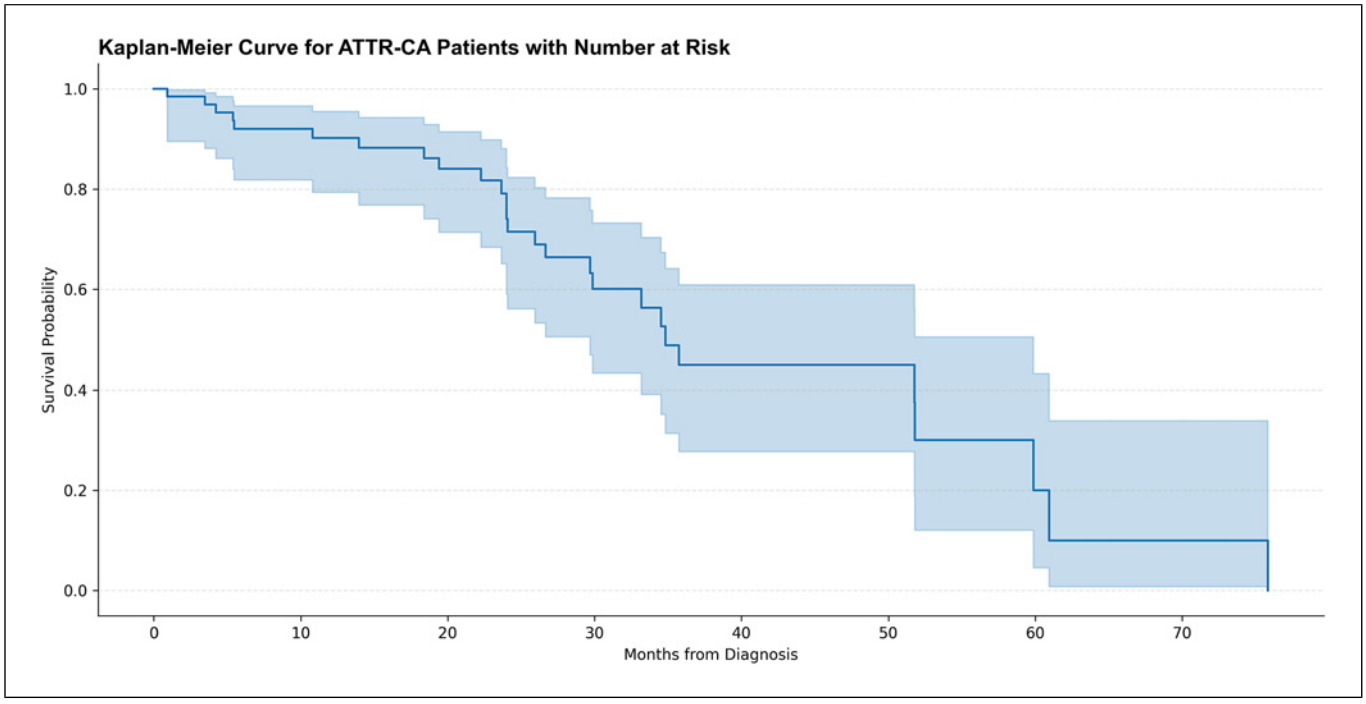

Fig. 2. Survival of patients with ATTR-CA.

The non-biopsy diagnosis of ATTR-CA with radionuclide bone scintigraphy in patients without monoclonal gammopathy has facilitated diagnosis and is considered reliable and applicable to most ATTR-CA patients [15]. Therefore, it can be argued that more emphasis should be placed on a more thorough work-up, despite advanced age or disease burden, to determine the correct subtype. A radionuclide bone scintigraphy, together with blood and urine tests, should perhaps be a minimum requirement in the diagnostic process. However, it should be kept in mind that bone scintigraphies are only performed in the capital region of Iceland, and therefore, it may not always be justified to transport elderly or sick patients between regions of the country to determine their Perugini scores if no specific ATTR-CA treatment is at any rate planned because of age or other underlying reasons. All Icelandic ATTR-CA patients who underwent a bone scintigraphy had a Perugini score of 2–3, and this strengthens the probability of a correct non-biopsy diagnosis of ATTR-CA. Icelandic patients with an unknown type of amyloidosis were relatively few and had both the highest mean and median age, perhaps because these patients were considered too frail to undergo further work-up to determine the subtype of CA.

All Icelandic patients with a known ATTR-CA diagnosis were assigned the wild-type subtype, and no hereditary cases have been found in Iceland to date. Genetic testing was performed in only 29.2% of ATTR-CA cases, thus undoubtedly raising questions as to whether any of these individuals may possibly belong to the hereditary variant. It could be an opportunity for HF specialists in Iceland to set themselves the goal of routinely taking a genetic test for all ATTR-CA patients from now on.

Clinical Presentation and Eligibility to Receive Disease-Modifying Treatment

Being classified in NYHA functional class I or II, defined as having no or slight limitation to physical activity, is one of the requirements to be eligible for novel disease-modifying treatment with ATTR medication, such as tafamidis. Our analysis showed that 56.9% of ATTR-CA patients were classified in either NYHA class I or II and were therefore likely to be eligible for ATTR treatment. However, 32.3% of all Icelandic ATTR-CA patients, currently alive or deceased, did receive disease-modifying treatment. Compared to figures reported in a Norwegian study (5%), a much higher proportion of the Icelandic ATTR population currently alive (50%) is receiving disease-modifying therapy [16].

Icelandic patients were less symptomatic than observed in a Swedish study with NYHA class I–II (Iceland 56.9% vs. Sweden 41.5%) [12]. The criteria for receiving ATTR treatment do not solely rely on the NYHA functional class. Operational since 2022, a consensus board of HF specialists and HF nurses at Landspitali University Hospital has been discussing potential candidates for ATTR treatment. Clinical assessment of ATTR-CA patients has been centralised to this hospital, which has the only cardiology department in Iceland and has a well-functioning HF outpatient clinic with dedicated HF nurses. Each patient meets with an HF nurse for an interview, undergoes a physical examination and echocardiography, answers QoL questionnaires, and completes a 6-min walk test. An HF specialist then joins the interview, receives a summary of the information obtained by the nurse, and has an opportunity to ask the patient (and relatives) additional questions and further examine the patient. The HF specialist and HF nurse present the cases at the consensus board, and factors, such as frailty, severe comorbidity, and dementia, are addressed. These factors can impact the decision of whether or not the patient is considered a candidate for ATTR therapy, despite belonging to a preferable NYHA functional class. The treatment is very costly and does not begin to show effect on overall survival until approximately 18 months after initiation [17]. This also significantly impacts the decision to be made.

Disease Burden Assessment by NAC Stage and Echocardiography

During the development of the NAC staging, Gillmore et al. [9] found, by univariable analyses, that an NT-proBNP level above 3,000 ng/L and an eGFR below 45 mL/min/1.73 m^2 were each found to be significantly associated with death. The degree of disease burden in the Icelandic cohort was assessed using modified NAC staging, while echocardiography was used to determine the HF phenotype. A rough estimate of each individual's prognosis was achievable by stratifying the patient into one of the three NAC stages at the time of diagnosis according to mean eGFR, NT-proBNP, and use of diuretic treatment. In ATTR-CA, the median survival for stages I, II, and III has been shown to be 6, 4, and 2 years, respectively [9]. The mean eGFR level in the Icelandic cohort was similar to that in a Norwegian study, but the median NT-proBNP in our study (3,250 ng/L) was more than 1,000 ng/L higher than in both the Norwegian (median 2,028 ng/L) [16] and Swedish (median 2,113 ng/L) [12] studies.

A study by Ioannou et al. [18] that looked at ATTR-CA referral patients showed that over time (divided into 5-year periods from 2002 to 2006, 2007 to 2011, 2012 to 2016, and 2017 to 2021) a greater proportion of patients had early-stage disease at diagnosis that was associated with lesser interventricular septal thickness and higher LVEF. This clearly reflects increased awareness of ATTR-CA during the same time period. The mean and median LVEFs in our study were similar to those in other studies [16, 19, 20]. The Icelandic patients had significantly greater interventricular septum thickness (19.0 mm) compared to other studies. A Swedish study reported a median thickness of 16.5 mm [12], a Norwegian study reported a median thickness of 15 mm [16], and other studies described a mean or median septum thickness of around 16–17 mm [19, 20]. The median posterior wall thickness was also significantly greater in our study (17.0 mm) than in the Swedish study (13 mm) [12], but it was similar to that in an older British study with a larger population [20]. These larger mean and median wall thicknesses probably reflect a more advanced stage in the course of the disease at the time of diagnosis. The Icelandic population was significantly older when they were diagnosed, so the disease probably had more time to progress, leading to greater amyloid deposition and increased thickening in the myocardium, although it had not always reached the point where it could have had a decisive effect on the LVEF.

Strategies for Earlier Detection

Approximately 26% of Icelandic ATTR-CA patients had a history of carpal tunnel syndrome, which is less common than in other studies, which have shown up to half of patients with this history [19, 20]. The percentage in this study may be an underestimate, as some carpal tunnel operations are performed in private practice and the extent of those operations is unknown due to a lack of systematic registration. However, studies from both Norway and Sweden showed proportions similar to ours, with 28% of the ATTR population having a history of carpal tunnel syndrome in each country [12, 16]. A history of spinal stenosis was more common in the Icelandic ATTR population (27.7%) than in the Norwegian (18%) [16] and Swedish (16%) [12] studies. The prevalence of severe aortic stenosis on echocardiography in our study (4.6%) was consistent with that in the Norwegian study (4%) [16].

As carpal tunnel syndrome can precede CA diagnosis by many years, this could be a means to screen such patients using conventional amyloidosis work-up with echocardiography as a first stage, followed by a bone

scintigraphy and immunofixation of light chains in serum and urine. Implementing treatment, although costly, may show a cost benefit in the long run.

Survival

This study showed a poorer median survival from the date of diagnosis in ATTRwt patients (1.88 years) compared to British (2.71 years) [20] and American (3.89 years) [19] studies. While short-term survival (1 year) is relatively high for ATTR-CA patients in our cohort, there is a substantial decline in survival over the following 2 years. The wide confidence intervals, particularly for the 3-year survival rate and median survival, indicate considerable variability in outcomes, which may be due to factors such as disease severity at diagnosis, treatment approaches, or individual patient characteristics. The Icelandic patients in this study had a higher median age at diagnosis than other studies and may, therefore, have had, on average, more advanced disease. Poor survival could also be influenced by the short follow-up time, but a repetition of the analyses from the ICE-CAR in the years to come will facilitate a more accurate median survival assessment.

Call for a New Diagnostic Strategy

Awareness of CA in Iceland was low until approximately 5 years ago (2019), when medical treatment for this chronic disease with high morbidity emerged and became accessible to Icelandic patients. It has opened the eyes of Icelandic cardiologists, especially HF specialists, but more needs to be done to make other medical specialties aware of the disease. Many potentially undiagnosed ATTR-CA patients are seen by general practitioners, geriatricians, orthopaedic surgeons, and internal medicine specialists, who may be unaware of the true underlying aetiology. Members of the different health care professions in Iceland need to be educated about the signs, symptoms, and available treatment of ATTR-CA. Clinical practices are evolving by writing national guidelines on CA diagnosis available to all Icelandic physicians. Furthermore, a session on amyloidosis in general with participation of neurologists, haematologists, nephrologists, and cardiologists will be prominent at the Annual Meeting of the Icelandic Medical Association held in Reykjavík in January 2025.

Study Limitations

As a retrospective study, this investigation has several inherent limitations. The patient sampling methodology evolved following the implementation of non-invasive diagnostic techniques [15], and many cases of CA likely remained undiagnosed prior to increased disease awareness. In particular, elderly patients may not have undergone comprehensive diagnostic evaluation. Another known limitation of our study is that the presence of apical sparing on the TTE is not always reported. Therefore, we re-evaluated all TTE images from Landspitali University Hospital, and the proportion of patients with a confirmed apical sparing pattern rose from 55.4% to 75.4%. With the greater emphasis on the centralised systemic work-up of patients with ATTR-CA by HF specialists, we predict that the number of patients with unknown apical sparing values in the future should decrease, improving the quality of the data to the level of a Swedish study that showed that 96% of patients had apical sparing [12].

Several other inherent biases may have influenced our findings. Selection bias may have occurred since only patients diagnosed and registered in ICE-CAR were included, potentially missing undiagnosed cases, particularly in women and rural areas with limited access to diagnostic tools. Patients who survived long enough to receive a diagnosis were included, potentially missing rapidly progressive cases. Additionally, our data may reflect referral bias, as geographic barriers to accessing bone scintigraphy in the capital region could have led to underdiagnosis in rural areas, with variation in referral patterns between different physicians and regions possibly affecting which patients reached specialist care. Lead-time bias should also be considered, as earlier diagnosis in recent years due to increased awareness and better diagnostic tools may artificially appear to improve survival times. Furthermore, diagnostic suspicion bias may have affected our cohort composition, as the threshold for investigation has evolved with increasing awareness of the condition. This is particularly relevant given the recognised gender bias in diagnostic suspicion and the age bias in diagnostic work-up, as previously discussed.

Measurement bias must be acknowledged due to the evolution of diagnostic techniques and criteria over the study period, as well as potential variability in echocardiographic interpretation between different readers. Information bias may have arisen from the retrospective nature of data collection and varying completeness of medical records. To minimise measurement bias, standardised definitions were used for all clinical variables and outcomes. Observer bias was reduced by having multiple clinicians review complex cases through the CA consensus board.

Conclusion

The true incidence of ATTR-CA has been underestimated until now and in all likelihood still is to some extent. The ultimate aim of Icelandic HF specialists is to

educate other physicians of the signs and symptoms, and increase CA referral rates. This will facilitate finding younger patients with mild or no symptoms so that they can implement effective treatment and thus slow disease progression or even avoid high morbidity and a severely compromised QoL; hopefully, they can influence mortality as well. Systematic prospective registration of all newly diagnosed ATTR cases, which has been implemented in connection with the foundation of the ICE-CAR, will, in the future, offer better insights into the disease itself and hopefully quantify the impact of early initiation of treatment. Additionally, concurrent genetic testing will hopefully identify hereditary cases, thus allowing contact tracing that may benefit more individuals before HF develops.

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Statement of Ethics

Written informed consent from participants was not required for the study presented in this article in accordance with national guidelines. This study protocol was reviewed and approved by the Icelandic Bioethics Committee (reference no. VSN 23-143) on 4 January 2024. Approval was also obtained from the Scientific Research Committee of Landspitali University Hospital on 9 April 2024.

Conflict of Interest Statement

Úlfarsson has received speaker fees from Pfizer. Hrafnkelsdóttir has received consulting fees from Pfizer.

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Author Contributions

The study was designed, and the manuscript was drafted by H.M. Bergmann, Æ.Ö. Úlfarsson, and I.J. Ingimarsdóttir. H.X. Jóhannsdóttir, K. Andersen, G.T. Gunnarsson, H. Einarsson, and T.J. Hrafnkelsdóttir revised and contributed to the final manuscript. Statistics and data analyses were performed primarily by H.M. Bergmann and H. Einarsson.

Data Availability Statement

Data are from the Icelandic Cardiac Amyloidosis Registry (ICE-CAR) and are not available to the public as it may compromise the privacy of research participants. Further enquiries can be directed to the corresponding author (I.J.I.) upon reasonable request.

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