Cardiac amyloidosis: description of a series of 143 cases

Amiloidosis cardiaca: descripción de una serie de 143 casos

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Abstract

Introduction and objectives. Recently, there have been important advances in the diagnosis and treatment of cardiac amyloidosis (CA). Our aim was to provide an updated description of its 2 most frequent types: the transthyretin CA (ATTR-CA) and the light chain CA (AL-CA).

Methods. Prospective registry of patients with CA diagnosed in 7 institutions in Galicia (Spain) between January 1, 2018 and June 30, 2020. Variables related to clinical characteristics, complementary tests, survival and causes of death were collected.

Results. One hundred and forty-three patients with CA were consecutively included, 128 ATTR-CA (89.5%) and 15 AL-CA (10.5%). Mean age was 79.6 ± 7.7 years and 23.8% were women. Most patients with ATTR-CA were diagnosed non-invasively (87.5%). On physical examination, 35.7, 35 and 7% had Popeye's sign, Dupuytren's contracture and macroglossia, respectively. Twelve-month and 24-month survival was 92.1 and 76.2% in the ATTR-CA group, and 78.6 and 61.1% in the AL-CA group (P = 0.152). The cause of death was cardiovascular in 80.8% of the cohort.

Conclusions. ATTR-CA can be diagnosed non-invasively in most cases and it is the most common type of CA in routine clinical practice. Furthermore, an increase in the short-term survival of CA appears to be observed, which could be due to advances related to its diagnosis and treatment.

Resumen

Introducción y objetivos. Recientemente se han producido importantes avances en el diagnóstico y tratamiento de la amiloidosis cardiaca (AC). Nos propusimos realizar una descripción actualizada de sus 2 tipos más frecuentes: la AC por transtirretina (AC-ATTR) y la AC por cadenas ligeras (AC-AL).

Métodos. Registro prospectivo de pacientes diagnosticados de AC en 7 hospitales de Galicia entre el 1 de enero de 2018 y el 30 de junio de 2020. Se recogieron variables relativas a características clínicas, pruebas complementarias, supervivencia y causas de muerte.

Resultados. Se incluyeron de forma consecutiva 143 pacientes con AC, 128 AC-ATTR (89,5%) y 15 AC-AL (10,5%). La edad media fue de 79,6 ± 7,7 años y un 23,8% fueron mujeres. La mayoría de los pacientes con AC-ATTR se diagnosticaron de forma no invasiva (87,5%). En la exploración física, un 35,7, un 35 y un 7% de los pacientes presentaban el signo de Popeye, contractura de Dupuytren y macroglosia, respectivamente. La supervivencia a los 12 y 24 meses fue del 92,1 y el 76,2% en el grupo AC-ATTR, y del 78,6 y el 61,1% en el grupo AC-AL (p = 0,152). La causa de muerte fue cardiovascular en el 80,8% de la cohorte.

Conclusiones. La AC-ATTR puede ser diagnosticada en la mayoría de los casos de manera no invasiva y es la forma de AC más frecuente en la práctica clínica habitual. Además, parece

observarse un aumento en la supervivencia a corto plazo de la AC que en parte podría deberse a los avances relacionados con su diagnóstico y tratamiento.

Keywords

Cardiac amyloidosis; Transthyretin; Light chain; Registry; Multicenter; Prospective

Palabras clave

Amiloidosis cardiaca; Transtirretina; Cadenas ligeras; Registro; Multicéntrico; Prospectivo

Introduction

Cardiac amyloidosis (CA) results from the deposition of insoluble fragments of a particular type of protein in the extracellular space of the heart, which eventually results in alterations in this organ's structure and function.[1] Although up to nine different types of proteins have been linked to the onset of CA,[2] approximately 95% of cases are due to the deposition of transthyretin, which causes two forms of amyloid transthyretin CA (ATTR-CA); that is, non-inhereted or wild-type (ATTRwt-CA) and inhereted or variant (ATTRv-CA), as well as amyloid light-chain CA (AL-CA).[3]

Important advances in the diagnosis and treatment of CA have been made in recent years. On the one hand, the ability to diagnose ATTR-CA without the need for performing invasive studies[4] has led to a significant increase in the number of cases detected and it is now believed to be the most frequent subtype of this disease.[2] On the other, the development of new specific treatments associated with an improvement in the prognosis of patients with ATTR-CA[5] and AL-CA.[6]

Despite the availability of studies focusing on the clinical characterization of CA, some of which have been published recently,7, 8 most are based on single-center, retrospective cohorts including patients who were examined years before the availability of the diagnostic and therapeutic novelties described above. For this reason, we believe that a more updated description of this entity is neeeded to bring us closer to the profile of CA patients that can be found today in routine clinical practice. With this goal in mind, we created a real-world, multicenter, prospective registry, whose main results we present in this document.

Methods

Study description

The Galician Registry of Cardiac Amyloidosis (AMI-GAL, *Registro de Amiloidosis Cardíaca en Galicia*) is a currently active, observational, prospective registry of patients with CA that was created on 1 January 2018 and in which a total of seven hospitals integrated within the public health system of Galicia, Spain (SERGAS, *Servizo Galego de Saúde*), participate. The study protocol was prepared in accordance with the provisions of the Declaration of Helsinki and approved by the Galician Research Ethics Committee. According to this protocol, each participant must sign a specific informed consent form prior to their inclusion in the registry.
In addition, it establishes the diagnosis of CA based on the following criteria:

- Detection of amyloid deposits–defined by positive staining with Congo red and subsequent apple-green birefringence under a polarized-light microscope–in a histological sample, characterizing the specific subtype through immunohistochemistry or mass spectrometry tests. If the diagnosis is reached with a non-cardiac specimen, the confirmation of CA requires an additional imaging test revealing signs of myocardial infiltration.
- In the case of ATTR-CA, a combination of a scintigraphy with 3,3-diphosphono-1,2-propanodicarboxylic acid or marked with ^{99m}Tc (^{99m}Tc-DPD) with a cardiac uptake grade of 2 or 3, the absence of a monoclonal component demonstrated by electrophoretic immunofixation in a blood and urine sample, as well as a determination of the presence of free light chains in a blood sample.

Although it is not considered a mandatory condition for a patient's inclusion in the registry, a sequencing study of the transthyretin gene is also advised for identifying pathogenic mutations and, therefore, differentiating between the ATTRwt-CA and ATTRv-CA subtypes.

Data collection

The analyzed data was sourced from the patients' medical records. Variables related to their clinical characteristics, ancillary tests, survival, and causes of death were collected. The list of all variables recorded, and the specific definitions of the most relevant ones can be found in Annex B.

Statistical analysis

Categorical variables are presented as proportions and continuous variables are presented as a mean ± standard deviation or median (interquartile range [IQR]) depending on whether they followed a normal distribution.

All patients were followed-up from their inclusion in the registry until 30 September 2020 or their date of death, whichever occurred first.

Survival curves were constructed for patients with ATTR-CA and AL-CA using the Kaplan-Meier method and compared using the log-rank test.

All statistical analyses were carried out using the Mac version of software SPSS® 25.

Results

Patients

A total of 143 patients diagnosed with CA (128 [89.5%] with ATTR-CA and 15 [10.5%] with AL-CA) were included in the registry between 1 January 2018 and 30 June 2020. The diagnosis of the entity had been reached prior to the date of inclusion in the registry in 24 (16,8%) of these patients (18 with ATTR-CA and six with AL-CA), which were called prevalent cases, with a median time of disease evolution of 710 days (IQR 451–1473). None of the prevalent cases of ATTR-CA had received disease-modifying treatments prior to their inclusion in the registry, whereas four of the prevalent cases of ALCA had received antineoplastic therapy before said moment (with two of them having achieved a very good hematologic response and the other two a partial response) and one had received antineoplastic therapy followed by a hematopoietic stem cell transplant (achieving a complete hematologic response). None of these patients had achieved an

organic cardiac response (defined as a decrease >300 ng/L and >30% in the absolute and relative levels of N-terminal prohormone brain natriuretic peptide [NT-proBNP], respectively, in patients with baseline levels ≥650 ng/L or a decrease ≥2 in the grade of the New York Heart Association [NYHA] functional class in patients with a baseline grade of 3 or 4)[9] and all of them had imaging data indicative of myocardial infiltration upon their inclusion in the registry.

Of the patients with ATTR-CA, 115 (89.8%) had ATTRwt-CA, two (1.6%) had ATTRvCA (with genetic variant p.Val50Met being identified in both cases), and 11 (8.6%) had an undetermined type due to not having undergone genetic testing. All of them had undergone a ^{99m}Tc-DPD scintigraphy that revealed a cardiac uptake grade of 2 (14 patients [10.9%]) or 3 (114 patients [89.1%]). The diagnosis was reached without the need for performing invasive studies in 112 patients (87.5%), whereas 16 (12.5%) had to undergo a biopsy (endomyocardial in 15 patients [93.7%] and of the abdominal subcutaneous fat in one [6.3%]) due to the presence of a monoclonal component in a blood and/or urine sample.

Of the patients with a diagnosis of ALCA, 11 (73.3%) had a lambda subtype and four (26.7%) had a kappa subtype. Four of them (26.7%) also had concomitant multiple myeloma. Ten patients (66.7%) of this group underwent a ^{99m}Tc-DPD scintigraphy, two (20%) of them with a positive result (one with a grade 2 and another with a grade 3) and eight (80%) with a negative result (three with a grade 0 and five with a grade 1). A biopsy was required to reach the diagnosis in all cases (endomyocardial in nine cases [60%], of the abdominal subcutaneous fat in five cases [33.3%], and of the digestive tract in one case [6.7%]).

Clinical characteristics

Table 1 outlines the baseline clinical characteristics of all patients upon their inclusion in the registry.

The overall mean age of these patients was 79.6 ± 7.7 years, although this figure was significantly higher in the group of patients with ATTR-CA (81 ± 6 years) compared with those with AL-CA (67.9 ± 10.8 years) ($p < 0.0001$). Thirty-four patients (23.8%) with ATTR-CA and six (40%) with AL-CA were women ($p = 0.019$).

The most frequent reason for consultation in both types of CA were heart failure symptoms (77 patients [60.2%] with ATTR-CA and eight [53.3%] with AL-CA), and the diagnosis was primarily reached by Cardiology Departments (110 patients [85.9%] with ATTR-CA and ten patients [66.6%] with AL-CA).

We observed a greater prevalence of a previous history of atrial fibrillation or flutter in patients with ATTR-CA (56.3%) compared with those with AL-CA (26.7%) ($p = 0.030$), whereas a history of ischemic heart disease (33.3% vs. 12.5%; $p = 0.031$) and peripheral neuropathy (13.3% vs. 1.6%; $p = 0.009$) was observed more frequently in the latter.

Regarding the physical examination findings, the group of patients with ALCA was characterized by having lower systolic blood pressure levels (113 ± 13 mmHg vs. 124 ± 19 mmHg; $p = 0.022$) and a greater prevalence of macroglossia (20% vs. 5.5%; $p = 0.037$) compared with those with ATTRCA. However, these patients exhibited symptoms compatible with Dupuytren's contracture more frequently than the former (38.3% vs. 6.7%; $p = 0.015$).

As for the medical treatment received by the patients of either group, we found no significant differences except for the prevalence of antiplatelet therapy (53.3% in AL-CA patients vs. 12.5% in ATTR-CA patients; $p < 0.0001$), anticoagulation therapy (26.7% in AL-CA patients vs. 57.8% in ATTR-CA patients; $p = 0.022$), loop diuretics (100% in AL-CA patients vs. 74.2% in ATTR-CA patients; $p = 0.025$), and ivabradine (6.7% in AL-CA patients vs. 0% in ATTR-CA patients; $p = 0.003$).

Additional tests

The results of the additional tests carried out at the time of the patients' inclusion in the registry are detailed in Table 2 below.

With respect to the laboratory findings, of note are the lower plasma potassium (4.1 ± 0.3 mEq/L vs. 4.5 ± 0.5 mEq/L; $p = 0.013$), total protein (6.2 ± 0.9 g/dl vs. 6.8 ± 0.5 g/dl; $p < 0.0001$), and albumin (3.9 ± 0.4 g/dl vs. 4.2 ± 0.4 g/dl; $p = 0.010$) levels, as well as the greater plasma NTproBNP (7131 ± 7038 pg/mL vs. 4008 ± 4007 pg/mL; $p = 0.011$) levels in the AL-CA group compared with the ATTR-CA group.

The main differential electrocardiographic finding was the heart rate, with both atrial fibrillation or flutter (41.4% vs. 13.3%) and pacemaker rhythm (14.1% vs. 0%) being more frequent in patients with ATTR-CA compared with those with AL-CA ($p = 0.008$).

We found no statistically significant differences in any of the transthoracic echocardiogram parameters analyzed, except for the E/E' ratio, which was higher in patients with AL-CA (19.1 ± 8.8) compared with those with ATTR-CA (15 ± 5.5) (p = 0.020).

Survival and causes of death

Over a median follow-up of 520 days (IQR 323–685), three patients (20%) with AL-CA received a hematopoietic stem cell transplant and 11 (73.3%) received antineoplastic treatment with regimens based on bortezomib (n = 7), melphalan (n = 2), carfilzomib (n = 1), and daratumumab (n = 1). Of these, two patients received a second line of treatment, one with lenalidomide and the other with daratumumab. Sixty-eight patients with ATTR-CA (53.1%) were treated with tafamidis for a median of 373 days (IQR 263–510) in the context of a research protocol started in March 2019.

Three patients (2.1%) underwent a heart transplantation (one with ATTR-CA and two with AL-CA), with both transplant recipients of the AL-CA group subsequently having received antineoplastic regimens based on bortezomib and a hematopoietic stem cell transplantation 164 and 230 days later, respectively.

A total of 26 patients (18.2%) passed away (21 with ATTRCA and five with AL-CA). The cause of death was cardiovascular in 21 cases (80.8%), including ten deaths due to refractory heart failure, seven sudden deaths, two due to acute peripheral arterial ischemia, one due to stroke, and another during the immediate postoperative period of a cardiac intervention. Among the non-cardiovascular causes, there were two deaths secondary to an infection, one to a neoplasm, and another to an acute post-traumatic subdural hematoma. The cause of death was unknown in one patient.

The survival rate at 12 and 24 months was 92.1% and 76.2%, respectively, in patients with ATTR-CA, and of 78.6% and 61.1%, respectively, in those with AL-CA (p = 0.152). The survival curves are shown in Fig. 1.

Discussion

In this paper we present a detailed description of a contemporary cohort of patients with CA obtained from a multicentric, prospective, real-world registry.

Until a few years ago, AL-CA was considered to be the most frequent form of this disease. Although we had little epidemiological information available, some previous studies10, 11, 12 estimated an incidence rate of 3–14 cases/1,000,000 person-years, owing to which CA was labeled thus far as a rare disease. However, recent evidence suggests that CA is much more common than previously believed and, although there are no specific prevalence studies available, that ATTR-CA is probably the most frequent subtype of this condition.[13] In the absence of focused studies, real-world registries are of great importance in understanding the epidemiology of a disease, as shown by the fact that, in our particular case, we found that almost 90% of all patients belonged to the ATTR-CA group. This finding reinforces current considerations and conveys the idea that, when faced with a patient with a suspected diagnosis of CA in routine clinical practice, the most likely subtype is ATTR-CA.

The year 2016 marked a turning point in the diagnosis of CA. The publication of Gillmore et al.'s study,[4] which described a 100% positive predictive value of a non-invasive ATTR-CA diagnosis protocol, greatly increased the chances of detecting this entity. In our study cohort, 87.5% of the patients with this subtype of the disease were diagnosed without the need for undergoing invasive studies and only 12.5% had to undergo a biopsy. These data differ from the results obtained from the recently published analysis of historical case series, in which the rate of non-invasive diagnoses only reached 75%,7, 8 and show that a non-invasive diagnosis of ATTR-CA is currently feasible in the vast majority of patients suspected to have this disease.

The participants in our study were mostly elderly patients, with a mean age of around 80 years, and of predominantly male sex. These findings, which are similar to those reported in other publications, can be explained by the inclusion of a majority of patients with ATTRwt-CA, an entity with a poorly understood pathophysiological mechanism that predominantly affects older men.[14]

In addition, the patients included in our cohort were characterized by a high prevalence of a history of cardiovascular disorders, with one third of them having previously been hospitalized for heart failure at least once. Although this figure is high, it still falls below

that found in other studies reporting a rate of up to 60%.7, 8 The occurrence of a syncopal episode was another frequently observed previous cardiovascular event that affected up to one fourth of all patients. Medical literature reporting a history of syncope in patients with CA is scarce, with reports of prevalences ranging between 8%[15] and 16.2%.[8] Finally, we observed a high proportion of patients with a prior history of atrial arrythmias (particularly atrial fibrillation), especially in the ATTR-CA group, in which case over half of the patients had experienced an episode. This is a well-known and widely described finding in the medical literature[16] that can be explained by the fact that this tachyarrhythmia is also related to aging.

One of the most characteristic systemic manifestations of CA is connective tissue involvement, with amyloid infiltration of the transverse carpal ligament and the synovial sheaths of the flexor tendons of the fingers (which cause carpal tunnel syndrome), the shoulder rotator cuff, the *ligamentum flavum* (which causes lumbar canal stenosis), and the quadricipital tendon having been described in the past.17, 18 Although we currently lack sufficient evidence to confirm this finding, it is possible that other connective tissue disorders, such as Dupuytren's contracture, might also be associated with this disease. In our study we found a non-negligible prevalence of a previous history of connective tissue disease in both groups of patients with CA, although lumbar canal stenosis and Dupuytren's contracture surgery were most frequently linked to ATTR-CA. Moreover, the prospective nature of this registry allowed us to evaluate the presence of symptomatic findings derived from the involvement of various connective tissues, detecting Popeye's sign–a clinical manifestation of rupture of the proximal tendon of the long portion of the brachial biceps muscle–and some degree of Dupuytren's contracture in over a third of the patients included in the registry.

In line with previously published results,19, 20 in our study we confirmed that the two most common electrocardiographic findings, and, therefore, the most useful ones for establishing the diagnostic suspicion of CA, were a Sokolow-Lyon index ≤1.5 mV and the presence of any pattern of pseudoinfarction. Other less prevalent electrocardiographic findings that were still present in more than half of the patients of the cohort and which might also be useful in suspecting a diagnosis of this disease were first-degree atrioventricular block and some type of bundle branch block.

Contrary to previous beliefs, in most cases, CA presents with a decreased left ventricular ejection fraction (LVEF) and an asymmetric pattern of left ventricular hypertrophy (LVH).7, 8, 16 We found that a transthoracic echocardiogram revealed a reduced LVEF in over a third of the patients included in our study, as well as an asymmetric pattern of LVH in almost 30% of them. We believe that it is essential to take these findings into account when establishing the suspicion of a diagnosis of CA considering the fact that if we limit this diagnosis to the most classic descriptions of the disease, with a normal LVEF and concentric LVH, the entity might go unnoticed in many cases.

Two recently published Spanish studies have granted CA a poor prognosis, particularly the AL-CA subtype. López-Sainz et al.[7] reported one and three-year survival rates of 83% and 59%, respectively, in patients with ATTR-CA, and of 65% and 43%, respectively, in patients with AL-CA. In another study,[8] the same rates were 85.1% and 57.3%, respectively, in patients with ATTR-CA, and 43.3% and 40.4%, respectively, in patients with ALCA. The data sourced from our cohort seem to be indicative of a mild improvement in the prognosis of this disease compared with these previous studies, with the annual survival rates of the patients with ATTR-CA and AL-CA being of 92.1% and 78.6%, respectively. Among the factors that could have favored these results, we can highlight two: on the one hand, the inclusion of participants in a prospective registry following a specific diagnostic protocol probably facilitated the disease's detection and a closer clinical follow-up by the researchers, and, on the other, the high percentage of patients who received treatments designed to slow down the amyloidogenic process and linked to an improvement in the prognosis of CA.5, 6

In terms of the patients with AL-CA who received specific treatment for their disease prior to their inclusion in the study or during their follow-up, 13 (86.7%) and four (26.7%) patients with this form of CA received antineoplastic treatment based on new-generation drugs and a hematopoietic stem cell transplant, respectively. In addition, two (13.3%) of these patients underwent a heart transplantation during their follow-up. The use of this type of therapies was significantly lower in the previously cited studies,7, 8 with 72% and 77.5% of the participants in these studies having received chemotherapy, 9.4% and 5% a hematopoietic stem cell transplant, and 4.7% and 7.5% a heart transplant, respectively.

As for the patients with ATTR-CA, more than half of those who participated in this study received treatment with tafamidis for a median duration of over 12 months. The

prevalence of the use of disease-modifying drugs in López-Sainz et al.'s study[7] was of only 13%, and, in the other study cohort,[8] although 46.1% of the patients had received tafamidis, the median treatment period was of only 50 days.

Despite the more favorable survival data found in our study cohort, our population was characterized by presenting with an advanced stage of the disease, with advanced functional classes being observed in over a third of the patients, in addition to a high prevalence of pulmonary and systemic congestion, very high levels of cardiac biomarkers, echocardiographic data indicative of increased left ventricular filling pressures, and the use of diuretic therapy in more than 75% of cases. The search for strategies that allow for reaching an earlier diagnosis of CA, together with the greater use of drugs designed to slow down the amyloidogenic process, will be the cornerstone for continuing to improve the prognosis of this disease.

The main novelty and strength of this registry lies in its multicenter and prospective design, which distinguishes it from prior historical cohorts of CA published to date.7, 8 Furthermore, its current data offer a contemporary description of the disease in our setting.

However, this study also has some limitations that merit comment. First, its observational nature entails that it could be subject to typical information, selection, and/or confounding biases. Moreover, although their inclusion was contemplated in the protocol, in 8.6% of the cases of ATTR-CA we were unable to determine whether they corresponded to the variant or wild-type form, and, despite the fact that both entities are caused by the deposition of transthyretin, they differ in terms of their clinical persentation, treatment, and prognosis. Finally, although its multicenter nature grants it a certain degree of validity for the extrapolation of its results to other populations, it also entails the potential existence of heterogeneity in the patients' clinical management by the participating investigators.

Conclusions

Our analysis of a contemporary cohort of CA demonstrated that ATTR-CA is the form of the disease that we might encounter more frequently in our routine clinical practice and that the ability to diagnose this entity in a non-invasive manner has led to a significant increase in the number of detected cases.

Although CA continues to be a disease linked to a poor life expectancy, the advances made in its diagnosis and the increased use of specific treatments seem to have prolonged the short-term survival of patients with this condition.

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Authorship

GBC is primarily responsible for the study's conception and design, the analysis and interpretation of its results, and the drafting of this manuscript. In addition, he contributed to the data collection and approval of the final version of the manuscript.

MLP, RBQ, EGB, IGO, ALL, and MGF contributed to the study's conception and design, the data collection, the critical review of the manuscript's contents, and the approval of its final version.

EBC, AVR, CGJ, ODC, and MGCL contributed to the study's conception and design, the critical review of the manuscript's contents, and the approval of its final version.

Conflicts of interest

GBC has received funding for conference travels, speaker fees, and an independent research grant (not related to this study) from Pfizer. EBC has received speaker fees from Pfizer. The rest of authors declare no conflicts of interest.

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Table 1. Patients' baseline clinical characteristics upon their inclusion in the registry.

	ATTRCA (n = 128)	ALCA (n = 15)	Total (N = 143)	*p*
Age (years)	81.0 ± 6.0	67.9 ± 10.8	79.6 ± 7.7	<0.0001
Female sex	28 (21.9)	6 (40.0)	34 (23.8)	0.119
Reason for consultation leading to the diagnosis				
Symptoms of heart failure	77 (60.2)	8 (53.3)	85 (59.4)	0.29
Syncope or episode of arrhythmia	15 (11.7)	1 (6.7)	16 (11.2)	
Differential diagnosis of LVH	24 (18.7)	2 (13.3)	26 (18.2)	
Chest pain	5 (3.9)	1 (6.7)	6 (4.2)	
Others	7 (5.5)	3 (20.0)	10 (7.0)	
Department that reached the diagnosis				
Cardiology	110 (85.9)	10 (66.6)	120 (83.9)	<0.0001
Internal Medicine	16 (12.5)	1 (6.7)	17 (11.9)	
Hematology	0 (0.0)	4 (26.7)	4 (2.8)	
Others	2 (1.6)	0 (0.0)	2 (1.4)	
Medical history				
Arterial hypertension	87 (68.0)	8 (53.3)	95 (66.4)	0.256
Hypercholesterolemia	75 (58.6)	9 (60.0)	84 (58.7)	0.917
Diabetes mellitus	27 (21.1)	4 (26.7)	31 (21.7)	0.620
Smoking habit	43 (33.6)	7 (46.7)	50 (35.0)	0.315
Previous hospitalization for HF	36 (28.1)	6 (40.0)	42 (29.4)	0.339
Atrial fibrillation/flutter	72 (56.3)	4 (26.7)	76 (53.1)	0.030
Syncope	30 (23.4)	3 (20.0)	33 (23.1)	0.765

Table 1. Patients' baseline clinical characteristics upon their inclusion in the registry.

	ATTRCA (n = 128)	ALCA (n = 15)	Total (N = 143)	*p*
Pacemaker implantation	21 (16.4)	1 (6.7)	22 (15.4)	0.323
Ischemic heart disease	16 (12.5)	5 (33.3)	21 (14.7)	0.031
Heart surgery	3 (2.3)	1 (6.7)	4 (2.8)	0.337
Cerebrovascular disease	20 (15.6)	1 (6.7)	21 (14.7)	0.354
Peripheral arterial disease	10 (7.8)	2 (13.3)	12 (8.4)	0.466
Venous thromboembolic event	6 (4.7)	1 (6.7)	7 (4.9)	0.737
Chronic obstructive pulmonary disease	16 (12.5)	3 (20.0)	19 (13.3)	0.418
Peripheral neuropathy	2 (1.6)	2 (13.3)	4 (2.8)	0.009
Carpal tunnel syndrome	36 (28.1)	5 (33.3)	41 (28.7)	0.673
Lumbar canal stenosis	24 (18.8)	1 (6.7)	25 (17.5)	0.244
Dupuytren's contracture surgery	12 (9.4)	0 (0.0)	12 (8.4)	0.215
Rotator cuff tendinopathy	20 (15.6)	2 (13.3)	22 (15.4)	0.816
Other connective tissue diseases	9 (7.0)	1 (6.7)	10 (7.0)	0.958
Clinical condition – symptoms				
NYHA functional class III or IV	45 (35.2)	9 (60.0)	54 (37.8)	0.060
Systolic blood pressure (mmHg)	124 ± 19	113 ± 13	123 ± 19	0.022
Heart rate (bpm)	73 ± 14	76 ± 17	74 ± 15	0.564
Jugular vein engorgement	52 (40.6)	10 (66.7)	62 (43.4)	0.054
Symptoms of pulmonary congestion	39 (30.5)	7 (46.7)	46 (32.2)	0.204
Peripheral edema	44 (33.4)	8 (53.3)	52 (36.4)	0.149
Popeye's sign	49 (38.3)	2 (13.3)	51 (35.7)	0.056

Table 1. Patients' baseline clinical characteristics upon their inclusion in the registry.

	ATTRCA (n = 128)	ALCA (n = 15)	Total (N = 143)	*p*
Dupuytren's contracture	49 (38.3)	1 (6.7)	50 (35.0)	0.015
Macroglossia	7 (5.5)	3 (20.0)	10 (7.0)	0.037
Medical treatment				
Antiplatelet	16 (12.5)	8 (53.3)	24 (16.8)	<0.0001
Anticoagulant	74 (57.8)	4 (26.7)	7 (54.5)	0.022
Loop diuretic	95 (74.2)	15 (100.0)	110 (76.9)	0.025
Thiazide diuretic	21 (16.4)	1 (6.7)	22 (15.4)	0.323
Beta-blocker	65 (50.8)	7 (46.7)	72 (50.3)	0.763
ACEI	24 (18.8)	1 (6.7)	25 (17.5)	0.244
ARA-2	30 (23.4)	5 (33.3)	35 (24.5)	0.399
MRA	36 (28.1)	5 (33.3)	41 (28.7)	0.673
Calcium antagonist	6 (4.7)	0 (0.0)	6 (4.2)	0.392
Amiodarone	5 (3.9)	1 (6.7)	6 (4.2)	0.614
Digoxin	6 (4.7)	0 (0.0)	6 (4.2)	0.392
Ivabradine	0 (0.0)	1 (6.7)	1 (0.7)	0.003
Nitrates	5 (3.9)	2 (13.3)	7 (4.9)	0.109
Hypolipidemic	73 (57.0)	7 (46.7)	80 (55.9)	0.444
Hypoglycemic	28 (21.9)	3 (20.0)	31 (21.7)	0.868

Data are presented as n (%) or mean ± standard deviation.

ACEI: angiotensin-converting enzyme inhibitor; AL-CA: amyloid light-chain cardiac amyloidosis; ARA-2: angiotensin-II receptor antagonist; ATTR-CA: amyloid transthyretin cardiac amyloidosis; HF: heart failure; LVH: left ventricular hypertrophy; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association.

Table 2. Results of the additional tests carried out at the time of the patients' inclusion in the registry.

	ATTRCA (n = 128)	ALCA (n = 15)	Total (N = 143)	*p*
Laboratory				
Hemoglobin (g/dl)	13.7 ± 1.7	13.4 ± 1.8	13.7 ± 1.7	0.576
Hematocrit (%)	41.6 ± 4.9	40.3 ± 5.0	41.5 ± 4.9	0.328
Leukocyte count ($\times 10^9$/L)	6.7 ± 1.8	6.6 ± 1.7	6.7 ± 1.8	0.868
Platelet count ($\times 10^9$/L)	187 ± 58	209 ± 87	189 ± 61	0.182
Urea (mg/dl)	75 ± 37	69 ± 38	74 ± 37	0.527
Creatinine (mg/dl)	1.32 ± 0.99	1.20 ± 0.42	1.30 ± 0.95	0.664
Sodium (mEq/L)	141 ± 3	140 ± 3	141 ± 3	0.207
Potassium (mEq/L)	4.5 ± 0.5	4.1 ± 0.3	4.4 ± 0.5	0.013
Glucose (mg/dl)	104 ± 27	93 ± 23	103 ± 27	0.123
Uric acid (mg/dl)	7.5 ± 2.2	8.1 ± 2.4	7.5 ± 2.2	0.292
Total protein (g/dl)	6.8 ± 0.5	6.2 ± 0.9	6.7 ± 0.6	<0.0001
Albumin (g/dl)	4.2 ± 0.4	3.9 ± 0.4	4.2 ± 0.4	0.010
Total cholesterol (mg/dl)	156 ± 35	172 ± 45	158 ± 36	0.102
Triglycerides (mg/dl)[a]	99 ± 50	121 ± 57	101 ± 51	0.109
Bilirubin (mg/dl)	1.09 ± 0.90	0.98 ± 0.60	1.08 ± 0.87	0.641
GPT (IU/L)	27 ± 16	27 ± 17	27 ± 16	0.917
GGT (IU/L)	94 ± 107	94 ± 82	94 ± 104	0.993
GOT (IU/L)[a]	30 ± 13	31 ± 13	30 ± 13	0.746
LDH (IU/L)[a]	342 ± 128	360 ± 124	344 ± 128	0.621
Alkaline phosphatase (IU/L [b]	184 ± 119	192 ± 115	185 ± 118	0.786

Table 2. Results of the additional tests carried out at the time of the patients' inclusion in the registry.

	ATTRCA (n = 128)	ALCA (n = 15)	Total (N = 143)	*p*
NT-proBNP (pg/mL)[c]	4008 ± 4007	7131 ± 7038	4345 ± 4503	0.011
Electrocardiogram				
Heart rate				
Sinus	57 (44.5)	13 (86.7)	70 (49.0)	0.008
Atrial fibrillation/flutter	53 (41.4)	2 (13.3)	55 (38.5)	
Pacemaker rhythm	18 (14.1)	0 (0.0)	18 (12.6)	
PR interval (ms)	214 ± 40	192 ± 57	210 ± 44	0.110
First-degree atrioventricular blockd	33 (57.9)	5 (38.5)	38 (54.3)	0.204
QRS complex (ms)	113 ± 23	103 ± 21	112 ± 23	0.130
Branch blocke	59 (53.6)	8 (53.3)	67 (53.6)	0.982
Sokolow-Lyon index ≤ 1.5 mV [e]	70 (63.6)	9 (60.0)	79 (63.2)	0.784
Low voltages in the limb leadse	47 (42.7)	9 (60.0)	56 (44.8)	0.207
Low voltages in the precordial leadse	31 (28.2)	3 (20.0)	34 (27.2)	0.504
Pseudoinfarction pattern [f]	58 (60.4)	10 (71.4)	68 (61.8)	0.428
Echocardiogram				
LVEF (%)	52.8 ± 12.4	53.5 ± 11.7	52.9 ± 12.3	0.834
LVEF <50%	53 (41.4)	5 (33.3)	58 (40.6)	0.547
Maximum left ventricular thickness (mm)	17.6 ± 3.1	16.6 ± 2.8	17.5 ± 3.0	0.244
Asymmetric left ventricular hypertrophy	38 (29.7)	3 (20.0)	41 (28.7)	0.432
LVEDV (mm)[g]	43.6 ± 7.3	45.3 ± 10.1	43.8 ± 7.6	0.435
Left atrial diameter (mm)[g]	46.5 ± 6.4	44.0 ± 4.9	46.2 ± 6.3	0.147

Table 2. Results of the additional tests carried out at the time of the patients' inclusion in the registry.

	ATTRCA (n = 128)	ALCA (n = 15)	Total (N = 143)	*p*
E/E' ratio[h]	15.0 ± 5.5	19.1 ± 8.8	15.4 ± 6.0	0.020
TAPSE (mm)	16.6 ± 3.8	17.3 ± 5.7	16.7 ± 4.1	0.533
Transtricuspid systolic gradient (mmHg)[i]	29.8 ± 9.9	29.5 ± 9.1	29.8 ± 9.7	0.918
Aortic stenosis grade ≥ moderate	16 (12.5)	0 (0.0)	16 (11.2)	0.146
Aortic failure grade ≥ moderate	4 (3.1)	0 (0.0)	4 (2.8)	0.487
Mitral failure grade ≥ moderate	18 (14.1)	4 (26.7)	22 (15.4)	0.201
Tricuspid failure grade ≥ moderate	29 (22.7)	4 (26.7)	33 (23.1)	0.727
Pericardial effusion	24 (18.8)	4 (26.7)	28 (19.6)	0.465

Data are presented as n (%) and mean ± standard deviation.

AL-CA: amyloid light-chain cardiac amyloidosis; ATTR-CA: amyloid transthyretin cardiac amyloidosis; GGT: gamma-glutamyl transpeptidase; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; LDH: lactate dehydrogenase; LVEDV: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone brain natriuretic peptide; TAPSE: tricuspid annulus plane systolic excursion.

All calculations are based on a population of n = 143, except for:

[a] n = 138.

[b] n = 140.

[c] n = 139.

[d] n = 70 (excluding patients with pacemaker rhythm or atrial fibrillation/flutter).

[e] n = 125 (excluding patients with pacemaker rhythm).

[f] n = 110 (excluding patients with pacemaker rhythm or complete left bundle branch block).

[g] n = 142.

[h] n = 120.

[i] n = 116.

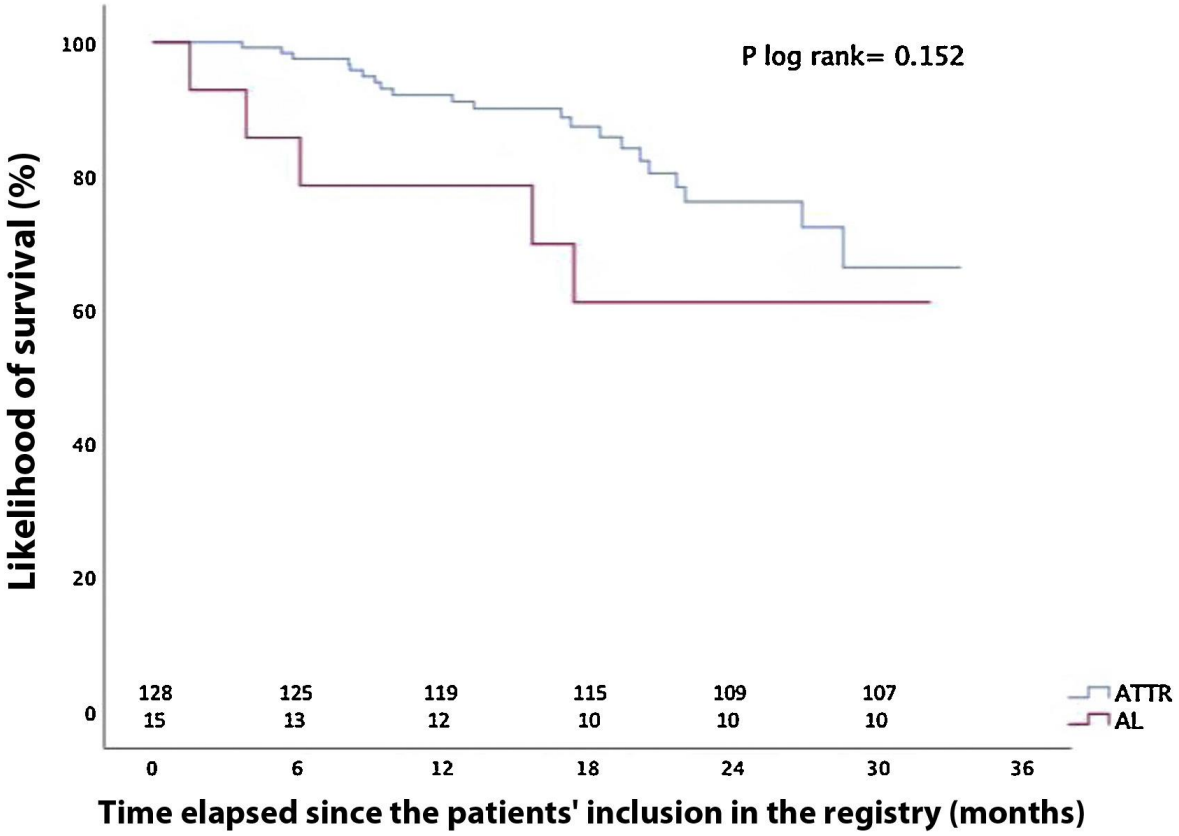

Fig. 1. Survival curves of patients with cardiac amyloidosis from the date of their inclusion in the registry.

AL: amyloid light-chain cardiac amyloidosis. ATTR: amyloid transthyretin cardiac amyloidosis.