Medicina Clínica (English Edition). 2021; 156(8): 369-378

Light chain and transthyretin cardiac amyloidosis: Clinical characteristics, natural history and prognostic factors

Amiloidosis cardiaca por cadenas ligeras y por transtirretina: características clínicas, historia natural y predictores pronósticos

Gonzalo Barge-Caballero[a,b,c], Raquel Vázquez-García[a], Eduardo Barge-Caballero[a,b,c], David Couto-Mallón[a,b,c], María J. Paniagua-Martín[a,b,c], Roberto Barriales-Villa[b,c,d], Pablo Piñón-Esteban[e], Alberto Bouzas-Mosquera[b,c,f], Jorge Pombo-Otero[g], Guillermo Debén-Ariznavarreta[h], José M. Vázquez-Rodríguez[b,c,e], María G. Crespo-Leiro[a,b,c]

[a] *Unidad de Insuficiencia Cardíaca Avanzada y Trasplante Cardiaco, Servicio de Cardiología, Complexo Hospitalario Universitario A Coruña, Spain*
[b] *Instituto de Investigación Biomédica de A Coruña (INIBIC), Spain*
[c] *Centro de Investigación Biomédica en Red (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain*
[d] *Unidad de Cardiopatías Familiares, Servicio de Cardiología, Complexo Hospitalario Universitario A Coruña, Spain*
[e] *Unidad de Hemodinámica, Servicio de Cardiología, Complexo Hospitalario Universitario A Coruña, Spain*
[f] *Unidad de Imagen y Función Cardíaca, Servicio de Cardiología, Complexo Hospitalario Universitario A Coruña, Spain*
[g] *Servicio de Anatomía Patológica, Complexo Hospitalario Universitario A Coruña, Spain*
[h] *Servicio de Hematología, Complexo Hospitalario Universitario A Coruña, Spain*

Abstract

Introduction and objectives

Light-chain amyloidosis (AL-CA) and transthyretin amyloidosis (ATTR-CA) are the most common types of cardiac amyloidosis (CA). We sought to study the clinical characteristics and prognosis of both diseases.

Methods

We conducted a single-centre, retrospective review of all patients diagnosed with CA between 1998 and 2018. Clinical characteristics, complementary tests, survival and other adverse clinical events were studied.

Results

We identified 105 patients with CA, 65 ATTR-CA and 40 AL-CA. Mean age was 74.4 years; 24.8% were women. In both groups, heart failure was the most frequent clinical presentation (55.2%). The most prevalent electrocardiographic findings were the pseudoinfarct pattern (68.5%) and a Sokolow-Lyon index <1.5 mV (67.7%), with no differences between the two subtypes of CA. One-year, 3-year, and 5-year survival was 43.3%, 40.4% and 35.4%, respectively, in AC-AL patients, and 85.1%, 57.3% and 31.4% in AC-ATTR patients (p = .004). AL-CA subtype (HR 3.41, CI95% 1.45−8.06, p = .005), previous admission for heart failure (HR 4.25, 95% CI 1.63−11.09, p = .003) and a NYHA class III-IV (HR 2.76, 95% CI 1.09−7.03, p = .033) were independent predictors of mortality, while beta-blocker therapy was associated with longer survival (HR .23, 95% CI .09–.59, p = .002).

Conclusions

Differences exist between the clinical presentation of AL-CA and ATTR-CA patients. Both diseases, particularly AL-CA, are associated with poor life prognosis.

Resumen

Antecedentes y objetivos

La amiloidosis cardiaca (AC) por cadenas ligeras (AC-AL) y por transtirretina (AC-ATTR) son los dos subtipos más frecuentes de la enfermedad. Nos propusimos caracterizar clínicamente estas entidades y analizar su pronóstico.

Material Métodos

Realizamos una revisión retrospectiva de todos los pacientes diagnosticados de AC entre 1998 y 2018 en un centro español. Además de recoger las características clínicas y los resultados de las pruebas complementarias al diagnóstico, analizamos la supervivencia y la incidencia de desenlaces clínicos adversos.

Resultados

Identificamos 105 pacientes con AC, 65 AC-ATTR y 40 AC-AL. La edad media era de 74,4 años; el 24,8% eran mujeres. En ambos grupos la insuficiencia cardiaca (IC) fue la forma de presentación clínica más frecuente (55,2%). Los hallazgos electrocardiográficos más prevalentes fueron el patrón de pseudoinfarto (68,5%) y un índice de Sokolow-Lyon <1,5 mV (67,7%), sin diferencias entre los dos subtipos. La supervivencia a 1, 3 y 5 años fue del 43,3%, 40,4% y 35,4%, respectivamente, en pacientes con AC-AL y de 85,1%, 57,3% y 31,4% en pacientes con AC-ATTR (p = 0,004). El subtipo AC-AL (HR 3,41, IC95% 1,45-8,06, p = 0,005), el ingreso previo por IC (HR 4,25, IC95% 1,63-11,09, p = 0,003) y una clase NYHA III-IV (HR 2,76, IC95% 1,09-7,03, p = 0,033) fueron predictores independientes de mortalidad, mientras que el tratamiento betabloqueante se asoció con una mayor supervivencia (HR 0,23, IC95% 0,09-0,59, p = 0,002).

Conclusiones

Existen ciertas diferencias en la presentación clínica de los pacientes con AC-AL y AC-ATTR. Ambas entidades, y muy especialmente la AC-AL, presentan un pobre pronóstico vital.

Keywords

Cardiac amyloidosis; Transthyretin; Light chain; Heart failure

Palabras clave

Amiloidosis cardiaca; Transtirretina; Cadenas ligeras; Insuficiencia cardiaca

Introduction

Cardiac amyloidosis (CA) is an infiltrative myocardial disease whose two most common mechanisms are the deposition of light chains in the context of plasma cell dyscrasia (AL-CA) and the deposition of transthyretin (ATTR-CA), either as a consequence of a structural alteration of this protein secondary to a genetic mutation (hereditary form, hATTR) or in its native conformation (natural form or wild-type, ATTRwt) due to a poorly characterized process associated with aging.

In recent years there has been growing interest in the study of CA derived from the arrival of new techniques that allow the non-invasive diagnosis of the ATTR subtype, as well as therapeutic advances that are associated with an improvement in the prognosis in both subtypes. Despite this, CA remains an under-detected entity and we have little up-to-date information on its natural history.1, 2, 3

Our working hypothesis argues that the two main forms of CA differ significantly in terms of their natural history. Therefore, the aim of the present study is to provide a detailed description of the clinical presentation and prognostic determinants in a cohort of patients with AL-CA or ATTR-CA treated in a Spanish reference center.

Material and Methods

Study description

An observational follow-up study was conducted based on the historical cohort of patients diagnosed with CA in our center between 1998 and 2018. The study protocol was approved by corresponding clinical research ethics committee.

Our centre has had a protocol for the detection of CA since 2016.[4] The basis for diagnosis is the demonstration of amyloid deposits, defined by positive Congo Red staining and the acquisition of an apple-green birefringence under polarised light microscopy, in a histological specimen, characterising the subtype by immunohistochemistry or mass spectrometry. In case the diagnosis is made on a non-cardiac specimen, confirmation of CA additionally requires an imaging test suggestive of myocardial infiltration. In addition, the combination of a 3,3-diphosphono-1,2-propanedicarboxylic acid bone scintigraphy labelled with 99mTc (99mTc-DPD) with a degree of cardiac uptake of 2 or 3 in the Perugini grading scale and the absence of a monoclonal component demonstrated by immunofixation electrophoresis in blood and urine and determination of free light chains in blood, allows the non-invasive diagnosis of ATTR-CA[5]; these patients, in turn, are classified into hATTR-CA or ATTRwt-CA based on the presence or absence of mutations in the transthyretin gene sequencing study.

Patients diagnosed with CA after implementation of the protocol were prospectively assessed in a specialized surgery. The identification of cases prior to 2016 was carried out using the Coding Unit records, with subsequent validation of the diagnosis by evaluating the information available in the medical records. Patients who had been diagnosed with CA at the time but who did not meet the criteria defined in the aforementioned protocol were excluded from the study.

Data collection

The information analysed was obtained from the patients' medical records. Variables related to clinical characteristics, ancillary tests, survival, adverse clinical outcomes, and causes of death were collected. The alternative clinical assessments prior to the correct diagnosis of CA, if any, were documented, as well as the hospital department and the date on which it was established.

The specific definitions of the most relevant clinical variables are detailed in the annex.

Statistical analysis

Categorical variables are shown as proportions and continuous variables as mean ± standard deviation or median (interquartile range), according to its adequacy to normality.

The occurrence of adverse clinical outcomes was documented throughout a follow-up that ended in June 2019. In patients who received a heart transplant, follow-up was censored on the date of the intervention. The survival curves of patients with AL-CA and ATTR-CA were constructed with the Kaplan-Meier method and compared using the log-rank test.

We carried out an exploratory analysis of possible survival predictors using the multivariate "backward stepwise" Cox regression model with an exit criteria «p-out» <0.05. In the initial step, those covariates that showed a statistical association with survival with a p value <0.10 in the univariate analysis were included. A significance level $p < 0.05$ was set for the rest of the contrasts. The statistical analysis was carried out with the SPSS 20 and Epidat 4.1 software.

Results

Patients

Between 1998 and 2018, 199 patients were diagnosed with CA. After reviewing the criteria defined by the diagnostic protocol, 65 (61.9%) cases of ATTR-CA (61 ATTRwt, 4 hATTR) and 40 (38.1%) of AL-CA (33 lambda, 7 kappa) were confirmed; these individuals constituted the study population. In total, 65 (61.9%) patients were diagnosed in the 2016−2018 period. Transthyretin gene sequencing was performed in all ATTR-CA patients, identifying mutations p.Val50Met (three cases) and p.Glu89Lys (one case). Among the patients with AL-CA, 16 (40%) had multiple myeloma.

As shown in Table 1, the diagnosis of CA corresponded to the cardiology department in most cases (66.6%), especially ATTR-CA (80%). The most common clinical reason for evaluation was heart failure (HF) (55.2%). The diagnosis of another heart disease had been previously established in 47 (44.8%) patients, with the most common being hypertrophic cardiomyopathy..

Table 1. Alternative diagnostic work-up and clinical assessment prior to cardiac amyloidosis.

	AL-CA (n = 40)	ATTR-CA (n = 65)	TOTAL (n = 105)
Year of diagnosis			
1998−2015	26 (65.0)	14 (21.5)	40 (38.1)
2016−2018	14 (35.0)	51 (78.5)	65 (61.9)
Department that made the diagnosis			
Cardiology	18 (45.0)	52 (80.0)	70 (66.6)
Internal Medicine	7 (17.5)	12 (18.5)	19 (18.1)
Haematology	9 (22.5)	0 (0.0)	9 (8.6)
Others	6 (15.0)	1 (1.5)	7 (6.7)
Clinical reason for evaluation that led to the diagnosis			
Symptoms and/or signs of heart failure	23 (57.5)	35 (53.8)	58 (55.2)
Differential diagnosis of ventricular hypertrophy	7 (17.5)	16 (24.6)	23 (21.9)
Syncope or arrhythmia study	1 (2.5)	6 (9.2)	7 (6.7)
Electrocardiogram alteration	0 (0.0)	2 (3.1)	2 (1.9)
Chest pain	1 (2.5)	2 (3.1)	3 (2.9)
Incidental	0 (0.0)	2 (3.1)	2 (1.9)
Others	8 (20.0)	2 (3.1)	10 (9.5)
Previous alternative clinical assessment			
No	27 (67.5)	31 (47.7)	58 (55.2)
Yes	13 (32.5)	34 (52.3)	47 (44.8)
Hypertrophic cardiomyopathy	6 (46.1)	10 (29.4)	16 (34.0)
Hypertensive heart disease	5 (38.5)	9 (26.5)	14 (29.8)
Ischemic heart disease	0 (0.0)	2 (5.9)	2 (4.3)
Valvular heart disease	0 (0.0)	2 (5.9)	2 (4.3)
Restrictive cardiomyopathy	1 (7.7)	0 (0.0)	1 (2.1)
HF with idiopathic preserved ejection fraction	1 (7.7)	8 (23.5)	9 (19.1)
HF with idiopathic reduced ejection fraction	0 (0.0)	3 (8.8)	3 (6.4)

AL-CA: light-chain cardiac amyloidosis. ATTR-CA: transthyretin cardiac amyloidosis. HF: heart failure.
Data shown as n (%).

Among the patients with ATTR-CA, 48 (73.8%) were diagnosed non-invasively and 17 (26.2%) by histological study [16 (94.1%) endomyocardial biopsies and one (5.9%) subcutaneous fat biopsy]. Endomyocardial biopsy was indicated in seven patients due to the coexistence of a monoclonal component in blood or urine and a grade 3 uptake scintigraphy; in all cases it was concluded that it was a monoclonal gammopathy of undetermined significance.

The diagnosis of AL-CA was established based on the findings of an endomyocardial biopsy in 19 (47.5%) patients and of extracardiac biopsies in 21 (52.5%).

Clinical features

The baseline clinical characteristics of the cohort are shown in Table 2. The mean age was 74.4 ± 10.7 years, with the ATTR-CA group (79.1 ± 8.0 years) being significantly older than the AL-CA (66.9 ± 10.4 years) ($p < 0.001$). Twenty-six patients were women (24.8%), with a greater relative presence in the AL-CA (47.5%) than in the ATTR-CA (10.8%) ($p < 0.001$).

We observed a higher prevalence of a previous history of atrial fibrillation or flutter in patients with ATTR-CA (53.8%) than in those with AL-CA (17.5%) ($p < 0.001$). The prevalence of prior admission for HF was 44.8%, with no differences between the two groups.

At diagnosis, signs of congestion were more common in the AL-CA subtype (80%) than in the ATTR-CA (60%) ($p = 0.033$). Nineteen (47.5%) patients with AL-CA and 25 (38.5%) with ATTR-CA had a NYHA III-IV functional class ($p = 0.36$).

Table 2. Baseline clinical characteristics of the cohort at cardiac amyloidosis diagnosis.

	AL-CA (n = 40)	ATTR-CA (n = 65)	TOTAL (n = 105)	P value
Age (years)	66.9 ± 10.4	79.1 ± 8.0	74.4 ± 10.7	< 0.0001
Female	19 (47.5)	7 (10.8)	26 (24.8)	< 0.0001
PREVIOUS HISTORY				
Arterial hypertension	17 (42.5)	36 (55.4)	53 (50.5)	0.20
Hypercholesterolemia	20 (50.0)	38 (58.5)	58 (55.2)	0.40
Diabetes mellitus	8 (20.0)	17 (26.2)	25 (23.8)	0.47
Smoking	13 (32.5)	23 (35.4)	36 (34.3)	0.76
Previous admission for heart failure	20 (50.0)	27 (41.5)	47 (44.8)	0.40
Atrial fibrillation or flutter	7 (17.5)	35 (53.8)	42 (40.0)	< 0.0001
Ventricular arrhythmia	1 (2.5)	1 (1.5)	2 (1.9) 0.73	
Syncope	3 (7.5)	14 (21.5)	17 (16.2)	0.58
Pacemaker implantation	1 (2.5)	7 (10.8)	8 (7.6)	0.12
Ischemic heart disease	7 (17.5)	7 (10.8)	14 (13.3)	0.32
Heart surgery	1 (2.5)	1 (1.5)	2 (1.9)	0.72
Cerebrovascular disease	6 (15.0)	8 (12.3)	14 (13.3)	0.69
Venous thromboembolic event	2 (5.0)	2 (3.1)	4 (3.8)	0.62
Chronic obstructive pulmonary disease	2 (5.0)	9 (13.8)	11 (10.5)	0.15
Peripheral neuropathy	4 (10.0)	5 (7.7)	9 (8.6)	0.68
Carpal tunnel syndrome	8 (20.0)	19 (29.2)	27 (25.7)	0.45
Lumbar canal stenosis	1 (2.5)	10 (15.4)	11 (10.5)	0.036
Dupuytren's contracture surgery	0 (0.0)	6 (9.2)	6 (5.7)	0.048
Rotator cuff tendinopathy	2 (5.0)	12 (18.5)	14 (13.3)	0.049
Proximal biceps tendinopathy	0 (0.0)	3 (4.6)	3 (2.9)	0.17
Quadriceps tendinopathy	1 (2.5)	4 (6.2)	5 (4.8)	0.39
CLINICAL SITUATION - SYMPTOMATOLOGY				
NYHA functional class				0.36
I-II	21 (52.5)	40 (61.5)	61 (58.1)	
III-IV	19 (47.5)	25 (38.5)	44 (41.9)	
Effort angina	3 (7.5)	1 (1.5)	4 (3.8) 0.12	
Body mass index (kg/m2)	26.7 ± 5.4	27.9 ± 3.3	27.4 ± 4.2	0.17
Systolic blood pressure (mmHg)	108 ± 17	122 ± 15	117 ± 17	< 0.0001
Diastolic blood pressure (mmHg)	65 ± 10	70 ± 10	68 ± 11	0.008
Heart rate (bpm)	79 ± 15	73 ± 13	75 ± 14	0.015
Signs of congestion	32 (80.0)	39 (60.0)	71 (67.6)	0.033
MEDICAL TREATMENT				
Antiplatelet	10 (25.0)	7 (10.8)	17 (16.2)	0.055
Anticoagulant	6 (15.0)	33 (51.6)	39 (37.5)	< 0.0001
Loop diuretic	25 (62.5)	47 (72.3)	72 (68.6)	0.29
Thiazide diuretic	4 (10.0)	5 (7.7)	9 (8.6)	0.68
Beta blocker	14 (35.0)	26 (40.0)	40 (38.1)	0.61
ACEI	10 (25.0)	14 (21.5)	24 (22.9)	0.68
ARBs	6 (15.0)	13 (20.0)	19 (18.1)	0.52
MRA	11 (27.5)	19 (29.2)	30 (28.6)	0.85
Calcium antagonist	1 (2.5)	9 (13.8)	10 (9.5)	0.054
Amiodarone	2 (5.0)	4 (6.2)	6 (5.7)	0.80
Digoxin	1 (2.5)	1 (1.5)	2 (1.9)	0.73
Ivabradine	1 (2.5)	0 (0.0)	1 (1.0)	0.20
Nitrates	1 (2.5)	2 (3.1)	3 (2.9)	0.86
Lipid-lowering	16 (40.0)	35 (53.8)	51 (48.6)	0.17
Hypoglycaemic	6 (15.0)	14 (21.5)	20 (19.0)	0.41

AL-CA: light-chain cardiac amyloidosis. ATTR-CA: transthyretin cardiac amyloidosis. NYHA: New York Heart Association. ACEI: angiotensin converting enzyme inhibitor. ARBs: angiotensin II receptor blockers. MRA: mineralocorticoid receptor antagonist.

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

Table 3. Results of the ancillary tests performed at the time of cardiac amyloidosis diagnosis.

	AL-CA (n = 65)	ATTR-CA (n = 40)	TOTAL (n = 105)	P value
LABORATORY				
Urea (mg/dL)	75.3 ± 48.9	68.7 ± 34.9	71.2 ± 40.7	0.43
Creatinine (mg/dL)	1.5 ± 1.3	1.2 ± 0.3	1.3 ± 0.9	0.06
Glomerular filtration rate (mL/min/1.73m^2)	56.9 ± 24.1	59.0 ± 22.0	58.1 ± 22.8	0.65
Sodium (mEq/L)	138.4 ± 3.6	140.3 ± 3.1	139.6 ± 3.4	0.006
Potassium (mEq/L)	4.4 ± 0.7	4.5 ± 0.4	4.5 ± 0.6	0.33
Haemoglobin (g/dL)	11.9 ± 2.2	13.4 ± 1.8	12.8 ± 2.1	< 0.0001
Haematocrit (%)	36.2 ± 6.5	40.8 ± 5.4	39.0 ± 6.3	< 0.0001
Leukocytes (·10^9/ L)	7.1 ± 3.1	6.3 ± 2.0	6.6 ± 2.5	0.10
Platelets (·10^9/ L)	229.5 ± 105.3	178.4 ± 62.6	197.9 ± 84.8	0.002
Glucose (mg/dL)	96.3 ± 21.0	99.2 ± 17.8	98.1 ± 19.0	0.45
Uric acid (mg/dL)	7.5 ± 2.8	7.6 ± 2.3	7.6 ± 2.5	0.90
Total protein (g/dL)	5.8 ± 1.1	6.7 ± 0.7	6.4 ± 1.0	< 0.0001
Albumin (g/dL)	3.4 ± 0.7	4.0 ± 0.5	3.8 ± 0.6	< 0.0001
Cholesterol (mg/dL)				
Total	190.1 ± 70.4	154.4 ± 37.4	168.0 ± 55.0	0.001
HDLc	45.2 ± 19.3	49.4 ± 16.6	48.0 ± 17.6	0.26
LDLc	124.5 ± 57.6	90.7 ± 26.6	102.5 ± 43.1	< 0.0001
Triglycerides (mg/dL)	141.3 ± 100.0	92.0 ± 35.5	110.8 ± 71.5	< 0.0001
Bilirubin (mg/dL)	1.2 ± 1.6	1.0 ± 0.5	1.0 ± 1.1	0.36
Alkaline phosphatase (IU/L)	336.6 ± 516.6	227.5 ± 145.6	269.1 ± 340.5	0.11
GOT (IU/l)	31.1 ± 23.5	27.6 ± 10.9	28.9 ± 16.8	0.30
GPT (IU/L)	27.6 ± 18.4	27.0 ± 17.6	27.2 ± 17.8	0.88
GGT (UI/L)	157.4 ± 339.0	115.7 ± 157.6	131.6 ± 242.5	0.39
LDH (IU/L)	450.3 ± 171.9	384.5 ± 100.9	410.8 ± 136.1	0.016
Iron (µg/mL)	58.1 ± 29.2	61.9 ± 26.0	60.5 ± 27.1	0.50
Ferritin (ng/mL)	208.1 ± 214.7	168.7 ± 116.9	183.0 ± 159.3	0.25
Transferrin saturation (%)	19.4 ± 9.0	19.2 ± 8.2	19.3 ± 8.4	0.89
Troponin I (ng/mL)[a]	0.2 ± 0.2	0.1 ± 0.3	0.2 ± 0.3	0.58
CPK (UI/L)[b]	69.7 ± 42.7	96.0 ± 66.5	86.8 ± 60.4	0.043
NT-proBNP (pg/mL)[c]	8319.1 ± 7851.9	4586.8 ± 5311.6	5800.9 ± 6447.2	0.013
24 h Proteinuria (g/24 h)[d]	2.5 ± 3.9	0.1 ± 0.1	1.1 ± 2.8	< 0.0001
SCINTIGRAPHY[e]				
Perugini grading scale				< 0.0001
Grades 0−1	7 (70.0)	0 (0.0)	7 (10.8)	
Grades 2−3	3 (30.0)	55 (100.0)	58 (89.2)	
HISTOLOGICAL STUDIES				
Amyloid endomyocardial biopsy +[f]	19 (100.0)	16 (100.0)	35 (100.0)	
Some amyloid extracardiac biopsy +[g]	29 (78.4)	6 (26.1)	35 (58.3)	< 0.0001
ELECTROCARDIOGRAM				
Sinus				< 0.0001
Rhythm	36 (90.0)	31 (47.7)	67 (63.8)	
Atrial fibrillation	3 (7.5)	25 (38.5)	28 (26.7)	
Atrial flutter	0 (0.0)	4 (6.2)	4 (3.8)	
Pacemaker rhythm	1 (2.5)	5 (7.7)	6 (5.7)	
PR interval (ms)[h]	186.6 ± 38.5	214.1 ± 42.8	199.3 ± 42.6	0.007
First degree atrioventricular block[h]	12 (33.3)	19 (61.3)	31 (46.3)	0.022
QRS complex (ms)[i]	99.7 ± 21.9	113.0 ± 25.1	107.8 ± 24.6	0.008
Bundle branch block[i]				
No	26 (66.7)	25 (41.7)	51 (51.5)	0.015
Complete left bundle branch block	2 (5.1)	5 (8.3)	7 (7.1)	
Complete right bundle branch block	5 (12.8)	10 (16.7)	15 (15.2)	
Left bundle branch hemiblock	5 (12.8)	14 (23.3)	19 (19.2)	
Bifascicular block	1 (2.6)	6 (10.0)	7 (7.1)	
Corrected QT interval (ms)[i]	464.0 ± 39.0	475.5 ± 32.4	471.0 ± 35.4	0.11
Cornell Index (mV)[i]	1.4 ± 0.7	1.5 ± 0.8	1.5 ± 0.8	0.38
Sokolow-Lyon index (mV)[i]	1.2 ± 0.6	1.25 ± 0.6	1.2 ± 0.6	0.68
Sokolow-Lyon index ≤ 1.5 mV[i]	29 (74.4)	38 (63.3)	67 (67.7)	0.25
Low voltages in limb leads[i]	30 (76.9)	30 (50.8)	60 (61.2)	0.01
Low voltages in precordial leads[i]	22 (56.4)	20 (33.3)	42 (42.4)	0.023
Ventricular hypertrophy criteria[j]				0.50
Cornell	5 (13.5)	5 (9.1)	10 (10.9)	
Sokolow-Lyon	0 (0.0)	0 (0.0)	0 (0.0)	
Pseudoinfarction pattern[j]	25 (67.6)	38 (69.1)	63 (68.5)	0.88
ECHOCARDIOGRAM				
LVEF (%)	57.7 ± 10.3	53.5 ± 13.4	55.1 ± 12.4	0.09

LVEF <50%	9 (22.5)	22 (33.8)	31 (29.5)	0.22
Wall motion abnormalities	6 (15.0)	8 (12.3)	14 (13.3)	0.69
Granular appearance of the myocardium (sparkling)	9 (22.5)	13 (20.0)	22 (20.9)	0.16
Left ventricular hypertrophy pattern				0.58
Concentric	30 (75.0)	45 (69.2)	75 (71.4)	
Asymmetric septal	8 (20.0)	13 (20.0)	21 (20.0)	
Sigmoid	2 (5.0)	7 (10.8)	9 (8.6)	
Interventricular septal thickness (mm)	16.7 ± 2.6	18.7 ± 4.1	18.0 ± 3.7	0.005
Posterior wall thickness (mm)	15.6 ± 2.8	16.5 ± 3.5	16.1 ± 3.2	0.16
LVEDD (mm)	40.3 ± 6.2	43.8 ± 6.8	42.4 ± 6.8	0.01
LVESD (mm)	27.0 ± 5.4	32.0 ± 7.3	30.0 ± 7.0	0.001
Biplane LVEDV (ml)[k]	64.6 ± 14.4	84.6 ± 27.1	77.1 ± 25.1	< 0.0001
Biplane LVESV (ml)[k]	27.2 ± 9.2	40.3 ± 21.9	35.4 ± 19.2	0.002
Transmitral flow pattern[l]				< 0.0001
Normal	2 (5.3)	1 (1.6)	3 (3.0)	
Impaired relaxation	5 (13.1)	10 (16.1)	15 (15.0)	
Pseudonormal	9 (23.7)	8 (12.9)	17 (17.0)	
Restrictive	18 (47.4)	9 (14.5)	27 (27.0)	
Non-assessable	4 (10.5)	34 (54.9)	38 (38.0)	
E/e' ratio[m]	17.9 ± 6.7	16.7 ± 10.9	17.2 ± 9.5	0.58
Left atrial diameter (mm)[n]	42.6 ± 6.1	45.5 ± 8.0	44.4 ± 7.4	0.06
RVEDD (mm)[o]	36.1 ± 6.0	36.1 ± 6.2	36.1 ± 6.1	0.99
TAPSE (mm)[p]	15.6 ± 5.5	16.0 ± 4.6	15.8 ± 4.9	0.72
Aortic stenosis ≥ mild[q]	1 (2.5)	9 (14.1)	10 (9.6)	0.052
Aortic regurgitation ≥ mild[q]	7 (17.5)	27 (42.2)	34 (32.7)	0.009
Mitral regurgitation ≥ mild[q]	26 (65.0)	45 (70.3)	71 (68.3)	0.57
Tricuspid regurgitation ≥ mild[q]	29 (72.5)	37 (57.8)	66 (63.5)	0.13
Pericardial effusion[q]	24 (60.0)	14 (21.9)	38 (36.5)	0.002
CARDIAC MAGNETIC RESONANCE				
LVEF (%)[r]	63.5 ± 8.4	54.3 ± 13.6	57.8 ± 12.6	0.01
LVEF <50%[r]	2 (11.1)	8 (27.6)	10 (21.3)	0.18
Left ventricular hypertrophy pattern[r]				0.26
Concentric	9 (50.0)	9 (31.0)	18 (38.3)	
Asymmetric septal	4 (22.2)	13 (44.8)	17 (36.2)	
Sigmoid	5 (27.8)	7 (24.2)	12 (25.5)	
Interventricular septum thickness (mm)[r]	16.6 ± 2.8	20.0 ± 4.2	18.7 ± 4.0	0.004
Posterior wall thickness (mm)[r]	13.1 ± 3.4	14.8 ± 4.6	14.2 ± 4.2	0.19
Maximum thickness (mm)[r]	17.4 ± 3.3	21.2 ± 4.9	19.7 ± 4.7	0.006
Presence of late enhancement[s]	10 (58.8)	24 (85.7)	34 (75.6)	0.04
Abnormal gadolinium kinetics[s]	7 (41.2)	7 (25.0)	14 (31.1)	0.22

AL-CA: light-chain cardiac amyloidosis. ATTR-CA: cardiac amyloidosis due to transthyretin. HDLc: high-density lipoprotein cholesterol. LDLc: low-density lipoprotein cholesterol. GOT: glutamic oxaloacetic transaminase. GPT: glutamic pyruvic transaminase. GGT: gamma glutamyl transpeptidase. LDH: lactate dehydrogenase. CPK: creatine phosphokinase. NT-proBNP: N-terminal brain natriuretic peptide. LVEF: left ventricular ejection fraction. LVEDD, left ventricle end-diastolic diameter. LVESD: left ventricle end-systolic diameter. LVEDV: left ventricular end-diastolic volume. LVESV: left ventricle end-systolic volume. RVEDD: right ventricle end-diastolic diameter. TAPSE: Tricuspid Annular Plane Systolic Excursion.
Data shown as n (%) and mean ± standard deviation.
Calculations based on the following sample sizes.
[a] n = 76.
[b] n = 95.
[c] n = 83.
[d] n = 85.
[e] n = 65.
[f] n = 35.
[g] n = 60.
[h] n = 67 (excluding patients with atrial fibrillation/flutter or pacemaker rhythm).
[i] n = 99 (excluding patients with pacemaker rhythm).
[j] n = 92 (excluding patients with pacemaker rhythm or complete left bundle branch block).
[k] n = 83.
[l] n = 100.
[m] n = 78.
[n] n = 95.
[o] n = 92.
[p] n = 94.
[q] n = 104.
[r] n = 47.
[s] n = 45.

Twenty-seven (25.7%) patients had a history of carpal tunnel syndrome (22 cases of bilateral involvement), with no differences in relation to the CA subtype. The mean time elapsed from diagnosis to CA was 6.9 ± 5.2 years. The ATTR-CA group showed a previous history of other soft tissue conditions, such as lumbar canal stenosis (15.4 vs. 2.5%, p = 0.036), Dupuytren's contracture operated on (9.2 vs. 0%, p = 0.048) and rotator cuff tendinopathy (18.5 vs. 5%, p = 0.049) more often than the AL-CA group. The diagnosis of these pathologies preceded that of CA in 9.1 ± 4.9, 8.5 ± 4.8 and 5.6 ± 5.4 years, respectively.

Lab tests

Table 3 shows the results of the different ancillary tests. Regarding the laboratory findings, a greater elevation of plasma NT-proBNP stands out (8319.1 ± 7851.9 vs. 4586.8 ± 5311.6 pg/mL, p = 0.013), a higher 24 -h proteinuria (2.5 ± 3.9 vs. 0.1 ± 0.1 g/24 h, p < 0.001) and lower albuminemia (3.4 ± 0.7 vs. 4 ± 0.5 g/dL, p < 0.001) in AL-CA patients, compared to ATTR-CA patients.

Bone scintigraphy

A 99mTc-DPD bone scintigraphy was performed in a total of 65 (61.9%) patients, 55 with ATTR-CA and 10 with AL-CA. In the ATTR-CA group, all the bone scintigraphies were positive (100%), five being grade 2 and 50 grade 3. Of the 10 scintigraphies performed on patients with AL-CA, 3 (30%) were positive (two grade 2 and one grade 3) and seven (70%) negative (two grade 0 and five grade 1).

Histological studies

Endomyocardial biopsy was performed in 35 (33.3%) patients, 16 with ATTR-CA and 19 with AL-CA, detecting amyloid in all cases (100%).

In 23 patients with ATTR-CA, 30 extracardiac biopsies were performed to search for amyloid (15 in abdominal fat, five in bone marrow, three in the salivary gland, three in the digestive system, three in the peripheral nerve and one in the quadriceps tendon). In the AL-CA group, 74 extracardiac biopsies were performed in 37 patients in order to detect amyloids (30 in bone marrow, 20 in abdominal fat, 13 in the digestive system, nine in the kidney, one in the salivary gland and one in the peripheral nerve). In 10 patients with AL-CA, a bone marrow biopsy was performed to study monoclonal gammopathy, but no Congo Red staining was performed. In total, six (26.1%) patients with ATTR-CA and 29 (78.4%) patients with AL-CA had a positive extracardiac biopsy (p < 0.001).

Electrocardiogram

Patients with AC-AL and AC-ATTR showed relevant differences regarding the electrocardiogram. Atrial fibrillation or flutter was observed in 29 (44.7%) patients with ATTR-CA; on the contrary, 36 (90%) patients with AL-CA were in sinus rhythm.

The ATTR-CA group showed a longer PR interval (214.1 ± 42.8 vs. 186.6 ± 38.5 ms, p = 0.007) and a wider QRS complex (113 ± 25.1 vs. 99, 7 ± 21.9 ms, p = 0.008) than AL-CA. The prevalence of 1st degree atrioventricular block (19% vs. 12%, p = 0.022) and some bundle branch block (58.3% vs. 33.3%, p = 0.015) were significantly higher in the ATTR-CA group.

The patients with AL-CA showed lower voltages more frequently than those with ATTR-CA in the limb leads (76.9 vs. 50.8%, p = 0.01) and in the precordial leads (56.4 vs. 33, 3%, p = 0.023); however, the prevalence of a Sokolow-Lyon index ≤1.5 mV was similar between both groups (74.4 vs. 63.3%, p = 0.25).

A pseudoinfarction pattern was evident in 63 (68.5%) patients, with septal being the most common, with no significant differences between the two CA subtypes.

Ten (10.9%) patients had electrocardiographic left ventricular hypertrophy based on the Cornell index, but none based on the Sokolow-Lyon index.

Cardiac imaging

In the echocardiographic study, the mean left ventricular ejection fraction (LVEF) of the cohort was 55.1 ± 12.4%, being <50% in 29.5% of cases, with no significant differences between patients with CA-AL and ATTR-CA.

The most common left ventricular hypertrophy pattern was concentric (71.4%), followed by asymmetric septal (20%) and sigmoid (8.6%). The patients with ATTR-CA showed greater interventricular septum thickness (18.7 ± 4.1 vs. 16.7 ± 2.6 mm, p = 0.005) compared to AL-CA patients.

The CA-LA group had a higher prevalence of pericardial effusion (60 vs. 21.9%, p = 0.002) and restrictive left ventricular physiology (47.4 vs. 14.5%, p < 0.001) compared to the CA-ATTR group.

Cardiac magnetic resonance imaging was performed in 47 (44.8%) patients. The mean LVEF with this technique was 57.8 ± 12.6%, resulting significantly lower in the ATTR-CA than in the AL-CA (54.3 ± 13.6 vs. 63.5 ± 8.4%, p = 0.01). The most common left ventricular hypertrophy pattern in the ATTR-CA group was asymmetric septal (44.8%), while in the AL-CA it was concentric (38.3%). A late gadolinium enhancement pattern was observed more frequently among patients with ATTR-CA than among those with AL-CA (85.7 vs. 58.8%, p = 0.04).

Clinical outcomes

During a median follow-up of 13.7 months (interquartile range 5.8–28.6 months), 49 (46.7%) patients died and four (3.8%) received a heart transplant.

Two patients (5%) with AL-CA received a hematopoietic stem cell transplant and 31 (77.5%) received antineoplastic treatment, with regimens based on bortezomib (n = 21), melphalan (n = 9) or both (n = 1); three patients received second-line treatment with lenalidomide and one with daratumumab. Thirty (46.1%) patients with ATTR-CA were treated with tafamidis for a median of 50 days (interquartile range 30–75 days), within the framework of a research protocol initiated in March 2019.

The cause of death was cardiovascular in 38 (86.4%) cases, including 23 deaths due to refractory HF, 11 sudden deaths, two deaths due to stroke and two deaths due to pulmonary embolism. Among non-cardiovascular causes, there were four deaths from infection, one death from gastrointestinal bleeding, and one death from kidney failure. The cause of death was not known in five patients.

Survival at 1, 3 and 5 years was 43.3, 40.4 and 35.4%, respectively, in patients with LA-CA and 85.1, 57.3 and 31.4% in patients with CA -ATTR (p = 0.004). Survival curves are shown in Fig. 1.

Table 4 shows the incidence rate of the main adverse clinical outcomes. Patients with CA-LA had more hospitalizations (1155 episodes per 1000 patient-years, 95% CI 904–1407) than patients with ATTR-CA (814 episodes per 1000 patient-years, 95% CI 658–995) (HR 1.42; 95% CI 1.04−1.93; $p = 0.021$), mainly at the expense of admissions for non-cardiovascular causes (AL-CA: 556 episodes per 1000 patient-years, 95% CI 396–761; CA -ATTR: 223 episodes per 1000 patient-years, 95% CI 146–326) (HR 2.50; 95% CI 1.48−4.27; $p < 0.0001$). We did not observe significant differences between the groups with respect to the incidence of hospitalization for HF (ATTR-CA: 463 episodes per 1000 patient-years, 95% CI 348–604; AL-CA: 342 episodes per 1000 patient-years, 95 CI % 219–509; HR 0.74, 95% CI 0.44−1.22; $p = 0.22$) or with respect to other adverse clinical outcomes.

The multivariate Cox regression analysis identified the AL-CA subtype, a history of admission for HF, and the NYHA III-IV functional class as independent predictors of mortality; beta-blocker treatment was associated with longer survival (Table 5).

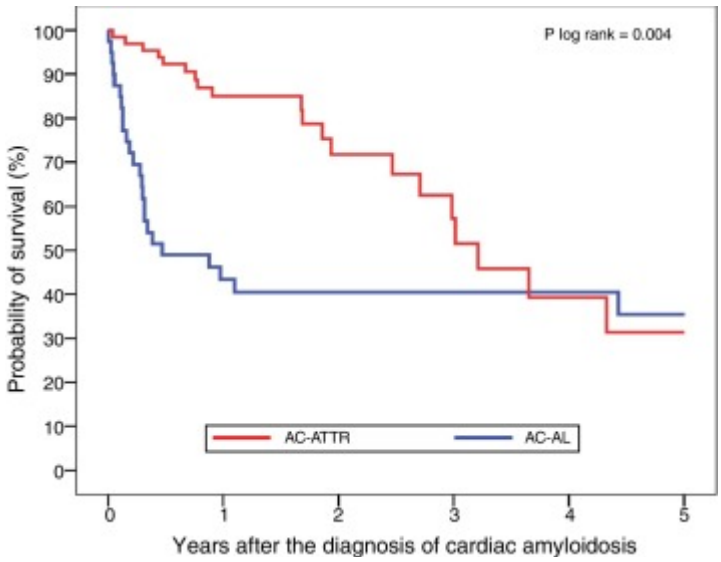

Fig. 1. Survival curves after the diagnosis of cardiac amyloidosis.
AL-CA: light-chain cardiac amyloidosis. ATTR-CA: transthyretin cardiac amyloidosis.

Table 4. Incidence rate of the main adverse clinical outcomes.

	AL-CA (n = 40)		ATTR-CA (n = 65)			
	N	Incidence rate (95% CI)	N	Incidence rate (95% CI)	HR (95% CI)	P value
Total admissions	81	1.155.5 (903.9−1407.1)	95	813.7 (658.3−994.7)	1.42 (1.04−1.93)	0.021
HF admissions	24	342.4 (219.4−509.4)	54	462.5 (347.5−603.5)	0.74 (0.44−1.22)	0.22
Admissions for non-HF cardiovascular causes	18	256.8 15 (152.2−405.8)		128.5 (71.9−211.9)	2.00 (0.95−4.26)	0.05
Admissions for non-cardiovascular causes	39	556.3 (395.6−760.5)	26	222.7 (145.5−326.3)	2.50 (1.48−4.27)	<0.0001
Visits to the emergency department for IC	12	171.2 (88.4−299.0)	17	145.6 (0.51−2.61)	1.18	0.66
Atrial fibrillation or flutter	6	95.3 (35.0−207.4)	5	85.6 (31.4−186.3)	0.92 (0.23−3.80)	0.88
Non-atrial fibrillation or flutter arrhythmic event	7	99.9 (40.1−205.8)	6	51.4 (18.6−111.9)	1.9 (0.6−7.0)	0.24
Syncope	7	99.9 (40.1−205.7)	13	111.3 (59.3−190.4)	0.90 (0.30−2.42)	0.83
Pacemaker implantation	2	28.6 (3.5−103.2)	7	66.2 (26.6−136.3)	0.43 (0.04−2.27)	0.31
Ischemic heart disease	3	42.8 (8.8−125.1)	3	25.7 (5.3−75.1)	1.66 (0.22−12.43)	0.55
Cerebrovascular disease	4	57.1 (15.5−146.1)	7	60.0 (24.1−123.5)	0.95 (0.20−3.74)	0.96
Venous thromboembolic event	4	57.1 (15.5−146.1)	1	8.6 (0.2−47.7)	6.66 (0.66−328.08)	0.077

AL-CA: light-chain cardiac amyloidosis. ATTR-CA: transthyretin cardiac amyloidosis. HR: hazard ratio. 95% CI: 95% confidence interval. HF: heart failure.
Incidence rates are shown as the number of episodes per 1000 patient-years.

Table 5. Univariate and multivariate Cox regression analysis.

	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Subtype AL-CA	2.17 (1.20−3.85)	0.01	3.41 (1.45−8.06)	0.005
Age (years)	0.97 (0.95−1.00)	0.048	–	–
Previous admission for HF	3.35 (1.81−6.20)	< 0.0001	4.25 (1.63−11.09)	0.003
NYHA functional class III-IV	2.45 (1.37−4.38)	0.002	2.76 (1.09−7.03)	0.033
Systolic blood pressure (mmHg)	0.98 (0.96−1.00)	0.055	–	–
Congestive symptomatology data	2.02 (1.03−3.97)	0.042	–	–
Beta-blocker treatment	0.54 (0.28−1.05)	0.068	0.23 (0.09−0.59)	0.002
Haemoglobin (g/dL)	0.83 (0.71−0.97)	0.017	–	–
Creatinine (mg/dL)	1.61 (1.21−2.15)	0.001	–	–
Bilirubin (mg/dL)	1.24 (1.00−1.53)	0.045	–	–
NT-proBNP (pg/mL)	1.06 (1.01−1.11)	0.009	–	–
TAPSE <15 mm	2.40 (1.35−4.27)	0.003		–

HR: hazard ratio. 95% CI: 95% confidence interval. AL-CA: light-chain cardiac amyloidosis. HF: heart failure. NYHA: New York Heart Association. NT-proBNP: N-terminal brain natriuretic peptide TAPSE: Tricuspid Annular Plane Systolic Excursion.

Discussion

In this paper we describe in detail the clinical presentation and natural history of patients with AL-CA and ATTR-CA based on the historical cohort of a Spanish hospital.

The diagnosis of CA is based on a targeted suspicion that arises from the recognition of characteristic clinical findings in a patient with ventricular hypertrophy. Diagnostic delay is common; as in other series,2 hypertrophic cardiomyopathy and hypertensive heart disease were the most common alternative clinical assessments in this study.

The implementation in 2016 of a specific protocol for CA screening in our centre, which included a non-invasive diagnostic algorithm for the ATTR-CA subtype[4] led to a significant increase in the number of cases detected. Slightly more than half of the cohort corresponds to patients diagnosed after the implementation of the protocol, of which approximately three-quarters are ATTR-CA. Within this subtype, the vast majority of patients had ATTRwt-CA, a disease with an insufficiently understood mechanism, predominantly affecting older men.[2, 3, 6]

In our study, the most common form of presentation of patients with CA was congestive symptoms; the development of clinical HF is, however, less common in other pathologies that present with ventricular hypertrophy.[7] A Spanish study revealed a prevalence of ATTR-CA of 13.3% in patients hospitalized for HF with preserved LVEF, highlighting the importance of diagnostic suspicion.[8] We have also observed a high prevalence of atrial arrhythmias, mainly atrial fibrillation, and conduction disorders, especially in the ATTR-CA group; other authors have also described a higher frequency of these abnormalities in patients with ATTR-CA, especially the «wild-type », compared to patients with AL-CA or other heart diseases.[6, 9, 10]

Amyloid deposition in soft tissues (ligaments and tendons) is common in patients with CA, especially the ATTR-CA subtype, and causes characteristic clinical manifestations that should lead to diagnostic suspicion. Carpal tunnel syndrome, a consequence of amyloid infiltration of the transverse carpal ligament and of the synovial sheaths of the flexor tendons of the fingers, has been widely described in the literature[11] and is considered a red flag of the disease. This abnormality is often bilateral and usually precedes the diagnosis of CA by several years, on average 7 in our series. Sporadic cases of amyloid infiltration of the rotator cuff in the shoulder,[12] the ligamentum flavum, which causes stenosis of the lumbar canal,[12] or the quadriceps tendon[13] have also been described. It is plausible to think that the rupture of the proximal tendon of the long head of the biceps brachii, whose clinical expression is the Popeye sign,[14] or Dupuytren's contracture may also be due to infiltrative pathology in these patients. More than a third of our patients with CA had a previous history of soft tissue pathology other than carpal tunnel syndrome; the prevalence of these alterations was significantly higher in the ATTR-CA subgroup.

The electrocardiogram is a key test to guide the diagnostic suspicion of CA. In our series, and as in other works,[15, 16] the two most common electrocardiographic findings were the pseudoinfarction pattern and the presence of a Sokolow-Lyon index <1.5 mV, both of which were observed in more than two thirds of CA cases with no differences between the two subtypes of the disease. This study also confirms that the classic low voltage pattern, although characteristic, is only present in just over half of patients with CA, with a clear prevalence in the AL-CA subtype.[17]

Traditionally, CA has been considered as an entity characterized by left ventricular hypertrophy with a concentric pattern, diastolic dysfunction and preserved LVEF. However, about a third of our patients had an LVEF < 50% at the time of diagnosis. A study[9] suggested that the presence of a reduced LVEF is more common in ATTR-CA than in AL-CA; our cohort shows a similar result in the subgroup that was studied by magnetic resonance imaging, with no differences between the two subtypes with respect to LVEF measured by echocardiography. In a similar way to that described by other authors,[2, 18] depending on the imaging technique used, between 30% and 60% of our patients had left ventricular hypertrophy with asymmetric or sigmoid septal distribution; these "atypical" patterns were more common in patients with ATTR-CA than in patients with AL-CA. Finally, the ATTR-CA subtype was characterized, in general, by greater expressiveness in imaging tests, greater myocardial thickness, greater left atrial enlargement, and a greater prevalence of late gadolinium enhancement patterns. On the contrary, the presence of pericardial effusion and restrictive physiology was especially common in patients with AL-CA.

CA is an entity with a poor prognosis, especially the AL-CA subtype[6, 9, 15, 19] and our series is no exception. The patients with AL-CA had a mean survival of less than 6 months, while the mean survival of patients with ATTR-CA was somewhat higher than 3 years. Most deaths were due to cardiovascular causes; it is known that, despite the multisystemic nature of this disease, cardiovascular involvement is the main determinant of its adverse prognosis.

The poor survival outcomes observed are primarily attributable to the advanced stage of the disease at diagnosis, with a high prevalence of previous HF hospitalisation, advanced functional classes, and high levels of serum biomarkers. Moreover, this historical cohort comprises a time when there were hardly any effective therapeutic alternatives for patients with CA. Tafamidis, a drug with a favourable prognostic impact on ATTR-CA, has only been used in our center since March 2019, within the framework of a research protocol. Although the majority of the patients with AL-CA received antineoplastic treatment, the use of other therapies such as hematopoietic stem cell transplantation and heart transplantation was limited. In this sense, it is worth noting that, although mortality in the AC-AL group was extraordinarily high during the first year (56%), patients who were able to overcome this period showed an acceptable medium-term survival, tending to match that of ATTR-CA patients. This result could reflect the selection of a subgroup of patients with a better prognosis as a consequence of a positive response to disease treatment.[20]

In addition to a reduced life expectancy, patients with CA have a significant morbidity. The incidence of hospital admissions due to decompensated HF was quantitatively higher in our cohort than that described in patients with HF of other etiologies.[21] The burden of non-cardiovascular hospitalizations was especially high in patients with AL-CA as a consequence of complications related to the systemic nature of the disease, such as infections, treatment toxicity, kidney failure, etc. Finally, the high proportion of patients with CA and cerebrovascular disease, both prevalent and incident, is particularly striking, which we correlate with their known high thromboembolic risk.[22]

The multivariate analysis allowed the identification of three independent predictors of a higher risk of death in patients with CA, including the AL-CA subtype, a history of hospitalization for HF, and a NYHA III-IV functional class; treatment with beta-blocking drugs was independently associated with longer survival. This finding is surprising since, although there are no studies that have addressed the possible effect of neurohormonal therapy in patients with CA, the most widespread opinion is that they should be used with caution due to the potential deleterious effects that bradycardia can have, especially in patients with advanced restrictive physiology.[23] We believe that future studies, with a targeted design, are needed to appropriately address these hypotheses.

Our study has some limitations. Given its observational and retrospective nature, it may be subject to typical data, selection, and confounding biases. Moreover, its single-centre nature entails the obvious limitations regarding the extrapolation of results to other populations. Lastly, the study addresses a historical cohort that includes patients diagnosed with CA over a long period of time; given the rapid advances in the diagnosis and treatment of the disease, it is possible that there is some heterogeneity in the clinical profile and prognosis of the individuals studied.

Conclusions

The detailed study of our historical cohort of 105 patients with CA shows that there are notable differences regarding the clinical presentation and natural history of the ATTR-CA and AL-CA subtypes. Both entities are associated with a poor vital prognosis, with early mortality being especially high in individuals with CA-LA. Our results show the need for an early diagnosis and the availability of therapies that effectively modify the course of the disease in patients with CA.

Funding

The research group responsible for this study receives regular funding from the Consorcio de Investigación Biomédica en Red de Enfermedades Cardiovasculares - CIBERCV (Biomedical Research Network Consortium on Cardiovascular Diseases) of the Carlos III Health Institute.

Conflict of interests

The authors declare no conflict of interest.

References

1. Kyle RA, Linos A, Beard CM, Linke RP, Gertz MA, O´Fallon WM, et al. Incidence andnatural history of primary systemic amyloidosis in Olmsted County, Minnesota,1950 through 1989. Blood. 1992;79(7):1817–22.
2. González-López E, Gagliardi C, Domínguez F, Quarta CC, de Haro-Del MoralFJ, Milandri A, et al. Clinical characteristics of wild-type transthyretin cardiacamyloidosis: disproving myths. Eur Heart J. 2017;38(24):1895–904.3..
3. Lane T, Fontana M, Martínez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al.Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis.Circulation. 2019;140(1):16–26.
4. Barge-Caballero G, Couto-Mallón D, Barge-Caballero E, Paniagua-Martín MJ,Barriales-Villa R, Pombo-Otero J, et al. How to face a clinical suspicionof cardiac amyloidosis? A practical approach to the diagnosis. Cardiocore.2017;52(1):27–34.
5. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A,et al. Non-biopsy diagnosis of cardiac transthyretin amyloidosis. Circulation.2016;133(24):2404–12.
6. Pinney JH, Whelan CJ, Petrie A, Dungu J, Banypersad SM, Sattianayagan P, et al.Senile systemic amyloidosis: clinical features at presentation and outcome. J AmHeart Assoc. 2013;2(2):e000098.
7. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy.Eur Heart J. 2014;35(39):2733–79.
8. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ,Cobo-Marcos M, Robles C, et al. Wild-type transthyretin amyloidosis as a cause ofheart failure with preserved ejection fraction. Eur Heart J. 2015;36(38):2585–94.
9. Czobor P, Hung YY, Baer D, McGlothlin D, Weisshaar D, Zaroff J. Amy-loid cardiomyopathy in a large integrated health care system. Am Heart J.2019;216:42–52.
10. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology,pathophysiology, and clinical outcomes. Circ Res. 2017;120(9):1501–17.
11. Kyle RA, Eilers SG, Linscheid RL, Gaffey TA. Amyloid localized to tenosyn-ovium at carpal tunnel release. Natural history of 124 cases. Am J Clin Pathol.1989;91(4):393–7.
12. Sueyoshi T, Ueda M, Jono H, Irie H, Sei A, Ide J, et al. Wild-typetransthyretin-derived amyloidosis in various ligaments and tendons. HumPathol. 2011;42(9):1259–64.
13. Barge-Caballero G, López-Bargiela P, Pombo-Otero J, Pardo-Martínez P. Quadri-ceps tendon rupture in wild-type transthyretin amyloidosis (ATTRwt). Eur HeartJ. 2019;40(16):1307.
14. Geller HI, Singh A, Alexander KM, Mirto TM, Falk RH. Association between rup-tured distal biceps tendon and wild-type transthyretin cardiac amyloidosis.JAMA. 2017;318(10):962–3.
15. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiacamyloidoses: disease profiles and clinical courses of the 3 main types. Circula-tion. 2009;120(13):1203–12.
16. Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. Prevalence and prognosis signif-icance of low QRS voltage among the three main types of cardiac amyloidosis.Am J Cardiol. 2014;114(7):1089–93.
17. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardio-graphic findings in primary systemic amyloidosis and biopsy-proven cardiacinvolvement. Am J Cardiol. 2005;95(4):535–7.
18. Martínez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS,et al. Magnetic resonance in transthyretin cardiac amyloidosis. J Am Coll Cardiol.2017;70(4):466–77.
19. Ng B, Connors LH, Davidoff R, Skinner M, Falk RH. Senile systemic amyloidosispresenting with heart failure: a comparison with light chain-associated amyloi-dosis. Arch Intern Med. 2005;165(12):1425–9.
20. Muchtar E, Gertz MA, Lacy MQ, Go RS, Buadi FK, Dingli D, et al. Ten-year sur-vivors in AL amyloidosis: characteristics and treatment pattern. Br J Haematol.2019;187(5):588–94.

21. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F,et al. European Society of Cardiology heart failure long-term registry (ESC-HF-LT): 1-year follow-up outcomes and differences accros regions. Eur J Heart Fail.2016;18(6):613–25.
22. Feng D, Syed IS, Martínez M, Oh JK, Jaffe AS, Grogan M, et al. Intracardiacthrombosis and anticoagulation therapy in cardiac amyloidosis. Circulation.2009;119(18):2490–7.
23. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretinamyloid cardiomyopathy JACC State-of-the-Art Review. J Am Coll Cardiol.2019;73(22):2872–91.