Rev Esp Cardiol. 2026;xx(x):xxx–xxx

Original article

# Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant

Alessia Argirò,[a,b,*] Federica Colio,[a,b] Manuel Garofalo,[a,b] Simone Longhi,[c] Luciano Potena,[c] Giulia Saturi,[c] Marco Allinovi,[b] Alessio Aloisio,[c] Aldostefano Porcari,[d,e] Awais Sheikh,[d] Marianna Fontana,[d] Julian Gillmore,[d] Pablo García-Pavía,[f] Manuel Gómez Bueno,[f,g] Silvia Menale,[h] William E. Moody,[i] Caitlin Thornton,[i] Lorena Herrador,[j,k] José González-Costello,[j,k,l] Fernando de Frutos,[f,j,k] Concetta Di Nora,[m] Igor Vendramin,[m] Massimo Imazio,[m] Marco Merlo,[e] Gianfranco Sinagra,[e] Marcus Anthony Urey,[n] Quan M. Bui,[n] Ahmad Masri,[o] Mohammad Alqabani,[o] Zhongli Chen,[p] Liang Chen,[q] Alessio Gasperetti,[r] Paolo Milani,[s,t] Giovanni Palladini,[s,t] Barbara Cattadori,[s,t] Alberto Cipriani,[u] Giulio Sinigiani,[u] Gino Gerosa,[u] Giuseppe Palmiero,[v] Giuseppe Limongelli,[v] Beatrice Musumeci,[w,x] Giacomo Tini,[w,x] Maurizio Pieroni,[a,b] Federico Perfetto,[a,b] and Francesco Cappelli[a,b]

[a] *Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy*
[b] *Department of Interventional Cardiology, Tuscan Regional Amyloid Center, Careggi University Hospital, Florence, Italy*
[c] *Cardiology Unit, Department of Cardiac Thoracic and Vascular, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*
[d] *Division of Medicine, National Amyloidosis Centre, University College London, Royal Free Hospital, London, United Kingdom*
[e] *Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy*
[f] *Departamento de Cardiología, Hospital Universitario Puerta de Hierro Majadahonda, Instituto de Investigación Sanitaria Puerta de Hierro-Segovia Arana (IDIPHISA), Majadahonda, Madrid, Spain*
[g] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain*
[h] *Cardiovascular Department, Azienda Ospedaliera Toscana Sudest, San Donato Hospital, Arezzo, Italy*
[i] *Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom*
[j] *Unidad de Insuficienia Cardiaca y Enfermedades Cardiacas Hereditarias, Departamento de Cardiología, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain*
[k] *Grupo Bioheart, Programa de Enfermedades Cardiovasculares, Respiratorias, Sistémicas y de Envejecimiento Celular, Instituto de Investigación Biomédica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain*
[l] *Departamento de Ciencias Clínicas, Facultad de Medicina, Universidad de Barcelona, Barcelona, Spain*
[m] *Cardiothoracic Department, University Hospital of Udine, Udine, Italy*
[n] *Division of Cardiovascular Medicine, Department of Medicine, University of California, San Diego, La Jolla, California, United States*
[o] *Amyloidosis Center, Knight Cardiovascular Institute, Oregon Health & Science University, Portland, United States*
[p] *Cardiac Arrhythmias Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[q] *State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Peking Union Medical College, Beijing, China*
[r] *Division of Cardiology, School of Medicine, Johns Hopkins University, Baltimore, United States*
[s] *Amyloidosis Research and Treatment Center, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia, Italy*
[t] *Department of Molecular Medicine, University of Pavia, Pavia, Italy*
[u] *Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua, Padua, Italy*
[v] *Inherited and Rare Cardiovascular Diseases, Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Monaldi Hospital, Naples, Italy*
[w] *Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy*
[x] *Division of Cardiology, Sant'Andrea University Hospital, Rome, Italy*

*Article history:*
Received 19 January 2026
Accepted 2 June 2026

*Keywords:*
Cardiac amyloidosis
Heart transplantation
Disease-modifying therapy

ABSTRACT

*Introduction and objectives:* To describe the clinical characteristics of patients with cardiac amyloidosis who have undergone heart transplantation (HT).

*Methods:* This retrospective multicenter study involving 14 referral centers included 113 patients with cardiac amyloidosis who underwent HT: 57 with transthyretin amyloidosis (ATTR) (22 with wild-type ATTR and 35 with variant ATTR) and 56 with light chain amyloidosis (AL).

*Results:* Compared with patients with ATTR, patients with AL amyloidosis showed more severe hemodynamic compromise before HT, with a lower cardiac index (1.7 L/min/m$^2$ [interquartile range, 1.4–2.0 L/min/m$^2$] vs 1.9 L/min/m$^2$ [interquartile range, 1.6–2.4 L/min/m$^2$]; $P$ = .027) and higher right atrial pressure. Post-transplant infections occurred in 23 patients with ATTR (40%) and 24 with AL (43%). New-onset neuropathy occurred in 11% of patients, while neuropathy progression was more frequent in ATTR compared with AL (23% vs 7.1%; $P$ = .044). Median follow-up was 4.6 years in ATTR and 5.4 years in AL. Five-year survival was similar in both groups (77% in AL vs 83% in ATTR). Sepsis was the leading cause of death (n = 11, 29% of deaths). Among patients with ATTR, 9 received tafamidis before HT and 7 after HT. Eight patients with ATTR received patisiran post-HT (1 pre-HT), and 3 received diflunisal post-HT. In AL, 70% received bortezomib-based therapy while 28% received daratumumab-based therapy. In AL,

* Corresponding author.
*E-mail address:* Alessia.argiro@unifi.it (A. Argirò).
𝕏@AlessiaArgiro

https://doi.org/10.1016/j.rec.2026.06.005


Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

hematologic responses improved after HT, with the complete response rate increasing from 42% before HT to 54% after HT.
*Conclusions:* HT is an effective treatment for carefully selected patients with cardiac amyloidosis, with comparable unadjusted survival between AL and ATTR. These findings warrant confirmation in prospective studies.


## Análisis multicéntrico de cohortes de receptores de trasplante cardiaco con amiloidosis cardiaca

*Palabras clave:*
Amiloidosis cardiaca
Trasplante cardiaco
Tratamiento modificador de la enfermedad

RESUMEN

*Introducción y objetivos:* Describir las características clínicas de los receptores de trasplante cardiaco (TxC) con amiloidosis cardiaca.
*Métodos:* Estudio multicéntrico retrospectivo que incluyó a 113 receptores de TxC con amiloidosis cardiaca de 14 centros de referencia: 57 con amiloidosis por transtirretina (ATTR) (22 con ATTR de tipo natural o *wild-type* y 35 con ATTR hereditaria) y 56 con amiloidosis de cadenas ligeras (AL).
*Resultados:* Los pacientes con AL presentaron un deterioro hemodinámico más grave antes del TxC, con un índice cardiaco más bajo (gasto cardiaco: 1,7 l/min/m$^2$ [IQR, 1,4-2,0] frente a 1,9 l/min/m$^2$ [IQR, 1,6-2,4], respectivamente; p = 0,027) y una presión auricular derecha más alta en comparación con los diagnosticados de ATTR. Las infecciones postrasplante se dieron en 23 pacientes con diagnóstico de ATTR (40%) y en 24 con AL (43%). Los casos de neuropatía de nueva aparición se documentaron en el 11% de los pacientes, mientras que la progresión de la neuropatía fue más frecuente en la ATTR en comparación con la AL (el 23 frente a 7,1%, respectivamente; p = 0,044). La mediana de seguimiento fue de 4,6 años en la ATTR y de 5,4 en la AL, con una supervivencia a 5 años similar en ambos grupos (el 77% en la AL y el 83% en la ATTR). La sepsis fue la principal causa de fallecimiento (n = 11; el 29% de las muertes). Entre los pacientes con ATTR, 9 recibieron tafamidis antes del TxC y 7 después. Tras el TxC, 8 pacientes con ATTR recibieron patisirán (1 antes del TxC) y 3 diflunisal. En pacientes con AL, el 70% recibieron tratamiento basado en bortezomib y el 28% en daratumumab. En AL, la respuesta hematológica mejoró tras el TxC, con un aumento de respuesta completa desde el 42% antes del TxC al 54% tras el TxC.
*Conclusiones:* El TxC es un tratamiento eficaz para pacientes cuidadosamente seleccionados con amiloidosis cardiaca, con una supervivencia no ajustada comparable entre los tipos AL y ATTR. Estos hallazgos requieren confirmación en estudios prospectivos.


### Abbreviations

AL: light chain amyloidosis
ATTRv: variant transthyretin amyloidosis
ATTRwt: wild-type transthyretin amyloidosis
CA: cardiac amyloidosis
HT: heart transplantation
MCS: mechanical circulatory support

## INTRODUCTION

Amyloidosis is an umbrella term for a group of conditions characterized by the extracellular deposition of amyloid fibrils, which are derived from various precursor proteins that misfold and are deposited, causing organ dysfunction.[1] In cardiac amyloidosis (CA), the most frequent precursors are amyloidogenic immunoglobulin light chains produced in the context of a plasma cell dyscrasia (light chain amyloidosis [AL]) and misfolded transthyretin (TTR). The propensity for TTR misfolding may be related to the presence of a genetic variant (variant transthyretin amyloidosis [ATTRv]) or due to senescence (wild-type transthyretin amyloidosis [ATTRwt]).[2]

The most common complication of CA is heart failure. It typically presents with preserved ejection fraction in the early stages but progresses to cardiac systolic dysfunction as amyloid deposition advances. Disease-modifying therapies, including TTR stabilizers and gene silencers in ATTR and antiplasma cell therapies in AL, can modify the natural history of the disease, reducing mortality and heart failure-related complications.[3–6] However, the only therapeutic option in patients with advanced heart failure due to CA is heart transplantation (HT).[7]

While the adverse outcomes of the early cohorts of HT recipients with CA raised concerns about treatment futility,[8] recent reports showed an improved prognosis, comparable to that of HT recipients with different underlying diseases.[9–12] In this study, we describe a multicenter cohort of patients with CA who underwent HT and discuss post-HT complications, disease progression, and the use of disease-modifying therapies.

## METHODS

### Patient selection and diagnosis

This is a retrospective review of patients with AL or ATTR who underwent HT in European, Chinese and US centers (*Hospital Universitario de Bellvitge*, Spain; University of Bologna, Italy; Peking Union Medical College, China; *Hospital Universitario Puerta de Hierro Majadahonda*, Spain; National Amyloidosis Center, United Kingdom; University of Pavia, Italy; University of Padua, Italy;

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

Oregon Health & Science University, United States; University of California San Diego, United States; University Hospital of Udine, Italy; University of Trieste, Italy; University Hospitals Birmingham, United Kingdom; University of Florence, Italy; La Sapienza University, Italy; The University of Campania Luigi Vanvitelli, Italy) (figure S1).

Before 2016, histological confirmation through tissue biopsy was required in all cases. After 2016, following the validation of nonbiopsy diagnostic algorithms for ATTR amyloidosis, patients without evidence of monoclonal gammopathy were diagnosed noninvasively using bone scintigraphy, while tissue biopsy was reserved for patients with a detectable monoclonal component to exclude AL amyloidosis.

Regarding bone scintigraphy, different technetium-labeled tracers (technetium-99m pyrophosphate, technetium-99m hydroxymethylene diphosphonate, or technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid) were used according to local availability and institutional practice. Similarly, assessment of monoclonal components was performed using serum and urine immunofixation and serum-free light chain assays, in accordance with guideline recommendations at each center.[2]

Smoldering multiple myeloma and multiple myeloma were diagnosed according to the International Myeloma Working Group (IMWG) criteria,[13] which were updated in 2014.[14]

### Data collection

Data were collected retrospectively via chart review from patients diagnosed between 1996 and 2024. Baseline laboratory values and information regarding extracardiac amyloidosis were recorded. Patients were monitored and treated according to standard institutional protocols before and after HT.

### Definitions and assessments

Gastrointestinal involvement was defined by the development of constipation, diarrhea, or both, and/or a history of gastrointestinal bleeding with biopsy verification for amyloid deposition. Hepatic involvement was defined as an alkaline phosphatase level > 1.5 times the upper institutional laboratory limit with liver biopsy confirmation.[10] Renal involvement criteria required urinary protein excretion > 0.5 g/24 h or renal biopsy confirmation.[15]

Peripheral neuropathy involvement required confirmation by an expert neurologist per center practice or use of medications for neuropathy treatment.

Patients were evaluated for postoperative complications, including postoperative bleeding, renal impairment, rejection, infection, cancer, graft failure, and death. Acute cellular rejection was defined as International Society for Heart and Lung Transplantation grade $\geq$ 2.[16]

Endomyocardial biopsies after HT were performed according to the local surveillance protocols of each center, either as part of routine post-transplant follow-up or when clinically indicated. Amyloid deposition in biopsy samples was assessed by Congo red staining, followed by deposit typing using immunofluorescence and/or laser microdissection with mass spectrometry.

Systematic screening with cardiac imaging modalities such as scintigraphy or single-photon emission computed tomography was not performed.

### Patient cohort and study periods

Patients were stratified on the basis of the date of HT into 3 eras: early (1999-2007), intermediate (2008-2015), and late (2016-2024). The years 2008 and 2016 were chosen as cutoff dates as they marked key changes in diagnostic criteria for CA and advances in the treatment of AL and ATTR.[2,10] Furthermore, 2008 represents an inflection point in the development of HT for CA, coinciding with the publication of more stringent patient selection criteria addressing extracardiac organ involvement,[17] which significantly influenced transplant candidacy. In addition, this period was characterized by major therapeutic advances in AL amyloidosis, particularly the inclusion of proteasome inhibitors such as bortezomib in treatment protocols.[18] In addition, in 2021, the human CD38-targeting antibody daratumumab was demonstrated to be safe and effective in the treatment of AL amyloidosis.[6]

### Ethics approval

Ethics approval was obtained from the coordinating center, and each participating center confirmed approval from its local institutional review board/ethics committee for the conduct of observational research. The study was conducted in accordance with the Declaration of Helsinki.

### Study aim

The aim of this study was to describe an international multicenter cohort of patients with CA who underwent HT. Specifically, we sought to characterize clinical features at diagnosis and at the time of transplantation, pretransplant support requirements, and post-transplant outcomes and disease progression, with particular attention to the use of disease-modifying therapies.

### Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]), while categorical variables are presented as counts and percentages. Between-group comparisons were evaluated using Wilcoxon rank sum test and chi-square tests as appropriate. Survival curves were created using the Kaplan-Meier method, and unadjusted survival rates were compared using the log-rank test. Survival analysis was performed using Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (95%CIs) for all-cause mortality. Univariable analyses were conducted for the entire cohort and separately for subgroups of patients with AL and ATTR amyloidosis. The proportional hazards assumption was assessed for each model using Schoenfeld residuals. To test the different distribution of amyloidosis subtypes across eras, the chi-square test for independence was used. Statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Baseline characteristics

A total of 113 patients were included: 57 with ATTR (22 with ATTRwt and 35 with ATTRv; table S1) and 56 with AL. Most patients were male (n = 47 [82%] in ATTR; n = 32 [57%] in AL). The median age at transplantation was 60.8 years [IQR, 53.2-64.1 years] in the ATTR group and 52.5 years [IQR, 46.3-59.2 years] in the AL group (table 1, table S2).

The median interval from diagnosis to HT was significantly shorter in AL than in ATTR (7.9 months [IQR, 3.8-16.3 months] in AL

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

**Table 1**
Clinical characteristics of heart transplant recipients with ATTR and AL

| Variable | Total (N = 113) | ATTR (n = 57) | AL (n = 56) | *P* |
|---|---|---|---|---|
| *Height, cm, median [IQR]* | 170.0 [164.0-176.3] | 172.0 [168.0-177.0] | 168.0 [163.0-176.0] | .13 |
| *Weight, kg, median [IQR]* | 71.0 [61.0-84.0] | 76.0 [64.0-86.0] | 67.5 [59.9-77.3] | .004 |
| *Male sex, n (%)* | 79/113 (70%) | 47/57 (82%) | 32/56 (57%) | .003 |
| *Race, n (%)* | | | | .60 |
| White | 101/113 (89%) | 52/57 (91%) | 49/56 (88%) | |
| Black | 5/113 (4.4%) | 3/57 (5.3%) | 2/56 (3.6%) | |
| Asian | 7/113 (6.2%) | 2/57 (3.5%) | 5/56 (8.9%) | |
| *Age at heart transplantation, y, median [IQR]* | 55.8 [48.7-62.5] | 60.8 [53.2-64.1] | 52.5 [46.3-59.2] | < .001 |
| *Age at diagnosis, y, median [IQR]* | 54.3 [46.5-60.2] | 57.0 [50.4-61.6] | 51.6 [44.9-57.4] | .011 |
| *Time from diagnosis to transplant, mo, median [IQR]* | 15.0 [7.0-33.0] | 31.5 [12.6-44.4] | 7.9 [3.8-16.3] | < .001 |
| *Time from listing to transplant, mo, median [IQR]* | 2.3 [0.8-5.4] | 4.0 [1.4-7.3] | 1.5 [0.6-3.1] | < .001 |
| *Follow-up after heart transplant, y, median [IQR]* | 4.8 [1.6-8.4] | 4.6 [1.9-8.4] | 5.4 [1.6-8.3] | > .90 |
| *Amyloidosis, n (%)* | | | | < .001 |
| AL | 56/113 (50%) | 0/57 (0%) | 56/56 (100%) | |
| ATTRwt | 22/113 (19%) | 22/57 (39%) | 0/56 (0%) | |
| ATTRv | 35/113 (31%) | 35/57 (61%) | 0/56 (0%) | |
| *Renal involvement, n (%)* | 13/113 (12%) | 4/57 (7.0%) | 9/56 (16%) | .13 |
| *Neuropathy, n (%)* | 34/113 (30%) | 25/57 (44%) | 9/56 (16%) | .001 |
| *Orthostatic hypotension, n (%)* | 16/113 (14%) | 9/57 (16%) | 7/56 (13%) | .60 |
| *Dysautonomia, n (%)* | 25/113 (22%) | 17/57 (30%) | 8/56 (14%) | .047 |
| *Hepatic involvement, n (%)* | 11/113 (9.7%) | 8/57 (14%) | 3/56 (5.4%) | .12 |
| *Gastrointestinal involvement, n (%)* | 9/113 (8.0%) | 4/57 (7.0%) | 5/56 (8.9%) | .70 |
| **Variables at the latest ambulatory evaluation before HT** | | | | |
| *NYHA class before HT, n (%)* | | | | .018 |
| II | 19/113 (17%) | 10/57 (18%) | 9/56 (16%) | |
| III | 66/113 (58%) | 39/57 (68%) | 27/56 (48%) | |
| IV | 28/113 (25%) | 8/57 (14%) | 20/56 (36%) | |
| *Glomerular filtration rate (MDRD) before HT, median [IQR]* | 66.0 [51.7-78.7] | 66.2 [51.0-77.8] | 62.3 [55.0-84.0] | .50 |
| *Total bilirubin, μmol/L, median [IQR]* | 10.0 [1.4-19.3] | 7.0 [1.7-14.9] | 11.0 [1.4-21.3] | .40 |
| *AST, U/L, median [IQR]* | 30.0 [24.0-38.5] | 32.5 [24.8-41.8] | 30.0 [23.8-36.5] | .50 |
| *ALT, U/L, median [IQR]* | 31.0 [19.8-43.3] | 26.0 [16.8-34.3] | 33.5 [25.5-46.3] | .035 |
| *Gamma-glutamyl transferase, U/L, median [IQR]* | 121.5 [61.5-223.8] | 95.5 [60.5-221.0] | 140.0 [63.3-217.0] | .40 |
| *Alkaline phosphatase, U/L, median [IQR]* | 134.0 [94.5-177.3] | 124.5 [103.0-162.8] | 152.0 [88.3-197.8] | .40 |
| *Troponin I, pg/mL, median [IQR]* | 142.3 [65.0-225.5] | 70.0 [45.0-169.5] | 177.0 [87.0-303.0] | .064 |
| *Troponin T, pg/mL, median [IQR]* | 100.0 [47.0-146.0] | 66.0 [32.8-95.3] | 120.0 [94.5-212.5] | .091 |
| *NT-proBNP, ng/mL, median [IQR]* | 5801.5 [3031.3-10 208.5] | 4474.0 [2704.0-6301.0] | 7178.0 [4040.8-14 582.0] | .003 |
| *Cardiac index, L/min/m², median [IQR]* | 1.8 [1.5-2.2] | 1.9 [1.6-2.4] | 1.7 [1.4-2.0] | .028 |
| *Mean right atrial pressure, mmHg, median [IQR]* | 13.0 [8.3-19.8] | 10.0 [5.0-17.8] | 15.5 [12.0-23.7] | .004 |
| *Pulmonary capillary wedge pressure, mmHg, median [IQR]* | 20.0 [15.0-24.0] | 18.0 [11.0-24.0] | 20.5 [18.0-24.0] | .15 |
| *Pulmonary artery systolic pressure, mmHg, median [IQR]* | 38.0 [31.5-44.0] | 37.0 [29.5-48.0] | 39.0 [34.0-43.0] | > .90 |
| *Pulmonary artery diastolic pressure, mmHg, median [IQR]* | 21.0 [14.0-27.0] | 19.0 [12.0-29.0] | 22.0 [17.5-26.0] | .40 |
| *Pulmonary artery saturation, %, median [IQR]* | 33.0 [21.0-56.9] | 28.0 [17.0-59.5] | 39.0 [29.3-49.4] | .50 |
| *Pulmonary vascular resistance, WU, median [IQR]* | 2.1 [1.5-2.9] | 2.1 [1.4-3.1] | 2.1 [1.6-2.8] | .60 |
| *Inotropic agents/vasopressors, n (%)* | 44/113 (39%) | 18/57 (32%) | 26/56 (46%) | .11 |
| *Advanced support before HT, n (%)* | 25/113 (22%) | 8/57 (14%) | 17/56 (30%) | .066 |
| *LVAD, n (%)* | 9/113 (8.0%) | 3/57 (5.3%) | 6/56 (11%) | .30 |
| *IABP, n (%)* | 8/113 (7.1%) | 4/57 (7.0%) | 4/56 (7.1%) | > .90 |
| *Impella, n (%)* | 2/113 (1.8%) | 1/57 (1.8%) | 1/56 (1.8%) | > .90 |
| *Artificial heart, n (%)* | 1/113 (0.9%) | 0/57 (0%) | 1/56 (1.8%) | .50 |
| *Emergency HT, n (%)* | 28/113 (25%) | 10/57 (18%) | 18/56 (32%) | .072 |
| *ECMO, n (%)* | 5/113 (4.4%) | 0/57 (0%) | 5/56 (8.9%) | .027 |
| *Transplant type, n (%)* | | | | < .001 |
| Heart | 94/113 (83%) | 38/57 (67%) | 56/56 (100%) | |

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

**Table 1** *(Continued)*
Clinical characteristics of heart transplant recipients with ATTR and AL

| Variable | Total (N = 113) | ATTR (n = 57) | AL (n = 56) | *P* |
|---|---|---|---|---|
| Heart/liver | 18/113 (16%) | 18/57 (32%) | 0/56 (0%) | |
| Heart/liver/kidney | 1/113 (0.9%) | 1/57 (1.8%) | 0/56 (0%) | |

AL, light chain amyloidosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; ECMO, extracorporeal membrane oxygenation; HT, heart transplantation; IABP, intra-aortic balloon pump; IQR, interquartile range; LVAD, left ventricular assist device; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.
Data are expressed as no. (%) or median [interquartile range].

vs 31.5 months [IQR, 12.6-44.4 months] in ATTR, $P < .001$). Similarly, the time from listing to HT was shorter in patients with AL (1.5 months [IQR, 0.6-3.1 months]) than in those with ATTR (4.0 months [IQR, 1.4-7.3 months], $P < .001$).

Before HT, patients with AL showed more advanced hemodynamic compromise compared with those with ATTR, including a lower cardiac index (1.7 L/min/m$^2$ [IQR, 1.4–2.0 L/min/m$^2$] vs 1.9 L/min/m$^2$ [IQR, 1.6–2.4 L/min/m$^2$]; $P = .027$) and higher right atrial pressure (15.5 mmHg [IQR, 12.0–23.7 mmHg] vs 10.0 mmHg [IQR, 5.0–17.8 mmHg]; $P = .004$).

## Mechanical circulatory support

Mechanical circulatory support (MCS) was used as a bridge to HT in 25 patients (22%) and included intra-aortic balloon pumps (n = 8), Impella (n = 2), extracorporeal membrane oxygenation (n = 5), left ventricular assist devices (n = 9), and a total artificial heart (n = 1). Left ventricular assist devices were implanted in 9 patients (3 ATTRv, 6 AL), with 6 deaths during follow-up (3 ATTRv, 3 AL).

Intra-aortic balloon pump support was used in 8 patients (4 AL and 4 ATTR), with 3 deaths occurring in AL patients. Two patients (1 ATTR, 1 AL) received an Impella device, with no deaths occurring during follow-up. Extracorporeal membrane oxygenation was required in 5 AL patients, 3 of whom died during follow-up. One patient with AL underwent total artificial heart implantation 1 year before HT and died perioperatively due to massive bleeding.

## Types of HT

Among the 57 patients with ATTR amyloidosis (22 ATTRwt and 35 ATTRv), transplantation strategies differed substantially. Overall, 38 patients (67%) underwent isolated HT, whereas 19 (33%) underwent combined organ transplantation. In patients with ATTRv (n = 35), 16 (46%) underwent isolated HT, 18 (51%) underwent combined heart–liver transplantation, and 1 (3%) underwent combined heart–liver–kidney transplantation. In contrast, all patients with ATTRwt (n = 22) underwent isolated HT. The characteristics of patients with ATTRwt and ATTRv are detailed in table S3. All AL patients underwent isolated HT.

## Complications after HT

Infections were the most common post-transplant complications, occurring in 23 patients with ATTR (40%) and 24 patients with AL (43%) (table 2, table S4). Pneumonia was the most frequent infection, reported in 8 patients with ATTR (35%) and 12 with AL (50%) (table S2). Sepsis occurred in 4 patients with ATTR (17%) and 1 with AL (4.2%). Gastroenteritis was reported in 2 patients with ATTR (8.7%) and 2 with AL (8.3%).

One episode of rejection occurred in 6 patients with ATTR (11%) and 12 with AL (21%), while more than 1 episode occurred in 4 patients with ATTR (7%) and 10 with AL (18%). Antibody-mediated rejection was observed in 2 patients with ATTR (3.5%) and 2 with AL (3.6%). Among the 36 patients who experienced rejection, 11 died. In 3 patients with AL, rejection was considered the cause of death (2 acute cellular rejections and 1 antibody-mediated rejection).

Cardiac allograft vasculopathy was diagnosed in 5 patients with ATTR (8.8%) and 3 with AL (5.4%).

## Disease progression after HT

New-onset neuropathy was diagnosed in 5 patients with ATTRv (14%), 1 with ATTRwt (4.5%), and 6 with AL (11%). The median time from HT to neuropathy onset was 4 months [IQR, 1.9-19.2 months] in ATTR and 32 months [IQR, 15.7-84.7 months] in AL. Progression of preexisting neuropathy occurred in 12 patients with ATTRv (34%), 1 with ATTRwt (4.5%), and 4 with AL (7.1%), after a median time of 14.8 months [IQR, 4-72 months] in ATTR and 32.2 months [IQR, 25.7-42.5 months] in AL. Patients with ATTR had a significantly higher risk of new-onset neuropathy and neuropathy progression compared with those with AL (log-rank test, $P = .044$).

Amyloid deposits in endomyocardial biopsies were detected in 2 patients with ATTRv (3.5%; variants p.Val142Ile and p.Val142del) after a median time of 67 months [IQR, 40.7-93.5 months] and in 5 patients with AL (8.9%) after a median time of 21 months [IQR, 5-129 months] from HT.

Only one patient carrying the p.Ile88Leu variant developed carpal tunnel syndrome and lumbar spinal stenosis after HT.

## Survival analysis

During a median follow-up of 4.6 years [IQR, 1.9–8.4 years] in the ATTR group and 5.4 years [IQR, 1.6–8.3 years] in the AL group, 16 patients with ATTR (28%) and 22 patients with AL (39%) died. There was no significant difference in overall survival between AL and ATTR (log-rank test, $P = .19$), with unadjusted 1-year, 3-year, and 5-year survival rates of 93%, 84%, and 80% in the overall cohort, 91%, 81%, and 77% in the AL group, and 94%, 86%, and 83% in the ATTR group (figure 1). Sepsis was the most common cause of death, accounting for 6 out of 16 deaths (38%) in the ATTR group and 5 out of 22 (23%) in the AL group. Four sepsis-related deaths occurred within 3 months after HT, and 7 occurred more than 36 months after HT.

Survival rates were comparable to those reported in 2 previously published cohorts of patients with CA[9,16] and to those of patients without CA from the same institutions (figure 1).

Among patients with amyloid deposits, the patient with the p.Val142del variant was treated with diflunisal after HT and died 120 months after HT due to neuropathy progression. One patient

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

**Table 2**
Complications after heart transplantation in patients with cardiac amyloidosis

| Variable | Total (N = 113) | ATTR (n = 57) | AL (n = 56) | *P* |
|---|---|---|---|---|
| *Complications after HT, n (%)* | 82/113 (73%) | 38/57 (67%) | 44/56 (79%) | .20 |
| *ISHLT rejection, n (%)* | | | | .068 |
| No episodes, n (%) | 77/113 (68%) | 45/57 (79%) | 32/56 (57%) | |
| 1 episode, n (%) | 18/113 (16%) | 6/57 (11%) | 12/56 (21%) | |
| > 1 episodes, n (%) | 14/113 (12%) | 4/57 (7.0%) | 10/56 (18%) | |
| *Antibody-mediated reaction, n (%)* | 4/113 (3.5%) | 2/57 (3.5%) | 2/56 (3.6%) | |
| *Infections, n (%)* | 47/113 (42%) | 23/57 (40%) | 24/56 (43%) | .80 |
| *Bleeding, n (%)* | 7/113 (6.2%) | 4/57 (7.0%) | 3/56 (5.4%) | > .90 |
| *Renal impairment after HT, n (%)* | 39/113 (35%) | 20/57 (35%) | 19/56 (34%) | .90 |
| *Cardiac allograft vasculopathy, n (%)* | 8/113 (7.1%) | 5/57 (8.8%) | 3/56 (5.4%) | .70 |
| *Stroke, n (%)* | 3/113 (2.7%) | 1/57 (1.8%) | 2/56 (3.6%) | .60 |
| *Cancer, n (%)* | | | | .20 |
| Skin | 7/113 (6.2%) | 4/57 (7.0%) | 3/56 (5.4%) | |
| Other | 4/113 (3.5%) | 0/57 (0%) | 4/56 (7.1%) | |
| *Graft failure, n (%)* | 4/113 (3.5%) | 1/57 (1.8%) | 3/56 (5.4%) | .40 |
| *Disease progression, n (%)* | 41/113 (36%) | 22/57 (39%) | 19/56 (34%) | .60 |
| *New-onset neuropathy, n (%)* | 12/113 (11%) | 6/57 (11%) | 6/56 (11%) | > .90 |
| *Neuropathy progression, n (%)* | 17/113 (15%) | 13/57 (23%) | 4/56 (7.1%) | .020 |
| *New-onset gastrointestinal involvement, n (%)* | 16/113 (14%) | 8/57 (14%) | 8/56 (14%) | > .90 |
| *New tenosynovial involvement, n (%)* | | | | > .90 |
| *Carpal tunnel, n (%)* | 1/113 (0.9%) | 1/57 (1.8%) | 0/56 (0%) | |
| *Lumbar spinal stenosis, n (%)* | 1/113 (0.9%) | 1/57 (1.8%) | 0/56 (0%) | |
| *Amyloid deposits on endomyocardial biopsy, n (%)* | 7/113 (6.2%) | 2/57 (3.5%) | 5/56 (8.9%) | .30 |
| *Severe dysautonomia, n (%)* | 6/113 (5.3%) | 5/57 (8.8%) | 1/56 (1.8%) | .20 |
| *Death, n (%)* | 38/113 (33%) | 16/57 (28%) | 22/56 (39%) | .30 |
| *Cause of death* | | | | .40 |
| Cancer, n (%) | 1/38 (2.6%) | 0/16 (0%) | 1/22 (4.5%) | |
| Digestive bleeding, n (%) | 1/38 (2.6%) | 1/16 (6.3%) | 0/22 (0%) | |
| Amyloidosis progression, n (%) | 5/38 (13%) | 1/16 (6.3%) | 4/22 (18%) | |
| Graft failure, n (%) | 3/38 (7.9%) | 1/16 (6.3%) | 2/22 (9.1%) | |
| Heart transplant rejection, n (%) | 2/38 (5.3%) | 0/16 (0%) | 2/22 (9.1%) | |
| Intestinal obstruction, n (%) | 1/38 (2.6%) | 0/16 (0%) | 1/22 (4.5%) | |
| Massive bleeding | 1/38 (2.6%) | 0/16 (0%) | 1/22 (4.5%) | |
| Multiorgan failure, n (%) | 1/38 (2.6%) | 1/16 (6.3%) | 0/22 (0%) | |
| Neuropathy progression, n (%) | 2/38 (5.3%) | 2/16 (13%) | 0/22 (0%) | |
| Nonamyloid-related death, n (%) | 1/38 (2.6%) | 0/16 (0%) | 1/22 (4.5%) | |
| Pneumonia, n (%) | 1/38 (2.6%) | 1/16 (6.3%) | 0/22 (0%) | |
| Sepsis, n (%) | 11/38 (29%) | 6/16 (38%) | 5/22 (23%) | |
| Sudden cardiac death, n (%) | 4/38 (11%) | 1/16 (6.3%) | 3/22 (14%) | |
| Unknown | 4/38 (11%) | 2/16 (13%) | 2/22 (9.1%) | |
| *Ejection fraction after HT, %, median [IQR]* | 60.0 [54.5-63.5] | 60.0 [54.3-62.0] | 60.0 [55.0-65.0] | .50 |

HT, heart transplantation; IQR, interquartile range; ISHLT, International Society for Heart and Lung Transplantation.
Data are expressed as no. (%) or median [interquartile range].

with AL and multiple myeloma, who did not achieve hematologic response before or after HT, died due to disease progression 34 months after HT.

## Disease-modifying therapy in ATTR

Before HT, 4 patients with ATTRv and 5 with ATTRwt were on tafamidis (table 3). The median time from tafamidis initiation to HT was 16.3 months [IQR, 6.8-27.8 months] in patients with ATTRv and 13.8 months [IQR, 10.9-27.6 months] in patients with ATTRwt. Four patients (2 ATTRwt and 2 ATTRv) were on tafamidis before and after HT. One patient with ATTRv was on patisiran, initiated 5.7 months before transplantation.

After HT, 5 patients with ATTRv and 2 with ATTRwt were treated with tafamidis, with a median initiation time of 15.3 months [IQR, 1.7-58.3 months] for ATTRv and 4.9 months [IQR, 2.4-7.3 months] for ATTRwt. Eight patients with ATTRv received patisiran after HT

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

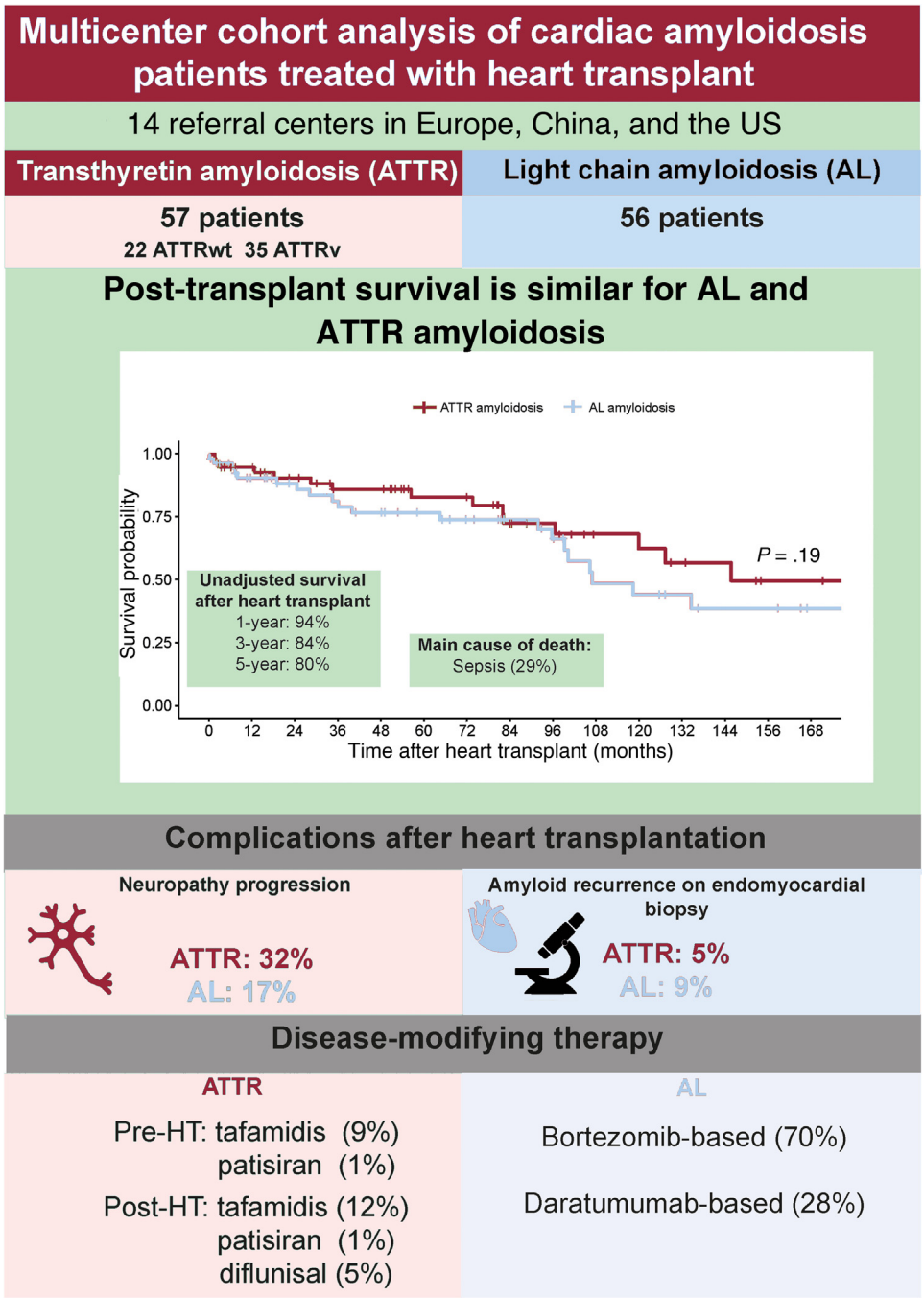


**Figure 1.** Central illustration. Unadjusted time-to-event analysis of post-heart transplantation mortality. AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; HT, heart transplantation; US, United States.

(1 of whom had already been on patisiran before HT), with a median initiation time of 83.1 months [IQR, 5.6-93.3 months]. Three ATTRv patients were treated with diflunisal post-HT, initiated at a median time of 74.2 months [IQR, 69.5-86.0 months] after HT.

### Disease-modifying therapy in AL

Among patients with AL, 40 (72%) had lambda light chain plasma cell dyscrasia. The most common underlying hematological disorder was multiple myeloma, diagnosed in 38 patients (69%), followed by smoldering myeloma in 10 (18%) (table 4). Twenty-one patients (42%) underwent autologous stem cell transplantation. Two patients underwent HT before initiation of chemotherapy. Chemotherapy was started a median of 8.54 months [IQR, 5.61-18.16 months] before HT and was administered for a median duration of 5.9 months [IQR, 3.15-10.01 months]. As first-line therapy, 37 patients (70%) received a bortezomib-based regimen, 15 (28%) received a daratumumab-based regimen, and 1 patient (2%) received upfront autologous stem cell transplantation. Before HT, the hematologic response was classified as no response in

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

**Table 3**
Disease-modifying therapy in patients with ATTR

| Variable | ATTRv (n = 15) | ATTRwt (n = 5) |
|---|---|---|
| Tafamidis before HT, n (%) | 4/15 (27%) | 5/5 (100%) |
| Time from tafamidis initiation to HT, mo, median [IQR] | −16.3 [−27.8 to −6.8] | −13.8 [−27.6 to −10.9] |
| Patisiran before HT, n (%) | 1/15 (6.7%) | 0/5 (0%) |
| Time from patisiran initiation to HT, mo, median [IQR] | −5.7 [−5.7 to −5.7] | |
| Tafamidis after HT, n (%) | 5/15 (33%) | 2/5 (40%) |
| Time from HT to tafamidis initiation, mo, median [IQR] | 15.3 [1.7-58.3] | 4.9 [2.4-7.3] |
| Duration of tafamidis therapy after HT, mo, median [IQR] | 33.5 [5.7-39.6] | 19.3 [16.9-21.7] |
| Patisiran after HT, n (%) | 8/15 (53%) | 0/5 (0%) |
| Time from HT to patisiran initiation, mo, median [IQR] | 83.1 [5.6-93.3] | |
| Duration of patisiran therapy after HT, mo, median [IQR] | 20.0 [8.0-27.9] | |
| Diflunisal after HT, n (%) | 3/15 (20%) | 0/5 (0%) |
| Time from HT to diflunisal initiation, mo, median [IQR] | 74.2 [69.5-86.0] | |
| Duration of diflunisal therapy after HT, mo, median [IQR] | 29.6 [26.0-42.3] | |

ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; HT, heart transplantation; IQR, interquartile range. Data are expressed as no. (%) or median [interquartile range].

11 patients (21%), partial response in 11 (21%), very good partial response in 9 (17%), and complete response in 22 (42%). After HT, chemotherapy was initiated a median of 5.65 months [IQR, 1.84-23.81 months] after HT and continued for a median duration of 9.37 months [IQR, 2.01-17.80 months]. Two patients received maintenance therapy with daratumumab. The post-transplant hematologic response was classified as no response in 8 patients (15%), partial response in 9 (17%), very good partial response in 7 (13%), and complete response in 29 (54%). Thirty-three patients (65%) received 1 line of therapy, 9 (18%) received 2 lines, and 5 (9%) received 3 lines (figure 2).

### Predictors of mortality

In the overall population, increased mortality risk was observed in patients who received advanced circulatory support (ventricular assist device, intra-aortic balloon pump, Impella, extracorporeal membrane oxygenation, or artificial heart; HR, 5.11; 95%CI, 2.37-11.0) and those with greater systemic involvement (1 involved organ system vs no systemic involvement: HR, 2.49; 95%CI, 1.01-6.12; ≥ 2 involved organ systems vs no systemic involvement: HR, 3.55; 95%CI, 1.44-8.75) (table S5). In subgroup analyses, advanced mechanical support remained associated with higher mortality in both patients with AL (HR, 5.59; 95%CI, 2.07-15.1) and those with ATTR (HR, 4.05; 95%CI, 1.08-15.2). Systemic involvement of ≥ 2 organ systems was associated with increased mortality only in patients with ATTR.

### HT distribution and outcomes in different eras

The distribution of amyloidosis subtypes varied by transplant era (figure 3). The proportion of patients with AL showed a nonmonotonic pattern that increased from the 1999 to 2007 period to the 2008 to 2015 period and then declined between 2016 and 2024. Over time, the proportion of patients with ATTRv decreased, while that of patients with ATTRwt increased. Among transplant eras, there was a trend toward improved survival in more recent periods (log-rank $P$ = .053, figure S2).

## DISCUSSION

In this multicenter study, we report the clinical characteristics, outcomes, and use of disease-modifying therapy in 113 patients with CA who underwent HT. The principal findings of the study are as follows: patients with AL amyloidosis presented with more advanced hemodynamic compromise at the time of HT, yet exhibited comparable survival to those with ATTR; extracardiac disease progression after HT was common in both AL and ATTR groups, confirming the multisystem nature of the disease; and disease-modifying therapy for ATTR was used infrequently before and after HT.

MCS was used as a bridge to HT in 25 patients (22%), a greater proportion compared with a cohort from the Mayo Clinic.[9] At that institution, 12.5% of patients (n = 7 of 55) were bridged to transplant with temporary MCS, including 1 patient with ATTRv supported with extracorporeal membrane oxygenation and 6 with intra-aortic balloon pump. In addition, 5 patients received durable MCS, 4 with a left ventricular assist device and 1 with a total artificial heart. A similar proportion of patients were bridged to transplant at the Cedars-Sinai Smidt Heart Institute, including 5 patients supported with a total artificial heart and 2 with biventricular assist devices.[19] Advanced MCS in this cohort was associated with a greater mortality risk. However, this likely reflects confounding by indication, as MCS is preferentially used in patients with more severe hemodynamic compromise.

Although MCS is technically challenging in CA due to small ventricular cavity size and restrictive physiology, MCS may be feasible in selected patients with favorable anatomy.[7] In a previous study, among 28 patients with restrictive physiology (1 AL, 9 ATTR), larger left ventricular end-diastolic and endsystolic dimensions were significantly associated with improved survival rates, and a left ventricular end-diastolic diameter > 46 mm was associated with reduced mortality after left ventricular assist device implantation.[20] These data support a tailored approach to MCS in amyloidosis, focusing on anatomical suitability rather than excluding patients based solely on etiology.[7]

### Survival outcomes in AL and ATTR

Despite presenting with more advanced hemodynamic compromise, patients with AL had survival outcomes similar to those

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

**Table 4**
Disease-modifying therapy in patients with AL

| Variable | n = 56 |
|---|---|
| *Light chain type, n (%)* | |
| *Kappa* | 15/55 (27%) |
| *Lambda* | 40/55 (72%) |
| *Positive immunofixation electrophoresis at diagnosis, n (%)* | 29/31 (94%) |
| *Free light chains lambda at diagnosis, mg/dL, median [IQR]* | 182.0 [18.0-246.0] |
| *Free light chains kappa at diagnosis, mg/dL, median [IQR]* | 16.3 [9.6-74.0] |
| *Bone marrow plasma cells at diagnosis, %* | 10.0 [5.8-14.3] |
| *Creatinine at diagnosis, mg/dL, median [IQR]* | 1.1 [0.9-1.2] |
| *Alkaline phosphatase, U/L, median [IQR]* | 126.0 [89.0-161.5] |
| *Proteinuria, g/24 h, median [IQR]* | 11.0 [0.2-240.0] |
| *Positive immunofixation electrophoresis before HT, n (%)* | 25/30 (83%) |
| *Free light chains lambda before HT, mg/dL, median [IQR]* | 25.1 [9.5-61.8] |
| *Free light chains kappa before HT, mg/dL, median [IQR]* | 17.3 [10.0-42.0] |
| *Hematological disease, n (%)* | |
| *MGUS* | 6/55 (11%) |
| *Smoldering myeloma* | 10/55 (18%) |
| *Multiple myeloma* | 38/55 (69%) |
| *Waldenström lymphoma* | 1/55 (1.8%) |
| *Autologous stem cell transplantation, n (%)* | 21/50 (42%) |
| *First AL-directed therapy, n (%)* | |
| *None* | 1/53 (1.9%) |
| *Bortezomib-based* | 37/53 (70%) |
| *Daratumumab-based* | 15/53 (28%) |
| *Number of therapy lines before HT, n (%)* | |
| 0 | 1/51 (2%) |
| 1 | 33/51 (65%) |
| 2 | 9/51 (18%) |
| 3 | 5/51 (9%) |
| 5 | 1/51 (2.0%) |
| 6 | 2/51 (2%) |
| 7 | 1/51 (2.0%) |
| *Hematologic response before HT, n (%)* | |
| No response | 11/53 (21%) |
| Partial response | 11/53 (21%) |
| Very good partial response | 9/53 (17%) |
| Complete response | 22/53 (42%) |
| *Hematologic response after HT, n (%)* | |
| No response | 8/54 (15%) |
| Partial response | 9/54 (17%) |
| Very good partial response | 7/54 (13%) |
| Complete response | 29/54 (54%) |
| Voluntary interruption of therapy | 1/54 (1.9%) |

AL, light chain amyloidosis; HT, heart transplantation; MGUS, monoclonal gammopathy of undetermined significance.
Data are expressed as no. (%) or median [interquartile range].

with ATTR. This finding likely reflects improved patient selection, younger age, and fewer comorbidities in the AL group. Earlier cohorts (HT between 2001 and 2007) reported worse post-transplant survival in AL compared with ATTR,[8] whereas the results of recent studies are consistent with our findings.[10,11] Improvements are likely attributable to advances in plasma cell-directed therapies[6] and stricter pretransplant screening protocols to exclude significant extracardiac involvement.[7,9]

Overall, survival among transplant recipients with CA has improved over time and is now comparable to that of nonamyloid transplant populations.[9–11] This positive trend is likely attributable to growing clinical experience in the management of advanced heart failure in CA, advances in AL-targeted therapies, and refinements in immunosuppression.[7]

Infections were the most common post-transplant complications, affecting 42% of patients, with similar rates in AL and ATTR, despite the potential added immunosuppressive burden from chemotherapy in AL. These findings are consistent with prior reports. For example, in a Stanford University cohort,[16] infections were reported in 61% of patients (total n = 31), and pneumonia was the most common.

Extracardiac progression is a major post-transplant challenge. Neurological progression (new-onset or worsening) occurred frequently (29% in ATTR and 14% in AL), as did gastrointestinal involvement (14% in both AL and ATTR). In contrast, only 1 patient with ATTRv developed carpal tunnel syndrome and lumbar spinal stenosis after HT. Comparable findings have been reported in a cohort of 12 patients from Columbia University.[10] Neurological progression occurred in 1 patient with ATTRwt and in 3 with ATTRv; gastrointestinal involvement was observed in 1 patient with ATTRwt and 4 patients with ATTRv. Interestingly, 4 patients developed new or relapsed carpal tunnel syndrome or lumbar spinal stenosis. Similarly, among 7 patients with ATTRwt who received transplants at the Mayo Clinic,[21] 1 had neurological progression, 2 had symptomatic gastrointestinal involvement, and 2 developed carpal tunnel syndrome requiring surgical release. These findings underscore the progressive multisystem nature of amyloidosis and highlight the importance of continued multiorgan monitoring and the potential role of disease-modifying therapies, even after HT.[10,21]

In this cohort, amyloid deposition in the cardiac allograft was found in 2 patients with ATTRv, of whom 1 died due to neuropathy progression. Similarly, in the Mayo Clinic cohort,[9] 1 patient with ATTRv showed amyloid deposition in the allograft and died from cardiac arrest 8 years post-HT. In addition, 5 patients with AL had evidence of allograft involvement; 1 patient without hematologic response before and after HT died due to disease progression. In contrast, over a 3-year follow-up, out of 51 patients with CA (13 AL, 38 ATTR) at the Cedars-Sinai Smidt Heart Institute,[19] no amyloid recurrence was detected in endomyocardial biopsies, suggesting that allograft deposition may take more time to develop. These observations reinforce the importance of achieving and maintaining deep hematologic response. With the introduction of novel agents such as daratumumab, outcomes are expected to improve in future cohorts.

In this study, only a minority of patients with ATTR received disease-modifying therapies either before or after transplantation. Even when prescribed, therapy was often initiated shortly before or long after HT. In the Columbia cohort,[10] no patients were on disease-modifying therapy before HT, and 2 patients were started on tafamidis and 1 on patisiran for neurological progression. The importance of specific therapy has been underscored by recent evidence. For instance, among patients with ATTRv amyloidosis experiencing polyneuropathy progression after liver transplantation, patisiran significantly improved neuropathy severity, quality of life, and autonomic symptoms.[22] The underuse of these drugs in our cohort likely reflects historical limitations in drug availability and reimbursement policies across countries, particularly in earlier eras. Broader use of targeted therapies may reduce recurrence risk and delay multisystem progression.

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

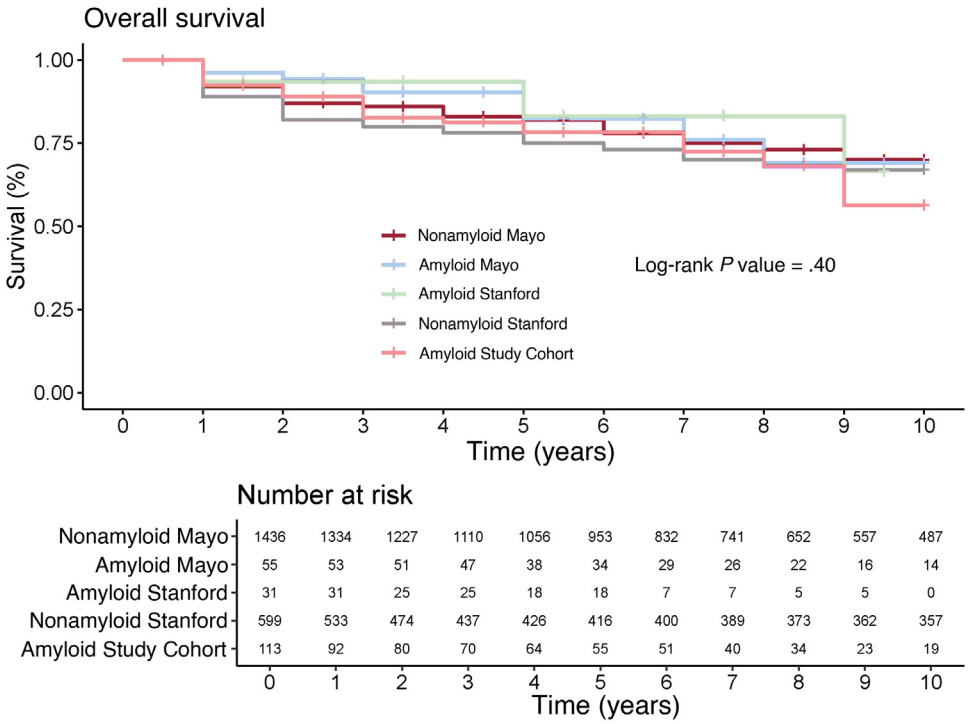


**Figure 2.** Survival analysis of the study cohort compared with amyloid and nonamyloid patient cohorts.

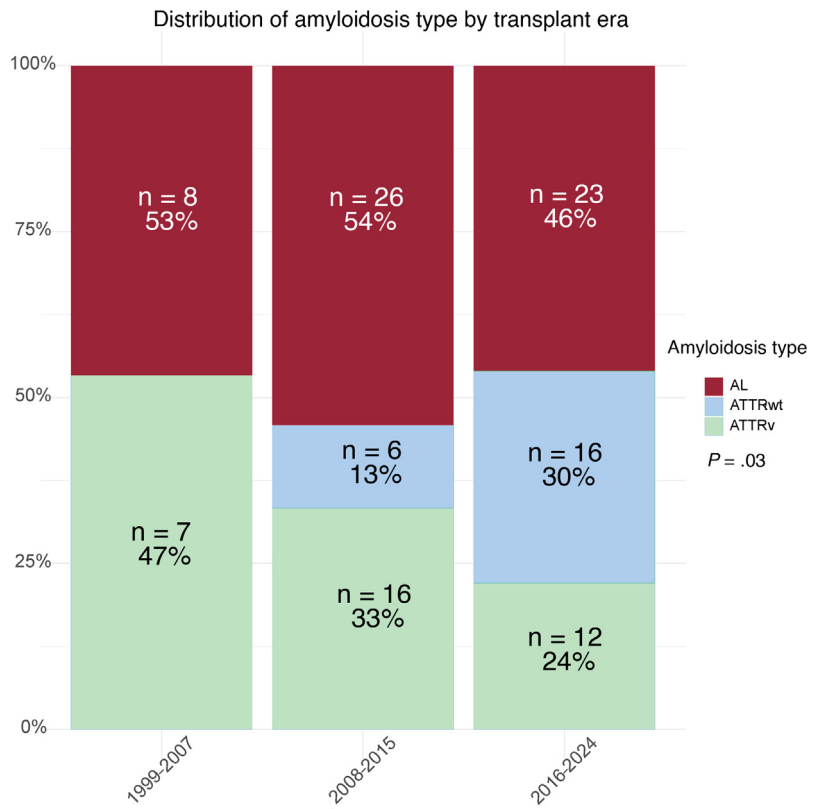


**Figure 3.** Distribution of amyloidosis type by transplant era. ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis.

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

When stratified into early (1999-2007), intermediate (2008-2015), and late (2016-2024) eras, we observed a trend toward improved outcomes in recent years. The increasing use of the noninvasive diagnostic algorithm[2] has contributed to an increase in the number of transplant recipients with ATTRwt, while the number of patients with ATTRv declined, likely reflecting the growing use of disease-modifying therapies in that subgroup.

The expanding availability of disease-modifying therapies is expected to reduce the need for HT in CA. However, for patients requiring transplantation, optimized integration of targeted therapies may prevent recurrence, prolong graft survival, and improve long-term outcomes.

This study represents one of the largest international multicenter cohorts of HT in CA introduces a 3-era temporal stratification, providing historical insight into the evolution of transplant practices and outcomes.

### Limitations

The retrospective design inherently introduces the risk of selection bias and unmeasured confounders. The sample size was relatively small, and the number of patients with long-term follow-up was limited. Important granular clinical data were not uniformly available among centers. Specific details regarding the type of temporary MCS (eg, Impella CP vs 5.5), induction immunosuppressive therapy, and pretransplant sensitization status were inconsistently captured. Given that infectious complications were a leading cause of morbidity and mortality in this cohort, the absence of detailed data on induction regimen limits our ability to fully characterize risk factors for post-transplant infections. Our study reflects real-world data, and specific institutional protocols regarding the selection and exclusion criteria for multiorgan transplantation were not available. Consequently, the absence of multiorgan transplants in the AL amyloidosis cohort may reflect a selection bias toward patients with isolated cardiac involvement or center-specific practices regarding systemic disease burden.

Institutional protocols for transplant eligibility, including criteria for multiorgan transplantation, were not uniformly available.

Although all diagnoses were established according to internationally accepted criteria valid at the time of diagnosis, differences in diagnostic algorithms and imaging availability may have contributed to heterogeneity. Access to disease-modifying therapies varied among countries and eras due to differences in drug approval, reimbursement policies, and local prescribing practices. The specific reasons for nonprescription were not captured. Consequently, treatment exposure was heterogeneous and may have influenced outcomes independently of disease characteristics, particularly in temporal comparisons.

Another important consideration is the heterogeneity among participating centers. Differences in referral patterns, patient selection criteria, and management strategies, including the use and timing of MCS, transplantation protocols, and disease-modifying therapies, may have influenced the observed outcomes. This variability reflects real-world clinical practice but may limit the comparability of patients among centers and should be taken into account when interpreting our findings. In addition, surveillance for amyloid recurrence was not standardized among centers and relied on local clinical practice. Routine imaging screening with scintigraphy or single-photon emission computed tomography was not performed, which may have led to underdetection of subclinical amyloid recurrence.

## CONCLUSIONS

This study, one of the largest international multicenter cohorts of HT in CA, introduces a 3-era temporal stratification that provides historical insight into the development of transplant practices and outcomes. Our data suggest that HT may represent a feasible and effective therapeutic option for patients with CA. Unadjusted post-transplant survival was similar in patients with AL and ATTR. However, this finding should be interpreted with caution, as it is subject to important limitations, including sample size and intercenter variability. A multidisciplinary approach, meticulous perioperative management, and rigorous post-transplant surveillance, including the integration of disease-modifying therapies, are essential to prevent recurrence and extend graft survival. Further prospective studies are needed. Survival analyses were unadjusted, and baseline differences between groups limit direct comparisons. Therefore, our findings should be interpreted as exploratory and hypothesis-generating.

### WHAT IS KNOWN ABOUT THE TOPIC?

- CA is a progressive infiltrative cardiomyopathy that can lead to advanced heart failure requiring HT.
- Historically, outcomes after HT were poorer in patients with AL due to systemic involvement and limited hematologic therapies.
- More recent advances in plasma cell-directed treatments and disease-modifying therapies for ATTR have improved overall prognosis.
- However, data on post-transplant outcomes, extracardiac disease progression, and real-world use of targeted therapies remain limited, particularly in contemporary multicenter cohorts.

### WHAT DOES THIS STUDY ADD?

- In this large international multicenter cohort of patients with CA who underwent HT, post-transplant survival was comparable between AL and ATTR, despite more advanced pretransplant hemodynamic compromise in AL.
- Extracardiac disease progression after HT was frequent in both subtypes, highlighting the multisystem nature of amyloidosis.
- Use of disease-modifying therapy for ATTR was limited before and after transplantation.
- Temporal analysis among 3 eras suggests outcome improvements over time, likely reflecting advances in patient selection, disease-modifying therapies, and transplant management.

## DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

## FUNDING

This work has received no funding.

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

## ETHICAL CONSIDERATIONS

Ethics approval was obtained from the coordinating center, and each participating center confirmed approval from its local institutional review board/ethics committee for the conduct of observational research. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for the collection and use of observational data was obtained from all participants in accordance with local regulations. The study adhered to SAGER (Sex and Gender Equity in Research) guidelines. Biological sex was recorded and reported in baseline characteristics. However, sex-stratified analyses were not performed due to the limited sample size and insufficient statistical power to detect sex-specific differences.

## STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

During the preparation of this work, the authors used Gemini (Google) to improve the language and readability of the manuscript. Following this process, the authors reviewed and edited the generated content and assume full responsibility for the integrity and accuracy of the final publication. No data were analyzed, generated, interpreted, or processed using AI. All study design, data collection, statistical analyses, and scientific conclusions were performed by the authors.

## AUTHORS' CONTRIBUTIONS

Conceptualization: F. Cappelli, A. Argirò, F. Perfetto, S. Longhi, L. Potena, M. Fontana, J. Gillmore, P. García-Pavía, W.E. Moody, C. Di Nora, M.A. Urey, Q.M. Bui, A. Masri, A. Gasperetti, P. Milani, G. Palmiero, A. Cipriani, G. Limongelli, B. Musumeci, G. Tini, M. Pieroni. Data curation: F. Colio, M. Garofalo, G. Saturi, M. Allinovi, A. Aloisio, A. Porcari, A. Sheikh, M. Gómez Bueno, S. Menale, C. Thornton, L. Herrador, J. González-Costello, F. de Frutos, I. Vendramin, M. Imazio, M. Merlo, G. Sinagra, Q.M. Bui, A. Masri, Z. Chen, L. Chen, P. Milani, B. Cattadori, G. Palmiero, G. Tini. Formal analysis: A. Argirò. Project administration: A. Argirò. Writing – original draft: A. Argirò, F. Colio, M. Garofalo, L. Potena, G. Saturi, M. Allinovi, A. Aloisio, A. Porcari, A. Sheikh, M. Gómez Bueno, S. Menale, C. Thornton, L. Herrador, J. González-Costello, F. de Frutos, C. Di Nora, I. Vendramin, M. Imazio, Q.M. Bui, A. Masri, Z. Chen, P. Milani, B. Cattadori, G. Sinigiani, G. Gerosa, G. Palmiero, G. Tini. Writing – review & editing: S. Longhi, L. Potena, M. Fontana, J. Gillmore, P. García-Pavía, W.E. Moody, J. González-Costello, F. de Frutos, M. Imazio, M. Merlo, G. Sinagra, M.A. Urey, A. Gasperetti, G. Palmiero, G. Limongelli, B. Musumeci, M. Pieroni, F. Perfetto, F. Colio.

## CONFLICTS OF INTEREST

Q.M. Bui is supported by an AHA Career Development Award (24CDA1272533) and reports consulting fees from Papillon Therapeutics. M.A. Urey receives honoraria for consulting from Alnylam, AstraZeneca, BridgeBio, and Pfizer. A. Masri reports research grants from Pfizer, Ionis, Attralus, Cytokinetics, and Janssen and consulting fees from Cytokinetics, BMS, BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Akros, Edgewise, Rocket, Lexeo, Prothena, BioMarin, AstraZeneca, Avidity, Neurimmune, and Tenaya. P. García-Pavía is associate editor of *Revista Española de Cardiología*; the journal's editorial procedure to ensure impartial handling of the manuscript has been followed. He reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio, Intellia, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio, General Electric, Intellia, Neurimmune, Novo Nordisk, and Pfizer; and research/educational support to his institution from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio, Intellia, Novo Nordisk, and Pfizer. F. Cappelli reports speaking fees and consulting activity from Pfizer, Alnylam, Bayer, BridgeBio, AstraZeneca, and Novo Nordisk. F. Perfetto reports speaking fees and consulting activity from Pfizer, Alnylam, and AstraZeneca. M. Pieroni reports speaking fees from Sanofi, Chiesi, Amicus, BMS, and Cytokinetics. M. Fontana is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/18/21/33447) and reports consultancy/advisory boards for Alnylam, Alexion/Caelum Biosciences, AstraZeneca, BridgeBio/Eidos, Prothena, Attralus, Intellia Therapeutics, Ionis Pharmaceuticals, Cardior, Lexeo Therapeutics, Janssen Pharmaceuticals, Pfizer, Novo Nordisk, Bayer, and Mycardium. J.D. Gillmore reports consultancy/advisory boards for Alnylam, AstraZeneca, Attralus, Eidos, Intellia Therapeutics, Ionis Pharmaceuticals, and Pfizer. A. Argirò reports consulting activity for Lexeo Therapeutics. All other authors have no conflicts of interest related to this work to declare.

## APPENDIX B. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2026.06.005.

## REFERENCES

1. Gillmore JD, Hawkins PN. Pathophysiology and treatment of systemic amyloidosis. *Nat Rev Nephrol.* 2013;9:574–586.
2. Garcia-Pavia P, Rapezzi C, Adler Y, et al.Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail.* 2021;23:512–526.
3. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med.* 2025;392:33–44.
4. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2018;379:1007–1016.
5. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2024;390:132–142.
6. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. *N Engl J Med.* 2021;385:46–58.
7. Witteles RM. Cardiac transplantation and mechanical circulatory support in amyloidosis. *JACC CardioOncol.* 2021;3:516–521.
8. Dubrey SW, Burke MM, Hawkins PN, et al. Cardiac transplantation for amyloid heart disease: the United Kingdom experience. *J Heart Lung Transplant.* 2004;23:1142–1153.
9. Lyle MA, Farina JMM, Wiedmeier-Nutor E, et al. Amyloidosis and heart transplantation in a new era. *Clin Transplant.* 2025;39:e70070.
10. Griffin JM, Chiu L, Axsom KM, et al. Outcomes after heart transplantation for al compared to ATTR cardiac amyloidosis. *Clin Transplant.* 2020;34:e14028.
11. Kraus MJ, Smits JM, Meyer AL, et al. Outcomes in patients with cardiac amyloidosis undergoing heart transplantation: the eurotransplant experience. *J Heart Lung Transplant.* 2023;42:778–785.
12. Razvi Y, Porcari A, Di Nora C, et al. Cardiac transplantation in transthyretin amyloid cardiomyopathy: outcomes from three decades of tertiary center experience. *Front Cardiovasc Med.* 2023;9:1075806.
13. International Myeloma Working, Group, Criteria for the classification of monoclonal gammopathies, multiple myeloma, related disorders: a report of the International Myeloma Working Group. *Br J Haematol.* 2003;121:749–757.
14. Rajkumar SV, Dimopoulos MA, Palumbo A, et al.International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15:e538–e548.
15. Leung N, Comenzo R, Gillmore J, et al. Renal response criteria for clinical trials in amyloid light chain amyloidosis. *Kidney Int Rep.* 2024;9:1986–1994.
16. Barrett CD, Alexander KM, Zhao H, et al. Outcomes in patients with cardiac amyloidosis undergoing heart transplantation. *JACC Heart Fail.* 2020;8:461–468.
17. Lacy MQ, Dispenzieri A, Hayman SR, et al. Autologous stem cell transplant after heart transplant for light chain (Al) amyloid cardiomyopathy. *J Heart Lung Transplant.* 2008;27:823–829.
18. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med.* 2008;359:906–917.

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005

19. Chen Q, Moriguchi J, Levine R, et al. Outcomes of heart transplantation in cardiac amyloidosis patients: a single center experience. *Transplant Proc.* 2021;53:329–334.
20. Grupper A, Park SJ, Pereira NL, et al. Role of ventricular assist therapy for patients with heart failure and restrictive physiology: improving outcomes for a lethal disease. *J Heart Lung Transplant.* 2015;34:1042–1049.
21. Rosenbaum AN, AbouEzzeddine OF, Grogan M, et al. Outcomes after cardiac transplant for wild type transthyretin amyloidosis. *Transplantation.* 2018;102:1909–1913.
22. Schmidt HH, Wixner J, Planté-Bordeneuve V, et al. Patisiran treatment in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy after liver transplantation. *Am J Transplant.* 2022;22:1646–1657.

Please cite this article in press as: Argirò A, et al. Multicenter cohort analysis of cardiac amyloidosis patients treated with heart transplant. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2026.06.005