ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 2042–2050
Published online 13 April 2023 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14337

ORIGINAL ARTICLE

Patients with cardiac amyloidosis are at a greater risk of mortality and hospital readmission after acute heart failure

Emmanuelle Berthelot[1,2]*, Amaury Broussier[3,4], Luc Hittinger[5], Cristiano Donadio[6], Xavier Rovani[7], Emmanuel Salengro[8], Richard Megbemado[9], Christian Godreuil[10], Joel Belmin[6], Jean Philippe David[3,4], Bastien Genet[11], Thibaud Damy[5] and FINC-94 Network

[1]*Université Paris Sud, Paris, France;* [2]*Department of Cardiology, AP-HP, Hopital Bicêtre, 78, rue du général Leclerc, Le Kremlin Bicêtre, 94043, Paris, France;* [3]*Department of Geriatrics, AP-HP, Henri-Mondor/Emile-Roux Hospitals, Paris, France;* [4]*Univsité Paris Est Créteil, INSERM, IMRB, Paris, France;* [5]*Department of Cardiology, Heart Failure and Amyloidosis Unit, Referral Center For Cardiac Amyloidosis, Université Paris Est, AP-HP, Henri-Mondor/Albert-Chenevier Hospitals, Paris, France;* [6]*Department of Geriatrics, AP-HP, Hôpital Charles Foix and Sorbonne Université, Paris, France;* [7]*Hopital Privé Paul Dégine, Paris, France;* [8]*Centre Hospitalier de Villeneuve St Georges, Paris, France;* [9]*Hôpital Sainte Camille, Paris, France;* [10]*Hôpital d'Instruction des Armées Bégin, Paris, France; and* [11]*BioStatistics Unit, AP-HP, Paris, France*

Abstract

Aims Cardiac amyloidosis (CA) is an under-diagnosed cause of heart failure (HF) and has a worse prognosis than other forms of HF. The frequency of death or rehospitalization following discharge for acute heart failure (AHF) in CA (relative to other causes) has not been documented. The study aims to compare hospital readmission and death rates 90 days after discharge for AHF in patients with vs. without CA and to identify risk factors associated with these events in each group.

Methods and results Patients with HF and CA (HF + CA+) were recruited from the ICREX cohort, after screening of their medical records. The cases were matched 1:5 by sex and age with control HF patients without CA (HF + CA−). There were 27 HF + CA + and 135 HF + CA− patients from the ICREX cohort included in the study. Relative to the HF + CA− group, HF + CA+ patients had a higher heart rate (P = 0.002) and N-terminal prohormone of brain natriuretic peptide levels ($P < 0.001$) and lower blood pressure ($P < 0.001$), weight, and body mass index values ($P < 0.001$) on discharge. Ninety days after discharge, the HF + CA+ group displayed a higher death rate, a higher all-cause hospital readmission rate, and a higher hospital readmission rate for AHF. Death and hospital readmissions occurred sooner after discharge in the HF + CA+ group than in the HF + CA− group.

Conclusions The presence of CA in patients with HF was associated with a three-fold greater risk of death and a two-fold greater risk of all-cause hospital readmission 90 days after discharge. These findings emphasize the importance of close, active management of patients with CA and AHF.

Keywords Cardiac amyloidosis; Acute heart failure; Stratification; Prognosis

Received: 22 August 2022; Revised: 13 February 2023; Accepted: 16 February 2023
*Correspondence to: Emmanuelle Berthelot, Department of Cardiology, AP-HP, Hopital Bicêtre, 78, rue du général Leclerc, Le Kremlin Bicêtre, Paris 94043, France.
Email: emmanuelle.berthelot@gmail.com

Introduction

Heart failure (HF) is a very common disease that affects 1–2% of adults in Europe.[1,2] As a major public health issue, HF is notably associated with a high hospital readmission rate after an acute cardiac event[3]: 20% at 30 days[4] and 67% at 12 months.[5] We have reported previously that arrhythmia and infection are the primary triggering factors for decompensation [i.e. acute heart failure (AHF)] causing hospital admissions.[6] A recent study showed that 66% of patients suffering from HF with preserved ejection fraction (HFpEF) and 64% of those suffering from HF with reduced ejection fraction

died in the 5 years following AHF.[7] In order to improve the management and prognosis of patients with HF, the European Society of Cardiology (ESC) recommends a phenotype-based approach and a better etiological diagnosis—particularly in HFpEF.[1]

Cardiac amyloidosis (CA) is underdiagnosed in HF in general and in HFpEF in particular. The different forms of CA are classified according to the composition of fibrils involved in infiltration of the various organs. The most frequent cardiac forms are transthyretin amyloidosis (ATTR) and immunoglobulin light chain amyloidosis (AL). ATTR amyloidosis is subdivided into a transthyretin wild-type form (ATTRwt) and a mutant (variant) form (ATTRv). ATTR might account for 13% of cases of HFpEF with left ventricular hypertrophy ≥12 mm.[8] The availability of specific, effective treatments for ATTR means that the diagnostic management of HFpEF should be improved. The diagnostic approach to cases of suspected CA has been standardized.[9–13] The median survival time depends on the type of amyloidosis, with estimates of 11 and 75 months for AL amyloidosis and ATTRwt-CM, respectively.[14–16] To the best of our knowledge, the hospital readmission and death rates for HF patients with vs. without CA have not been reported.

We hypothesized that relative to HF patients without CA (HF + CA−), HF patients with CA (HF + CA+) have a worse prognosis and differ with regard to the causes of hospital readmission after AHF. Hence, the objectives of the present study were to compare the rate of death and hospital readmission rates 90 days after discharge for AHF in HF + CA− vs. HF + CA+ patients and to identify the main risk factors for hospital readmission in each group.

Methods

Study design

ICREX-94 was a non-interventional, observational, longitudinal, multicentre cohort study conducted in 10 cardiology or geriatric cardiology departments from public- or private-sector hospitals in the Val-de-Marne county of France. Patients were included prospectively but the data were recorded retrospectively. In 2016, the 10 departments had formed the FINC94 network in order to share experience, train healthcare professionals, and conduct clinical studies in the field of HF.

Between October 2017 and January 2019, consecutive patients aged 18 or over and having been discharged from hospital alive after admission for AHF were screened for eligibility. The diagnosis of AHF was based on the patient's signs and symptoms, a serum N-terminal prohormone of brain natriuretic peptide (NTproBNP) level >100 pg/mL on admission, and echocardiographic evidence of HF, in line with the ESC guidelines.[1] Patients who did not understand French or who were unable to provide informed consent. The study was performed in compliance with the tenets of the Declaration of Helsinki and was approved by an institutional review board [*Commission éthique et déontologie de la Faculté de Médecine Paris-Saclay* (Le Kremlin-Bicêtre, France); reference: 20181128163709]. All the patients gave their written, informed consent to participation in the study.

Baseline data collection

Data collection at baseline has been described in detail elsewhere.[6] Briefly, we documented the type of HF (i.e. right-sided, left-sided or both), the aetiology of HF, the date of diagnosis, the clinical characteristics (including geriatric comorbidities such as dementia and depression), electrocardiogram (ECG) data (sinus rhythm, atrial fibrillation, etc.), laboratory data (such as the blood haemoglobin level and the serum NTproBNP and creatinine levels), echocardiographic characteristics [such as the left ventricular ejection fraction (LVEF)], medications (including the doses), and whether the patient had a pacemaker or an implantable cardioverter defibrillator. We also determined the Human Development Index (HDI, a composite, long-term index of life expectancy, education, and *per capita* income) for each study participant, based on their region of residence.

Definition of cases and controls

The medical records of ICREX-94 participants were reviewed. Twenty-seven patients with HF had a definitive diagnosis of CA and thus formed the HF + CA + group. These cases were matched 1:5 by sex and age with control HF patients without CA (forming the HF + CA− group).

Diagnosis of cardiac amyloidosis

CA was diagnosed according to the ESC guidelines.[10] When CA was suspected, scintigraphy with a bisphosphonate tracer (99mTc-hydroxymethylene diphosphonate) was performed, and blood and urine samples were analysed with protein electrophoresis, immunofixation, and a light chain assay. When the light chain assay was positive, a confirmatory cardiac biopsy was taken and stained for light chains, as described elsewhere.[17]

Follow-up data collection

Patients were followed up for 90 days after discharge from hospital, via direct phone calls and correspondence by mail. If the patient did not reply to our calls or letters, we

contacted his/her family, caregiver, family physician, or cardiologist. Hospital readmissions within 90 days of discharge were recorded, and the same clinical, ECG, and laboratory data were collected as on first admission. The readmitted patients' medical records were analysed independently by two clinical endpoints committees, and the cause and mode of hospital readmission were determined. Any disagreement between the two committees was resolved by a third committee.

Statistical analysis

Continuous variables were presented as the mean [standard deviation (*SD*)] or the median [interquartile range (IQR)]. Categorical variables were presented as the number (percentage). Values of continuous variables were compared in an unpaired *t*-test or (for non-normally distributed data) a Mann–Whitney test. The normality of the data distribution was assessed graphically (i.e. without using QQ plots or statistical tests). Values of categorical variables were compared in a chi-squared test or Fisher's exact test, as appropriate. We first studied differences between excluded controls and included controls with regard to demographic variables, personal medical history, clinical and laboratory features at admission for AHF, ultrasound findings, reasons for admission, and treatments on admission (*Supporting information Appendix S1*). Next, CA cases were matched 1:5 by sex and age with control HF patients without CA (forming the HF + CA− group) using the Match function in R Studio software and a calliper of one. Cases and controls were also compared with regard to their characteristics upon discharge (clinical variables and medications), during follow-up and on hospital readmission (the indication, clinical characteristics, laboratory variables, and ultrasound findings). We plotted survival curves for the 90 day death and hospital readmission rates (stratified by CA status) and compared them in a log-rank test. Multivariable conditional Cox regression models with an exact method were applied. The final models for all-cause mortality and hospitalization were chosen with reference to the level of concordance and the Akaike information criterion. Adjustment variables were included in the model if they were judged to be clinically relevant and gave a P value <0.20 in our unadjusted analyses, in line with Sun et al.'s conservative approach.[18] The results were quoted as unadjusted and adjusted hazard ratios (95% confidence interval). The proportional hazards hypothesis (Schoenfeld residuals and a graphic evaluation) and log-linearity (Martingale residuals) were checked for all models. All tests were two-sided, and the threshold for statistical significance was set to $P < 0.05$. Because this was an exploratory analysis, we did not adjust for multiple testing.[19]

Results

Characteristics of the study population of ICREX-94 participants

Between October 2017 and January 2019, 27 HF + CA+ cases were identified and matched 1:5 with 135 HF + CA− controls (i.e. ICREX-94 participants without CA). Hence, 162 of the 305 patients in the ICREX-94 cohort were included in the present study. In the HF + CA+ group, 13 participants had ATTRwt-CA, 6 had ATTRv-CA, and 7 had AL-CA (all 7 with lambda chains, and 1 with kappa chains). Overall, the mean (*SD*) age was 76,[9] and 144 of the patients (89%) were women (*Table 1*). Regarding comorbidities, 114 (70%) patients had a history of HF, 72 (44%) had a history of coronary artery disease, 61 (38%) had a history of diabetes, 108 (67%) were in atrial fibrillation, 29 (18%) had an LVEF >50%, and 68 (42%) had an LVEF <40%.

Characteristics of the patients, as a function of their cardiac amyloidosis status on initial admission to hospital

The clinical profiles of the patients hospitalized for AHF differed according to the CA status on admission (*Table 1*). Relative to the patients in the HF + CA− group, the patients in the HF + CA+ group had a lower HDI ($P < 0.01$), a higher serum NTproBNP level ($P = 0.005$), and a lower blood sodium level ($P < 0.001$) and were less likely to be smokers ($P < 0.02$). On discharge, the patients in the HF + CA + group had a higher heart rate ($P = 0.002$), a higher NTproBNP levels ($P < 0.001$), a lower systolic blood pressure, a lower body weight, and a lower body mass index (BMI) ($P < 0.001$). Regarding medications on discharge, the HF + CA+ patients took higher doses of diuretics ($P < 0.001$) and lower doses of beta-blockers ($P < 0.001$) and ACEis ($P = 0.04$) and were more likely to have received a pacemaker ($P = 0.003$) or an implantable cardioverter-defibrillator ($P < 0.001$), relative to the HF + CA− group. There were no intergroup differences in age (as expected), diabetes, hypertension, LVEF on admission, and the length of hospital stay for the initial AHF event (*Table 2*).

Patient outcomes at 90 days

At 90 days, 17 of the 162 patients discharged from hospital had died: 9 (33%) in the HF + CA+ group and 8 (6%) in the HF + CA− group ($P < 0.001$ and log rank <0.001; *Table 2* and *Figure 1B*).

The HF + CA+ group had a higher all-cause hospital readmission rate (52%, vs. 27% in the HF + CA− group;

Table 1 Baseline characteristics on admission to hospital for AHF, by CA status

	Total study population (n = 162)	HF + CA+ (n = 27)	HF + CA− (n = 135)	P[a]
Demographic and clinical characteristics				
Age, mean (*SD*)	76 (±9)	76 (±8)	76 (±9)	0.73
Age >85 years old, *n* (%)	27 (17)	3 (11)	24 (18)	0.82
Female, *n* (%)	144 (89)	24 (89)	120 (89)	0.99
Coronary heart disease, *n* (%)	72 (44)	8 (30)	64 (47)	0.09
Atrial fibrillation, *n* (%)	108 (67)	20 (74)	88 (65)	0.37
Hypertension, *n* (%)	112 (69)	15 (56)	97 (72)	0.09
Diabetes, *n* (%)	61 (38)	7 (26)	54 (40)	0.17
Chronic kidney disease, *n* (%)	82 (51)	18 (67)	64 (47)	0.07
COPD, *n* (%)	36 (22)	3 (11)	33 (24)	0.13
History of heart failure, *n* (%)	114 (70)	23 (85)	91 (67)	0.07
Mild neurocognitive disorder, *n* (%)	10 (6)	3 (11)	7 (5)	0.37
Stroke, *n* (%)	24 (15)	2 (7)	22 (16)	0.24
Smoking, *n* (%)	24 (15)	0 (0)	24 (18)	0.02
Alcohol use, *n* (%)	15 (9)	0 (0)	15 (11)	0.07
HDI, mean (*SD*)	0.52 (±0.16)	0.45 (±0.25)	0.53 (±0.13)	0.01
Laboratory data and ultrasound findings				
NTproBNP, median [IQR]	4575 [2279–10 424]	9294 [3534–13 292]	3730 [1765–8443]	0.005
Creatininemia (μmol/L)	150 (±164)	152 (±50)	149 (±179)	0.93
Blood potassium, mean (*SD*)	4.3 (±0.5)	4.2 (±0.5)	4.3 (±0.5)	0.37
Blood sodium, mean (*SD*)	138 (±4)	136 (±5)	139 (±4)	<0.001
LVEF on admission, median [IQR]	40 [30–50]	45 [35–50]	30 [39–50]	0.25
>50%	29 (18)	3 (11)	26 (19)	0.99
40–50%	42 (26)	7 (26)	35 (26)	0.40
<40%	68 (42)	7 (26)	61 (45)	0.50
Missing data	23 (14)	10 (37)	13 (10)	—

Abbreviations: AHF, acute heart failure; CA, cardiac amyloidosis; HF, heart failure; COPD, chronic obstructive pulmonary disease; HDI, Human Development Index; NTproBNP, N terminal pro brain natriuretic peptide; LVEF, left ventricular ejection fraction.
[a]*P*: chi-squared test or Fisher's exact test for categorical variables, and Student's test or the Wilcoxon–Mann–Whitney test for continuous variables.

P = 0.001) and a higher hospital readmission rate due to AHF (48% vs. 23%, respectively; *P* = 0.001) (*Figure* 1C). Death and hospital readmission occurred earlier in the HF + CA+ group than in the HF + CA− group (respectively 42 vs. 128 days for death and 19 vs. 40 days for hospital readmission; *Table 2* and *Figure 1A*).

The two risk factors associated with all-cause death and hospital readmission for AHF at 90 days were CA status and diuretic use on admission (*Table 3*).

Discussion

In a prospective study of patients with and without CA hospitalized for AHF, we found that amyloidosis status was associated with (i) a lower survival rate at 90 days and (ii) a higher frequency of hospital readmissions for any cause and for AHF relatively soon after the initial discharge. These findings demonstrate that morbidity and mortality rates are greater in HF patients with CA than in patients with other types of HF.

Death following hospital admission for acute heart failure

Cardiac involvement is common in patients with systemic amyloidosis and is characterized by a poor prognosis and a limited choice of treatment modalities.[20,21] The latest treatment strategies focus on (i) the prevention and treatment of complications and (ii) stopping or delaying amyloid deposition with specific treatments.[21–23] Depending on the type of amyloidosis, these treatments include chemotherapy and immunotherapy for AL-CA and TTR stabilizers for ATTR-CA.[21] In a previous study, HF with amyloidosis was associated with greater probabilities of in-hospital mortality and 30 day readmission and a longer mean length of stay.[24]

Our results showed that in a cohort of patients with decompensated AHF, CA was associated with a greater mortality rate—despite the similar age, sex ratio and LVEF, a lower BMI, and a higher dose of diuretics on discharge, relative to the HF + CA− group. On admission, the HF + CA+ group had a higher NTproBNP level, a lower blood sodium level, and a lower HDI. On discharge, the HF + CA+ group had a higher heart rate and a lower blood pressure—both of which are factors known to be associated with a poor outcomes in HF.[1]

Table 2 Discharge characteristics and follow-up, by CA status

	Overall (n = 162)	HF + CA+ (n = 27)	HF + CA− (n = 135)	P[a]
Clinical characteristics on discharge				
BMI (kg/m^2), mean (*SD*)	27 (±7)	23 (±3)	28 (±7)	<0.001
Height (cm), mean (*SD*)	170 (±8)	172 (±6)	169 (±8)	0.06
Weight (kg), mean (*SD*)	75.2 (±19.7)	65.4 (±9.70)	78.5 (±21.1)	0.004
Heart rate (ppm), mean (*SD*)	73 (±13)	80 (±9)	70 (±13)	0.002
SBP (mmHg), mean (*SD*)	120 (±20)	108 (±20)	124 (±19)	<0.001
DBP (mmHg), mean (*SD*)	69 (±12)	71 (±9)	68 (±13)	0.17
Length of stay, median [IQR]	10 [7–13]	11 [6.5–13]	10 [7–13.5]	0.72
Prescriptions on discharge				
Beta-blockers, *n* (%)	106 (65)	0 (0)	106 (79)	<0.001
Dose (mg), median [IQR]	3.75 [2.5–6.25]	0 [0–0]	3.75 [2.5–6.25]	-
ACEis, *n* (%)	71 (44)	4 (15)	67 (50)	<0.001
Dose (mg), median [IQR]	3 [2.375–5]	7.5 [5–7.5]	2.5 [2–5]	0.04
ARBs, *n* (%)	12 (7)	0 (0)	12 (9)	0.22
Dose (mg), median [IQR]	16 [8–45]	-	16 [8–45]	-
Diuretics, *n* (%)	139 (86)	26 (96)	113 (84)	0.20
Dose (mg), median [IQR]	80 [40–134]	160 [120–250]	80 [40–120]	<0.001
Aldosterone antagonists, *n* (%)	37 (23)	5 (19)	32 (24)	0.62
Dose (mg), median [IQR]	25 [12.5–25]	50 [25–50]	25 [12.5–25]	0.04
Anti-arrhythmic, *n* (%)	61 (38)	14 (52)	47 (35)	0.11
Pacemaker, *n* (%)	26 (16)	10 (37)	16 (12)	0.003
Defibrillator, *n* (%)	30 (19)	13 (48)	17 (13)	<0.001
Follow-up				
90 day all-cause mortality, *n* (%)	10 (6)	8 (30)	2 (1)	<0.001[1]
Time to death, median [IQR]	116 [42–170]	42 [23.2–59.5]	128 [118–262]	0.02
90 day all-cause hospital readmission, *n* (%)	51 (31)	14 (52)	37 (27)	0.001[1]
Time to all-cause hospital readmission, median [IQR]	31 [19–83]	19[13–34]	40 [25–94.25]	0.02
Hospital readmission for AHF, *n* (%)	44 (27)	13 (48)	31 (23)	0.03
Hospital readmission for other reasons, *n* (%)	20 (12)	3 (11)	17 (12)	0.99

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARNi, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CA, cardiac amyloidosis; COPD, chronic obstructive pulmonary disease; HDI, Human Development Index; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; SBP, systolic blood pressure.

The data are quoted as the number (%), or mean ± *SD*.

[a]*P*: chi-squared test or Fisher's exact test for categorical variables, and Student's test or the Wilcoxon-Mann–Whitney test for continuous variables.

The death rate 90 days after AHF is not frequently reported. In the GREAT study,[25] this rate was 15%. In the OPTIMIZE registry, the 60 to 90 day post-discharge mortality rate was 8.6%.[26] In a recent trial, the estimated annual rate of death due to a cardiovascular cause was around 7%.[27,28]

The prognosis of patients with CA depends on the type of amyloidosis: ATTRwt-CA, ATTRv-CA, or AL-CA.[14–16] Among patients with ATTR-CA, the median time to death was significantly shorter for individuals not taking a transthyretin stabilizer (2.2 years, vs. 5.4 years in those taking a transthyretin stabilizer; $P < 0.0001$ in a log-rank test).[29] Few data on the prognosis at 90 days have been published.[8]

In the present study, the 90 day death rate was much higher in the HF + CA+ group (33%) than in the HF + CA− group (6%). A high mortality rate in patients with CA (whatever the type) has already been reported.[14–16] This is an important message to adapt the care management of these patients.[30] Consequently, identification of such patients at high risk of early death becomes a major goal to implement advanced individual treatment strategies to enable subsequent treatment depending on the cause.

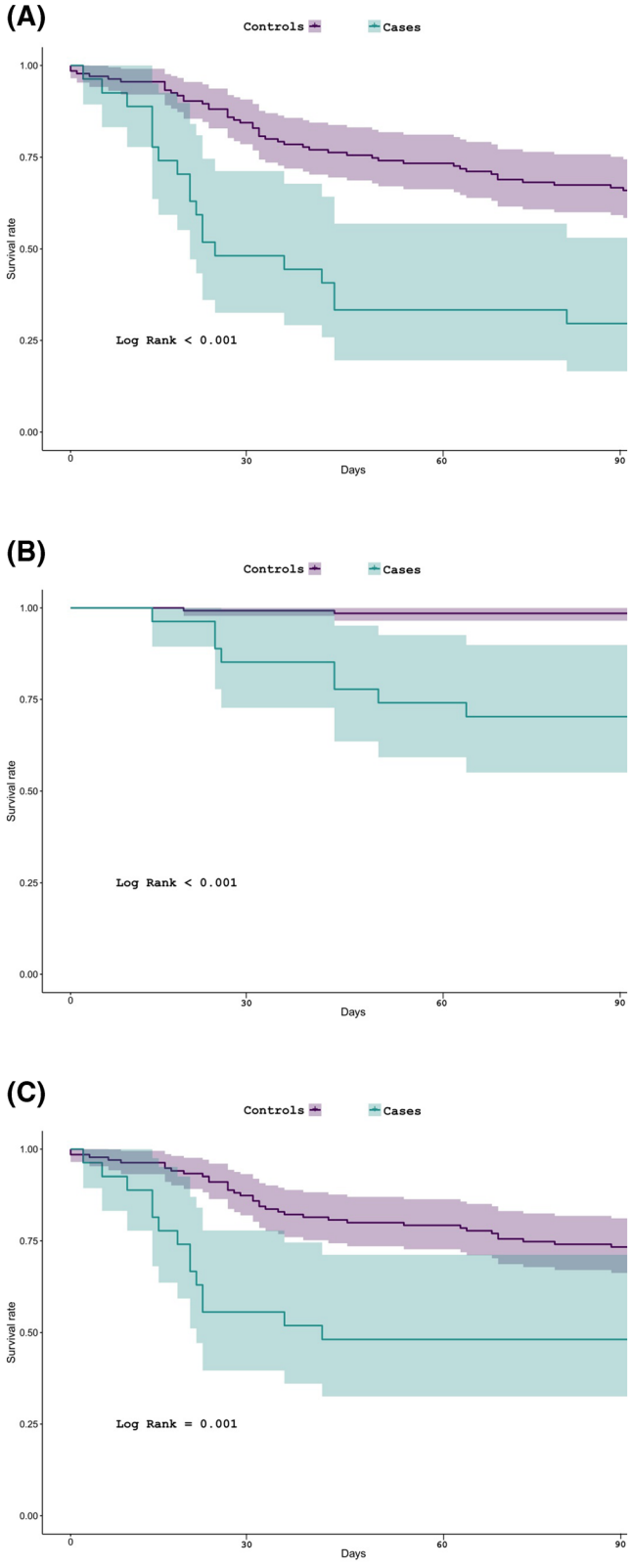
Cardiac amyloidosis and the hospital readmission rate for acute heart failure

We found that the risk of hospital admission for HF following AHF was higher for patients with CA. In our study, the 90 day all-cause readmission rate was 31.0% overall, 52% in the HF + CA + group, and 27% in the HF + CA− group. This difference was due to a higher hospital readmission rate for AHF in the HF + CA+ group (48%) than in the HF + CA− group (23%). Only CA status and the dose of diuretic on admission were predictive of hospital readmission.

The 90 day hospital readmission rate observed here is in line with the literature data.[27,28] However, there are few published data on the hospital readmission of patients with CA over this timeframe. Maurer et al. observed 0.48 vs. 0.70 cardiovascular-disease-related hospitalizations per year for patients treated with tafamidis vs. placebo, respectively.[21]

The difference in prognosis between the HF + CA+ and HF + CA− groups (particularly in terms of hospital readmission for AHF) might be explained by the severity of cardiac dysfunction and greater frailty in patients with CA, relative

Figure 1 (*A*) Survival curve for all-cause hospital readmission or death at 90 days, as a function of cardiac amyloidosis (CA) status. (*B*) Survival curve for all-cause mortality at 90 days, as a function of CA status. (*C*) Survival curve for all-cause hospital readmission at 90 days as a function of CA status.



DOI: 10.1002/ehf2.14337

Table 3 Unadjusted and adjusted composite Hazard Ratios of all-cause-rehospitalization or death at 90 days stratified by CA status

	HR	95% CI	HR[a]	95% CI[a]
HF + CA−	Ref	Ref	Ref	Ref
HF + CA+	2.33	1.43–3.79	2.70	1.16–6.26
HDI[b]	0.46	0.07–3.03	1.90	0.12–29.1
Chronic kidney disease	1.05	0.57–1.94	0.49	0.18–1.37
NTproBNP (pg/mL)[c]	1.20	0.60–2.38	1.01	1.00–1.20
Diuretic use on admission	2.43	1.02–5.86	1.85	0.47–7.20
Atrial fibrillation	0.78	0.41–1.52	1.06	0.41–2.74
Defibrillator	1.07	0.48–2.10	0.43	0.10–1.82

Abbreviations: CA, cardiac amyloidosis; CI, confidence interval; HDI, Human Development Index; HR, hazard ratio.
[a]Adjusted for amyloidosis status, HDI level, chronic kidney disease, N-terminal prohormone of brain natriuretic peptide, diuretic use at admission, atrial fibrillation, and presence of a defibrillator at discharge.
[b]Defined as a binary variable = above or below the median value (0.52).
[c]Defined as a binary variable = above or below the median value (4575 pg/mL).

to patients without CA.[31] The prevalence and prognostic impact of frailty among HF patients has been thoroughly described in the literature.[32,33] Frailty also appears to have a prognostic impact in HF patients with CA.[31,32] However, these studies appeared to show that the patients' greater frailty was related to the severity of CA and the duration of disease.[33] This specific frailty pattern observed might be due to extracardiac amyloid infiltrations. For example, our HF + CA+ patients body had a lower weight and a lower BMI on discharge. The BMI is a good index of the level of muscle mass, and the diagnosis of malnutrition is now largely based on anthropometric variables.[34,35] Sarcopenia and malnutrition are highly prevalent in patients with chronic HF and have a major, negative prognostic impact.[36,37] Thus, amyloidosis of the digestive tract might account for the lower muscle mass observed in the HF + CA+ group. The fact that the heart rate was higher in the CA group might also explain (at least in part) the poorer prognosis. The number of patients with a BMI below the normal range to demonstrate that the patients with CA were in fact more likely to be malnourished is 8 (6%) in HF + CA− group and 7(26%) in HF + CA+ group (*P* value = 0.05). It highlights that the patients with CA were more likely to be malnourished than the patients without CA.

Lastly, the dose of diuretic appeared to be correlated with the severity, as recently reported for patients with NTproBNP.[38]

Implications for the clinical management of patients with cardiac amyloidosis

Our results showed that death and hospital readmission are frequent following discharge in both groups but especially in HF + CA+ patients. These high frequencies had been observed in an earlier study.[24] The readmissions for AHF are associated with high morbidity and mortality rates and high healthcare costs.[2–5] Preventing or reducing these outcomes will require better care for patients with CA. First, CA should be diagnosed earlier via the systematic screening of patients with the 'red flags' described in a recent ESC working group statement.[10] A special management programme should be developed for patients having experienced an episode of AHF. The optimal follow-up for patients with CA has not yet been addressed. Experts have recommended a six monthly consultation with an ECG and a complete set of blood tests (including the NTproBNP and troponin levels) and a yearly echocardiogram and 24 h Holter ECG testing in clinically stable patients. The poor observed prognosis (with more hospital admission and a greater mortality rate) emphasizes the need for innovative care pathways for these patients.

Implications for clinical research

Our results demonstrated that the AHF rate is high among patients with CA. This finding might influence clinical trials in at least two ways. Firstly, this information must be taken into account when calculating the CA trial's sample size and planned duration. Secondly, it is important to diagnose CA in trials exclude patients with CA from trials of drugs that might not have a beneficial physiopathological impact.[39]

Limitations

To the best of our knowledge, the present study is one of the first to have documented the prognosis of HF patients with CA compared with other causes of HF in the same timeframe. However, our study had some limitations. First, the small sample size might have limited the strength of the results. Most of the HF patients with CA were referred to a specialist amyloidosis unit, and so selection bias cannot be ruled out. Two thirds of the patients recruited from the unit did not have CA. In view of the broad inclusion criteria of the ICREX-94 study, one third of the patients in the HF + CA− group had an index admission for HF. These patients might have a worse prognosis than patients in the HF + CA+ group. Second, the small number of patients prevented us from providing and testing a dedicated CA management scheme after discharge and then comparing the risk of death and hospital readmission as a function of the type of CA. Similarly, we were not able to analyse the impact of specific treatments for CA, such as chemotherapy, immunotherapy, and stabilizers.[19] Data on the ejection fraction were missing for almost 40% of the patients with CA. Further studies are needed to determine whether or not better care and monitoring during follow-up for patients with CA will improve the prognosis.

Conclusions

Our results demonstrated that the 90 day readmission and death rates were higher in HF patients with CA than in those without. The higher morbidity and mortality rates in patients with CA emphasize the need for (i) early amyloidosis screening and diagnosis and (ii) specific multidisciplinary management programmes after hospitalization for AHF.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Baseline characteristics between Excluded Controls (EC) and Included Controls (IC) after pairing.

References

1. Authors/Task Force Members, McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Bohm M et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**: 1787–1847.
2. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018; **391**: 572–580.
3. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare Fee-for-Service Program. *N Engl J Med* 2009; **360**: 1418–1428.
4. Patil S, Shah M, Patel B, Agarwal M, Ram P, Alla VM. Readmissions among patients admitted with acute decompensated heart failure based on income quartiles. *Mayo Clin Proc* 2019; **94**: 1939–1950.
5. Nichols GA, Reynolds K, Kimes TM, Rosales AG, Chan WW. Comparison of risk of re-hospitalization, all-cause mortality, and medical care resource utilization in patients with heart failure and preserved versus reduced ejection fraction. *Am J Cardiol* 2015; **116**: 1088–1092.
6. Berthelot E, Broussier A, Damy T, Donadio C, Cosson S, Rovani X, Salengro E, Billebeau G, Megbemado R, Rekik N, Godreuil C, Richard K, Shourick J, Assayag P, Belmin J, David JP, Hittinger L, for the FINC-94 network. Good performance in the management of acute heart failure in cardiogeriatric departments: the ICREX-94 experience. *BMC Geriatr* 2021; **21**: 288.
7. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, Gottdiener JS, Psaty BM, Vasan RS. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. *JACC Heart Fail* 2018; **6**: 678–685.
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 of heart failure with preserved ejection fraction. *Eur Heart J* 2015; **36**: 2585–2594.
9. Merlo M, Pagura L, Porcari A, Cameli M, Vergaro G, Musumeci B, Biagini E, Canepa M, Crotti L, Imazio M, Forleo C, Cappelli F, Perfetto F, Favale S, di Bella G, Dore F, Girardi F, Tomasoni D, Pavasini R, Rella V, Palmiero G, Caiazza M, Carella MC, Igoren Guaricci A, Branzi G, Caponetti AG, Saturi G, la Malfa G, Merlo AC, Andreis A, Bruno F, Longo F, Rossi M, Varrà GG, Saro R, di Ienno L, de Carli G, Giacomin E, Arzilli C, Limongelli G, Autore C, Olivotto I, Badano L, Parati G, Perlini S, Metra M, Emdin M, Rapezzi C, Sinagra G. Unmasking the prevalence of amyloid cardiomyopathy in the real world: results from Phase 2 of the AC-TIVE study, an ITALIAN NATIONWIDE SURVEY. *Eur J Heart Fail* 2022; **24**: 1377–1386.
10. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, Burazor I, Caforio ALP, Damy T, Eriksson U, Fontana M, Gillmore JD, Gonzalez-Lopez E, Grogan M, Heymans S, Imazio M, Kindermann I, Kristen AV, Maurer MS, Merlini G, Pantazis A, Pankuweit S, Rigopoulos AG, Linhart A. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2021; **42**: 1554–1568.
11. Tomasoni D, Aimo A, Merlo M, Nardi M, Adamo M, Bellicini MG, Cani D, Franzini M, Khalil A, Pancaldi E, Panichella G, Porcari A, Rossi M, Vergaro G, Lombardi CM, Sinagra G, Rapezzi C, Emdin M, Metra M. Value of the HFA-PEFF and H $_2$ FPEF scores in patients with heart failure and preserved ejection fraction caused by cardiac amyloidosis. *Eur J Heart Fail* 2022; **24**: 2374–2386.
12. Maestro-Benedicto A, Vela P, de Frutos F, Mora N, Pomares A, Gonzalez-Vioque E, Briceño A, Cabrera E, Cobo-Marcos M, Dominguez F, Gonzalez-Lopez E, Segovia J, Lara-Pezzi E, Garcia-Pavia P. Frequency of hereditary transthyretin amyloidosis among elderly patients with transthyretin cardiomyopathy. *Eur J Heart Fail* 2022; **24**: 2367–2373.
13. Ng B, Connors LH, Davidoff R, Skinner M, Falk RH. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain–associated amyloidosis. *Arch Intern Med* 2005; **165**: 1425.
14. Antonopoulos AS, Panagiotopoulos I, Kouroutzoglou A, Koutsis G, Toskas P, Lazaros G, Toutouzas K, Tousoulis D, Tsioufis K, Vlachopoulos C. Prevalence and clinical outcomes of transthyretin amyloidosis: a systematic review and meta-analysis. *Eur J Heart Fail* 2022; **24**: 1677–1696.
15. Porcari A, Razvi Y, Masi A, Patel R, Ioannou A, Rauf MU, Hutt DF, Rowczenio D, Gilbertson J, Martinez-Naharro A, Venneri L, Whelan C, Lachmann H, Wechalekar A, Quarta CC, Merlo M, Sinagra G, Hawkins PN, Fontana M, Gillmore JD. Prevalence, characteristics and outcomes of older patients with hereditary versus wild-type transthyretin amyloid cardiomyopathy. *Eur J Heart Fail* 2023; ejhf.2776.
16. Damy T, Jaccard A, Guellich A, Lavergne D, Galat A, Deux JF, Hittinger L, Dupuis J, Frenkel V, Rigaud C, Plante-Bordeneuve V, Bodez D, Mohty D. Identification of prognostic markers in transthyretin and AL cardiac amyloidosis*. *Amyloid.* 2016; **23**: 194–202.
17. Bonnefous L, Kharoubi M, Bézard M, Oghina S, le Bras F, Poullot E, Molinier-Frenkel V, Fanen P, Deux JF, Audard V, Itti E, Damy T, Audureau E. Assessing cardiac amyloidosis subtypes by unsupervised phenotype clustering analysis. *J Am Coll Cardiol* 2021; **78**: 2177–2192.
18. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen

risk factors for use in multivariable analysis. *J Clin Epidemiol* 1996; **49**: 907–916.
19. Bender R, Lange S. Adjusting for multiple testing—when and how? *J Clin Epidemiol* avr 2001; **54**: 343–349.
20. Kharoubi M, Bodez D, Bézard M, Zaroui A, Galat A, Guendouz S, Gendre T, Hittinger L, Attias D, Mohty D, Bergoend E, Itti E, Lebras F, Hamon D, Poullot E, Molinier-Frenkel V, Lellouche N, Deux JF, Funalot B, Fannen P, Oghina S, Arrouasse R, Lecorvoisier P, Souvannanorath S, Amiot A, Teiger E, Bougouin W, Damy T. Describing mode of death in three major cardiac amyloidosis subtypes to improve management and survival. *Amyloid* 2022; **29**: 79–91.
21. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018; **379**: 1007–1016.
22. Adam RD, Coriu D, Jercan A, Bădeliţă S, Popescu BA, Damy T, Jurcuţ R. Progress and challenges in the treatment of cardiac amyloidosis: a review of the literature. *ESC Heart Fail* 2021; **8**: 2380–2396.
23. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, Patterson TA, Riley S, Schwartz JH, Sultan MB, Witteles R. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail* 2021; **23**: 277–285.
24. Arora S, Patil NS, Strassle PD, Qamar A, Vaduganathan M, Fatima A, Mogili K, Garipalli D, Grodin JL, Vavalle JP, Fonarow GC, Bhatt DL, Pandey A. Amyloidosis and 30-day outcomes among patients with heart failure. *JACC CardioOncology* 2020; **2**: 710–718.
25. Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi D et al. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail* 2017; **19**: 201–208.
26. O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, Greenberg BH, Yancy CW, Young JB, Fonarow GC. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2008; **156**: 662–673.
27. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004.
28. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, Komajda M, Miller A, Pehrson S, Teerlink JR, Brueckmann M, Jamal W, Zeller C, Schnaidt S, Zannad F, For the EMPEROR-Reduced Trial Committees and Investigators. Effect of Empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-reduced trial. *Circulation* 2021; **143**: 326–336.
29. Rosenblum H, Castano A, Alvarez J, Goldsmith J, Helmke S, Maurer MS. TTR (transthyretin) stabilizers are associated with improved survival in patients with TTR cardiac amyloidosis. *Circ Heart Fail* 2018; **11**: e004769.
30. Damy T, Chouihed T, Delarche N, Berrut G, Cacoub P, Henry P, Lamblin N, Andrès E, Hanon O. Diagnosis and management of heart failure in elderly patients from hospital admission to discharge: position paper. *J Clin Med* 2021; **10**: 3519.
31. Khan MS, Sreenivasan J, Lateef N, Abougergi MS, Greene SJ, Ahmad T, Anker SD, Fonarow GC, Butler J. Trends in 30- and 90-day readmission rates for heart failure. *Circ Heart Fail* 2021; **14**: e008335.
32. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: a systematic review and meta-analysis. *Int J Cardiol* 2017; **236**: 283–289.
33. Zhang Y, Yuan M, Gong M, Tse G, Li G, Liu T. Frailty and clinical outcomes in heart failure: a systematic review and meta-analysis. *J Am Med Dir Assoc* 2018; **19**: 1003–1008.e1.
34. Marengoni A, Zucchelli A, Vetrano DL, Aloisi G, Brandi V, Ciutan M, Panait CL, Bernabei R, onder G, Palmer K. Heart failure, frailty, and pre-frailty: a systematic review and meta-analysis of observational studies. *Int J Cardiol* 2020; **316**: 161–171.
35. Bouillanne O, Hay P, Liabaud B, Duché C, Cynober L, Aussel C. Evidence that albumin is not a suitable marker of body composition-related nutritional status in elderly patients. *Nutrition* 2011; **27**: 165–169.
36. Fine NM, McMillan JM. Prevalence and prognostic significance of frailty among patients with transthyretin amyloidosis cardiomyopathy. *Circ Heart Fail* 2021; **14**: e008105.
37. Broussier A, David JP, Kharoubi M, Oghina S, Segaux L, Teiger E, Laurent M, Fromentin I, Bastuji-Garin S, Damy T. Frailty in wild-type transthyretin cardiac amyloidosis: the tip of the iceberg. *J Clin Med* 2021; **10**: 3415.
38. Cheng RK, Levy WC, Vasbinder A, Teruya S, de Los Santos J, Leedy D, Maurer MS. Diuretic dose and NYHA functional class are independent predictors of mortality in patients with transthyretin cardiac amyloidosis. *JACC CardioOncology* 2020; **2**: 414–424.
39. Oghina S, Bougouin W, Bézard M, Kharoubi M, Komajda M, Cohen-Solal A, Mebazaa A, Damy T, Bodez D. The impact of patients with cardiac amyloidosis in HFpEF trials. *JACC Heart Fail* 2021; **9**: 169–178.