Frailty in heart failure according to the presence or absence of wild-type transthyretin cardiac amyloidosis

Amaury Broussier, Marie Paugam, Nina Liu, Silvia Oghina, Mounira Kharoubi, Charlotte Lafont, Amira Zaroui, Arnault Galat, Luc Hittinger, Emmanuel Teiger, et al.

ESC HEART FAILURE
ESC Heart Failure (2024)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.15026

ORIGINAL ARTICLE

Frailty in heart failure according to the presence or absence of wild-type transthyretin cardiac amyloidosis

Amaury Broussier[1,2]*, Marie Paugam[3], Nina Liu[2], Silvia Oghina[1,4], Mounira Kharoubi[1,4], Charlotte Lafont[1,5], Amira Zaroui[1,4], Arnault Galat[1,4], Luc Hittinger[4], Emmanuel Teiger[4], Jean Philippe David[1,3], Sylvie Bastuji-Garin[1,5] and Thibaud Damy[1,4]

[1]*INSERM, IMRB, Univ Paris Est Creteil, Creteil, France;* [2]*Department of Geriatrics, AP-HP, Hopitaux Universitaires Henri-Mondor, Limeil-Brevannes, France;* [3]*Department of Internal Medicine and Geriatrics, AP-HP, Hopitaux Universitaires Henri-Mondor, Creteil, France;* [4]*Department of Cardiology, Heart Failure and Amyloidosis Unit, AP-HP, Hopitaux Universitaires Henri-Mondor, Creteil, France; and* [5]*Department of Public Health, AP-HP, Hopitaux Universitaires Henri-Mondor, Creteil, France*

Abstract

Aims Wild-type transthyretin cardiac amyloidosis (ATTRwt CA) is a common, underdiagnosed cause of heart failure (HF) in the elderly. Concurrent extracardiac amyloid infiltration might be responsible for a specific frailty phenotype. This study aims to compare the prevalence and characteristics of frailty parameters in HF patients, with or without ATTRwt CA.

Methods In a comparative cross-sectional study, we prospectively included consecutive HF patients with or without ATTRwt CA (the HF + ATTRwt+ and HF + ATTRwt− groups, respectively) between April 2018 and April 2021. Logistic regression models were used to compare the groups with regard to frailty as assessed using multidimensional geriatric tools.

Results We included 123 patients (68 HF + ATTRwt+ and 55 HF + ATTRwt−). The mean age was 80.9 (standard deviation 6.3) years, 87% were male, 34% had left ventricular systolic dysfunction and 34% were New York Heart Association (NYHA) III. Relative to the HF + ATTRwt− group, patients in the HF + ATTRwt+ group were more likely to have shrinking [odds ratios = 2.9 (95% confidence interval, 1.1 to 1.7), $P = 0.03$], balance disorders [1.8 (1.1 to 2.8), $P = 0.02$], memory complaints [2.5, (1.0 to 5.9), $P = 0.05$] and overactive bladder [1.5 (1.1 to 2.2), $P = 0.03$], independently of age, sex, NYHA class and diabetes status. The proportion of very frail patients was higher (albeit not significantly) in the HF + ATTRwt+ group than in the HF + ATTRwt− group [2.4 (0.9 to 6.9), $P = 0.10$].

Conclusions ATTRwt CA is associated with a specific frailty phenotype. Patients with ATTRwt CA should be screened for frailty and managed collaboratively by cardiologists and geriatricians, with a view to improving quality of life.

Keywords cardiac amyloidosis; frailty; heart failure; transthyretin; wild type

Received: 12 April 2024; Revised: 12 July 2024; Accepted: 2 August 2024
**Correspondence to: Amaury Broussier, Department of Geriatrics,, AP-HP, Hopitaux Universitaires Henri-Mondor, F-94456 Limeil Brévannes, France. Email: amaury.broussier@aphp.fr*
Sylvie Bastuji-Garin and Thibaud Damy contributed equally to the work.
***Funding information**: This research received no external funding.*

Introduction

Cardiac amyloidosis (CA) is a systemic disease characterized by cardiac and extracardiac amyloid infiltration, that is, the progressive deposition of abnormal, insoluble fibrils of misfolded proteins in the tissues.[1] Immunoglobulin light chains and transthyretin (TTR) are the most frequently involved proteins.[2] In a recent, autopsy-based study, 43% of an unselected population of patients aged 75 years and over presented with CA (half due to light chain deposition and half due to TTR deposition).[3] The prevalence of CA increases with age, with values of 25% in patients aged 75–79 year and >50% in patients aged 90 years and over.[3] Wild-type TTR cardiac amyloidosis (ATTRwt CA) was observed in 13% of patients with heart failure (HF) with a preserved ejection fraction,[4] 16% of patients undergoing percutaneous aortic valve replacement for severe aortic stenosis[5] and 20% of investigated patients in an HF cohort with an elevated myocardial wall thickness (more than 14 mm)[6]. The pathophysiological impacts of cardiac and extracardiac infiltrations have been characterized in detail.[7] Studies of patients with ATTR CA have highlighted the clinical importance of extracardiac

amyloid infiltration, which results in disorders such as carpal tunnel syndrome, lumbar spinal stenosis, hearing loss and autonomic neuropathy.[8–11] Patients with ATTR CA present with physical decline, exercise intolerance and exhaustion, which in turn result in low functional capacity, poor quality of life and a worse prognosis than the HF patients without CA.[7,12–14] It has been shown that the prognosis of patients with ATTR CA is linked to the progression of cardiac damage.[15] However, recent studies suggest that frailty has a prognostic impact on ATTR CA, independently of the disease stage, the New York Heart Association (NYHA) class and treatment with tafamidis.[16]

Frailty is a clinical syndrome that reflects a decrease over time in functional reserves and thus a reduced ability to adapt to external stress factors. It increases the likelihood of adverse health outcomes, such as falls, disability, hospitalization and death.[17] The prognostic link between frailty and HF has been well documented.[18,19] In a previous observational study, we found that frailty was frequent among patients with ATTRwt CA, with a prevalence of 50% (according to the physical frailty phenotype) or 33% (according to the Short Emergency Geriatric Assessment).[20] We also observed significant age-independent associations between several frailty parameters, and both the severity of CA and the duration of amyloid disease.[20]

We hypothesized that extracardiac amyloid infiltration by TTR favours impairments in certain frailty domains, which might result in a specific frailty phenotype in patients with ATTRwt CA.

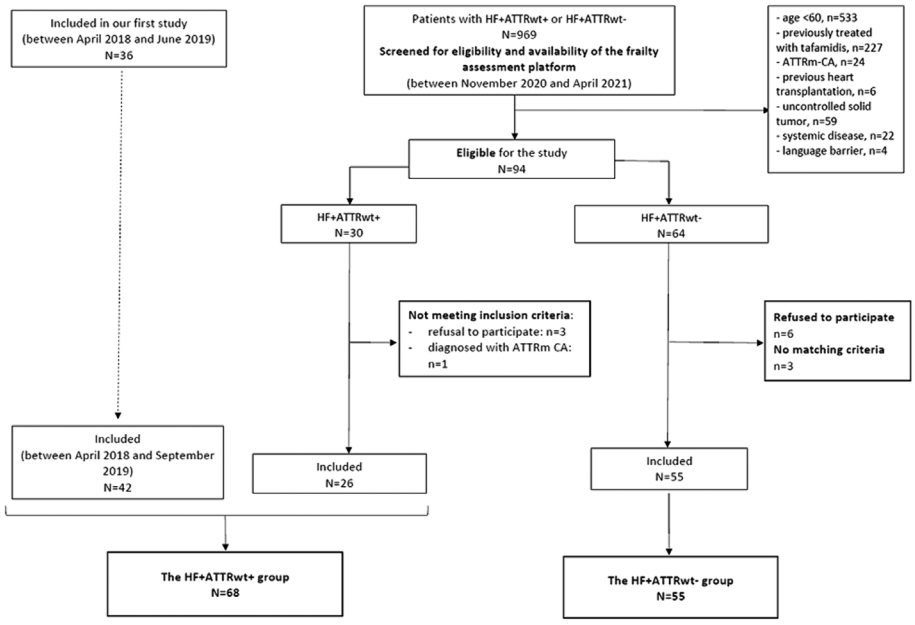
The objective of the present study was to compare the prevalence and characteristics of frailty among patients with HF, according to the presence or absence of ATTRwt CA.

Methods

Study design and participants

We performed a comparative, cross-sectional study of HF patients with or without ATTRwt CA (forming the HF + ATTRwt+ and control HF + ATTRwt− group, respectively). All the study participants had been referred to the Heart Failure and Amyloidosis Unit in the Department of Cardiology at Henri-Mondor University Hospital (Creteil, France) and had agreed to undergo a multidimensional geriatric assessment. The consecutive participants were included prospectively between April 2018 and April 2021 (*Figure* 1). The first 36 patients in the HF + ATTRwt+ group (included between April 2018 and June 2019) have been described previously.[20] HF + ATTRwt− patients (control group) were individually matched for age (±3 years), sex and NYHA class to HF + ATTRwt+ patients. Unmatched HF+ATTRwt− patients were not included in the study. All participants provided their written informed consent before inclusion. The study complied with the principles of the Declaration of Helsinki. The study was approved by the local institutional review board (Hôpital Henri-Mondor, Creteil, France: authorization

Figure 1 Study flow chart. Flow chart for the comparative, cross-sectional study. A total of 123 HF patients were included: 68 in the HF + ATTRwt+ group and 55 in the matched HF + ATTRwt− group. ATTRm, muted transthyretin amyloidosis; HF, heart failure; HF + ATTRwt, heart failure patients with wild-type transthyretin cardiac amyloidosis; HF + ATTRwt−, heart failure patients without wild-type transthyretin cardiac amyloidosis.



numbers 1431858 for the HF + ATTRwt+ group and 2022-137 for the control group) and registered with the French National Data Protection Commission (*Commission nationale de l'informatique et des libertés*, Paris, France; authorization number 2215384 v 0).

Inclusion criteria

In both groups, the inclusion criteria were age ≥60 year and HF diagnosed according to the European Society of Cardiology (ESC)'s latest guidelines. The exclusion criteria were age <60 year, acute HF on inclusion, previous heart transplantation, an uncontrolled solid tumour at diagnosis, systemic disease with cardiac involvement, a language barrier hindering geriatric assessment, legal protection measures and refusal to participate in the study. As tafamidis has been shown to improve quality of life and performance in the 6 min walk test, HF + ATTRwt+ patients having been treated with this drug for more than 3 months were not included. Patients with muted TTR amyloid CA were also not included. None of the participants in the control HF + ATTRwt− group had CA.

Blood samples were collected and assayed for N-terminal prohormone of brain natriuretic peptide (NTproBNP) and creatinine. All patients underwent standard transthoracic echocardiography (Vivid 7, GE Healthcare, Buc, France). The left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane method. ATTRwt CA was diagnosed according to the ESC's latest guidelines.[21] The diagnosis was confirmed by the observation of strong cardiac uptake (a visual score ≥2) of a bisphosphonate tracer (99mTc-hydroxymethylene diphosphonate) on cardiac scintigraphy and the absence of a TTR gene mutation. In order to rule out light chain amyloidosis, blood and urine samples were analysed with protein electrophoresis, immunofixation and a light chain assay. If gammopathy was present, the diagnosis of ATTRwt CA was confirmed after positive Congo Red staining and immunostaining for TTR (in the absence of light chain staining) on extracardiac and/or endomyocardial biopsy.

Geriatric assessment

As described previously, frailty was assessed in the cardiogeriatric unit at Emile Roux University Hospital (Limeil-Brévannes, France),[20] using both the physical frailty phenotype (Fried's model[17]) and a multidomain assessment.[22] First, Fried's model defines the physical frailty phenotype as robust, pre-frail or frail by considering shrinking (loss of >4.5 kg in bodyweight in the previous 12 months), weakness (grip strength (dynamometer-measured maximum dominant-hand grip strength (JAMAR®, Sammons Preston, Bolingbrook, IL, USA) < 30 kg in men and <20 kg in women), exhaustion (defined as an answer of 'yes' to the question 'Did you feel any significant or unusual fatigue over the previous year?'), slowness (gait speed <1 m/s) and a low level of physical activity (performance of physical activity or sport for less than 30 min three times a week). Patients meeting three or more criteria were considered to be frail, those meeting one or two criteria were considered to be pre-frail, and those not meeting any criteria were considered to be robust. Second, we administered the Short Emergency Geriatric Assessment questionnaire [SEGA, classifying patients as very frail (score >11), frail (score >8) or not frail (score ≤8) [23] and performed a comprehensive geriatric assessment (CGA) (according to Rockwood's approach[22] and using a series of validated scales). Comorbidities were evaluated on the modified Cumulative Illness Rating Scale. Autonomy was assessed using the activities of daily living (ADL) scale and the Instrumental Activities of Daily Living (IADL) scale.[24] The risk of malnutrition was evaluated with the Mini Nutritional Assessment (MNA) Short Form.[25] Mobility and muscle strength were assessed with the Short Physical Performance Battery (SPPB),[26] gait speed over 10 m, and dynamometer-measured maximum dominant-hand grip strength (JAMAR®, Sammons Preston, Bolingbrook, IL, USA; weakness: <30 kg in men and <20 kg in women).[27] Balance was assessed using the one-leg standing test.[28] Overall cognitive performance was evaluated with the Mini-Mental State Examination (after adjustment for age and educational level), the five-word screening test (verbal episodic memory), the seven-point clock-drawing test (executive and visuospatial functions) and the Frontal Assessment Battery (frontal lobe functions).[29] We used the Geriatric Depression Scale to evaluate mood.[30] Sphincter disorders were assessed using the Urinary Symptom Profile questionnaire.[31]

Statistical analysis

Quantitative and qualitative variables were described as the median [interquartile range (IQR)] and the frequency (percentage), respectively. We compared the frailty variables in the HF + ATTRwt+ and HF + ATTRwt− patients by applying a chi-squared test, Fisher's test, Student's *t* test or the Mann–Whitney test, as appropriate. For variables with $P < 0.20$, the corresponding odds ratios (OR) [95% confidence interval (CI)] were estimated in an exact logistic regression after adjustment for the matching variables in the first instance (age, sex and NYHA class), then for matched variables and diabetes in the second.

All statistical analyses were performed with STATA software (V14.1, StataCorp, College Station, TX, USA). The threshold for statistical significance was set to $P \leq 0.05$. *P* values between 0.05 and 0.10 were denoted as indicating a trend.

Results

In total, 136 patients with HF were found to be eligible (*Figure* 1). Ultimately, 123 patients were included in the study: 68 in the HF + ATTRwt+ group and 55 in the matched HF + ATTRwt− group.

Baseline characteristics of the study population

At inclusion, the mean age was 80.9 [standard deviation (*SD*) 6.3] years, and there were 107 men (87%) (*Table* 1). About a third of the patients were classified as NYHA class III or IV, 34% had left ventricular systolic dysfunction (LVEF <45%), and the median serum NTproBNP level was 1838 (911–4059) pg/mL. Relative to the control group, patients in the HF + ATTRwt+ group had a significantly higher heart rate (P = 0.008), a significantly higher LVEF (P = 0.02), a significantly lower creatinine level (P = 0.03), and were less likely to have diabetes (P = 0.005).

Associations between frailty and amyloidosis status

In the overall study population, about half of the patients were frail (53.7%, according to the physical frailty phenotype, or 47.2% according to the SEGA questionnaire); the HF + ATTRwt+ and control groups did not differ significantly in this respect (*Table* 2). The percentage of very frail patients (according to the SEGA) was higher in the HF + ATTRwt+ group than in the control group, although the difference was not statistically significant. Relative to control patients, patients in the HF + ATTRwt+ group left home less often

Table 1 Characteristics of the HF patients with or without ATTRwt CA.

Characteristics	All HF+	HF+		*P* value[a]
		ATTRwt+	ATTRwt−	
N	123	68	55	
Matching criteria				
Male sex	107 (87)	59 (87)	48 (87)	0.93
Age, years, mean ± *SD*	80.9 ± 6.3	81.8 ± 6.3	79.8 ± 6.2	0.08
NYHA class				0.68
I	11 (9)	5 (7)	6 (11)	
II	69 (57)	40 (60)	29 (53)	
III	42 (34)	22 (33)	20 (36)	
IV	0 (0)	0 (0)	0 (0)	
Other demographic variables				
Living alone	32(27)	18(28)	14 (25)	0.78
BMI, mean ± *SD*	26.3 ± 4.2	26.0 ± 4.0	26.7 ± 4.4	0.32
Cardiology assessment				
Heart rate (bpm), mean ± *SD*	69 ± 13	72 ± 14	66 ± 11	0.008
Systolic blood pressure, mmHg, mean ± *SD*	132 ± 19	130 ± 19	136 ± 19	0.07
Diastolic blood pressure, mmHg, mean ± *SD*	73 ± 14	75 ± 14	71 ± 13	0.09
Orthostatic hypotension	29 (27)	14 (26)	15 (28)	0.83
LVEF, mean ± *SD*	49 ± 13	51 ± 12	46 ± 13	0.02
≥45%	80 (66)	48 (72)	32 (58)	0.09
<45%	41 (34)	18 (27)	23 (42)	
NTproBNP, ng/L, median [IQR]	1838 [911–4,059]	2,601 [1,228–4,513]	1,204 [448–2,733]	0.10
Creatinine, μmol/l, median [IQR]	108 [89–132]	106 [86–128]	116 [90–163]	0.03
Comorbidity assessment				
Comorbidities				
CIRS-G score, mean ± *SD*	15.7 ± 4.8	15.9 ± 4.7	15.5 ± 5.0	0.64
Charlson-G, mean ± *SD*	7.0 ± 2.0	6.9 ± 2.1	7.1 ± 2.0	0.59
Hypertension	95 (80)	53 (83)	42 (76)	0.38
Dyslipidaemia	62 (52)	32 (49)	30 (56)	0.49
Diabetes	39 (33)	14 (22)	25 (45)	0.005
Chronic obstructive pulmonary disease	9 (8)	3 (5)	6 (11)	0.19
Kidney failure (clearance <60 mL/min, CKD-EPI)	95 (79)	48 (74)	47 (85)	0.12
Depression	18 (15)	12 (18)	6 (11)	0.25
Obesity (body mass index ≥30)	23 (19)	9 (14)	14 (25)	0.11
Stroke	12 (10)	6 (9)	6 (11)	0.76
Cognitive disorders	12 (10)	8 (12)	4 (7)	0.36
Medications taken daily				
≥5 medications per day	106 (86)	57 (84)	49 (89)	0.40

Note: NB, The data are quoted as the frequency (%), unless otherwise stated.
Abbreviations: ATTRwt CA, wild-type transthyretin cardiac amyloidosis; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale-Geriatric; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; *SD*, standard deviation; SEGA, Short Emergency Geriatric Assessment.
[a]*P* value from a χ^2 test, Fisher's test, Student's *t*-test or non-parametric Mann–Whitney test, as appropriate.

Table 2 Frailty parameters in HF patients with or without ATTRwt CA.

		HF+			Adjusted for the matching criteria[a]	
	All HF+	ATTRwt+	ATTRwt-	*P* value[b]	OR [95% CI]	*P* value
N	123	68	55			
Frailty scores						
SEGA, total score, mean ± *SD*	9 ± 4	9 ± 4	9 ± 3	0.63		
≤8, not frail	65 (53)	35 (52)	30 (55)	0.22	Ref category	
>8 and ≤11, frail	32 (26)	15 (22)	17 (31)			
>11, very frail	26 (21)	18 (26)	8 (15)		2.3 [0.9–6.3]	0.10
Physical frailty phenotype[c]						
Robust	3 (2)	2 (3)	1 (2)	0.56		
Pre-frail	54 (44)	27 (40)	27 (49)			
Frail	66 (54)	39 (57)	27 (49)			
Autonomy and lifestyle						
ADL scale score <6	38 (31)	23 (34)	15 (27)	0.43		
IADL scale score <8	96 (78)	52 (76)	44 (80)	0.64		
IADL-sf scale score <4[d]	49 (41)	29 (45)	20 (36)	0.36		
Going outside less than once a week	17 (14)	13 (20)	4 (7)	0.04	3.6 [1.1–12.2]	0.04
Physical activities	58 (49)	31 (48)	27 (49)	0.94		
Nutrition status						
Risk of malnutrition (MNA score <12)	52 (43)	31 (46)	21 (38)	0.37		
Shrinking (unintentional weight loss in the past year >4.5 kg)	29 (24)	21 (31)	8 (15)	0.03	2.7 [1.0–6.7]	0.04
Mobility and balance						
Walks with help	35 (30)	22(35)	13 (24)	0.18		
Gait speed m/s, mean ± *SD*	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.55		
Gait speed <.8 m/s	45 (38)	25 (39)	20 (36)	0.76		
Time taken to walk 10 m in a dual task, s, median [IQR]						
Motor dual task	11 [9.9–13.8]	11 [10–13]	11 [9.6–14.6]	0.60		
Cognitive dual task	12.2 [10–16.5]	12 [10–17]	12 [9.9–16]	0.72		
SPPB performance						
High (≥10)	49 (40)	25 (37)	24 (44)	0.45		
Moderate (7–9)	44 (36)	24 (35)	20 (37)			
Low (≤6)	29 (24)	19 (28)	10 (19)			
Completion time in a five-time sit-to-stand-test ≥13.7 s (SPPB≤2)	87 (71)	53 (78)	34 (63)	0.07	2.0 [0.9–4.8]	0.10
Weakness [(grip strength <30 kg (men) or <20 kg (women)]	98 (83)	56 (89)	42 (76)	0.07	2.5 [0.9–7.2]	0.09
Non-accidental fall(s) in the past year	14 (25)	24 (35)	14 (25)	0.24		
One-leg standing test (seconds)	5 [3–8]	4 [2.5–7]	5 [3–15]	0.12	1.6 [1.1–2.5]	0.02
Cognitive performance						
Memory complaints	38 (31)	26 (39)	12 (22)	0.04	2.3 [1.0–5.2]	0.055
MMSE adjusted for age and educational level, median [IQR]	27 [23–28]	27 [23–28.5]	26 [23–28]	0.30		
5-Word test score <10	42 (34)	21 (31)	21 (38)	0.40		
7-Point clock-drawing test <7	79 (71)	40 (68)	39 (75)	0.40		
Frontal Assessment Battery <16	84 (69)	48 (72)	36 (65)	0.46		
Risk of depression, GDS ≥ 5/15	57 (48)	32 (48)	25 (47)	0.89		
Sphincter disorders						
Urinary Symptom Profile, median [IQR]						
Total score	5 [1–10]	5 [1–10]	4.5 [2–10]	0.86		
Stress urinary incontinence subscore	0 [0–0]	0 [0–0]	0 [0–1]	0.70		
Overactive bladder subscore	4 [1–8]	5 [3–8]	4 [0–8]	0.06	1.6 [1.1–2.2]	0.01
Dysuria subscore	0 [0–1]	0 [0–1]	1 [0–2]	0.28		
Urinary incontinence subscore	34 (29)	18 (29)	16 (30)	0.94		

Note: The data are quoted as the frequency (%), unless otherwise stated.
Abbreviations: ADL, activities of daily living; ATTRwt CA, wild-type transthyretin cardiac amyloidosis; CHS, Cardiovascular Health Study; CI, confidence interval; GDS, Geriatric Depression Scale; HF, heart failure; IADL, instrumental activities of daily living; IADL-sf, instrumental activities of daily living scale, short form; IQR, interquartile range; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; OR, odds ratio; SEGA, Short Emergency Geriatric Assessment; SPPB, Short Physical Performance Battery.
[a]The associations between each frailty variable and the presence of wild-type transthyretin cardiac amyloidosis were adjusted for matching criteria (age, sex and New York Heart Association class) using multiple logistic regression models (one for each relevant variable).
[b]*P* value from a χ^2 test, Fisher's test, Student's *t*-test or non-parametric Mann–Whitney test, as appropriate.
[c]The physical frailty phenotype was built according to the following modified CHS criteria: shrinking, self-reported exhaustion, weakness, slowness and low physical activity (no regular physical activity). Individuals meeting ≥3 criteria are considered to be frail, those meeting 1 or 2 criteria are considered to be pre-frail and those meeting no criteria are considered to be robust.
[d]The IADL-sf comprised the 'telephone', 'medication', 'finances' and 'transportation' items.

(*P* = 0.04) and were more likely to present with shrinking (*P* = 0.04), balance disorders (according to the one-leg standing test) (*P* = 0.02), memory complaints (*P* = 0.055) and overactive bladder (*P* = 0.01). We observed non-significant trends towards an association with ATTRwt CA status for upper limb weakness (grip strength) and lower limb weakness (in the sit-to-stand test) (*Table* 2). Further adjustment for diabetes status did not substantially modify the associations, apart from the frequency of leaving home (*P* = 0.09) (*Figure* 2 and *Table* S1).

Discussion

To the best of our knowledge, the present study is the first to have compared HF + ATTRwt+ and HF + ATTRwt− patients with regard to frailty (using several different tools). In fact, several frailty parameters (shrinking, balance disorders, memory complaints and overactive bladder) were significantly associated with amyloidosis status, independently of age, sex, NYHA class and diabetes. The proportion of very frail patients (according to the SEGA questionnaire) was higher (albeit not significantly) in the HF + ATTRwt+ group than in the control group. These findings suggest the link between frailty and both cardiac and extracardiac amyloid infiltration.

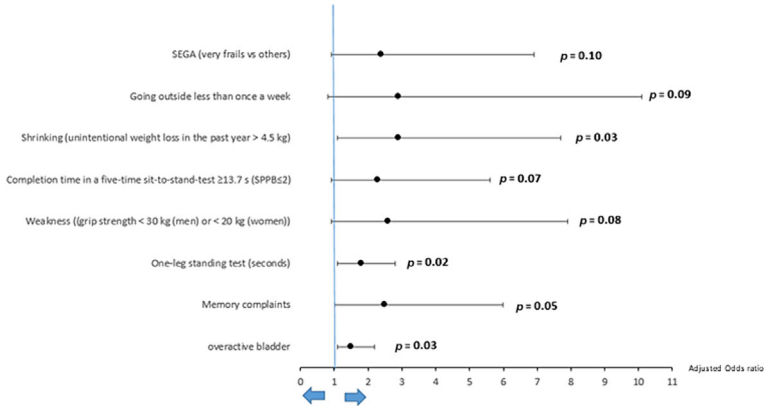
Comparison of our results with the literature data

In our study, the prevalence of frailty among HF + ATTRwt+ patients was 57% (according to the physical frailty phenotype) or 48% (according to the SEGA); in our previous study, the corresponding values were respectively 50% and 33%.[20] In any case, these prevalences were higher than the value of 39% (according to the Clinical Frailty Scale) reported for another cohort of patients with ATTRwt CA.[16] In our control group, the prevalence of frailty was 49% (according to the physical frailty phenotype) or 46% (according to the SEGA questionnaire); these values are close to the median [IQR] of 44.5% [36.2–52.8] reported in a meta-analysis of data on HF patients.[32] Thus, the prevalence of frailty in our cohort was somewhat higher than in the literature. This might be due to the older age and greater disease severity in patients recruited by a dedicated HF and amyloidosis unit in a university hospital.

Frailty and amyloid infiltration

The proportion of very frail patients (according to the SEGA questionnaire) was higher (albeit not significantly) in the HF + ATTRwt+ group than in the control group. We also observed specific intergroup differences in some frailty domains (shrinking, balance disorders, cognition, and sphincter disorders), which might have been due to amyloid infiltration of extracardiac tissues. For example, shrinking might be related to amyloidosis in the digestive tract; gastrointestinal involvement is prevalent in amyloidosis (49.2%, according to Sánchez et al.[33]) and can lead to bacteraemia and septicaemia in frail patients.[34] Poterucha et al. previously described that body mass index was lower in patients with ATTR CA than in non-amyloid patients.[35] Balance disorders might be associated with the high prevalence of autonomic neuropathy (50% in patients with ATTRwt CA) and lumbar spinal stenosis by ATTR deposits in the ligamentum flavum.[36] Memory complaints and sphincter disorders could be explained respectively by a reduction in cerebral blood flow and higher doses of diuretics. Lastly, and even though frailty

Figure 2 Multivariate regression analysis, adjusted for the matching criteria and diabetes. Adjusted odds ratios were estimated using multivariate regression analysis, adjusted for the matching criteria and diabetes. Dots indicate odds ratio; horizontal lines indicate 95% confidence interval. Relative to control patients, patients in the HF + ATTRwt+ group were more likely to present with shrinking (*P* = 0.03), balance disorders (according to the one-leg standing test) (*P* = 0.02), memory complaints (*P* = 0.05) and overactive bladder (*P* = 0.03). SEGA, short emergency geriatric assessment; SPPB, short physical performance battery.



assessment tools are frequently administered to patients with HF (regardless of whether or not they have ATTR CA), specific validation in this setting is required.

Clinical implications: the measurement and management of frailty in patients with ATTRwt CA

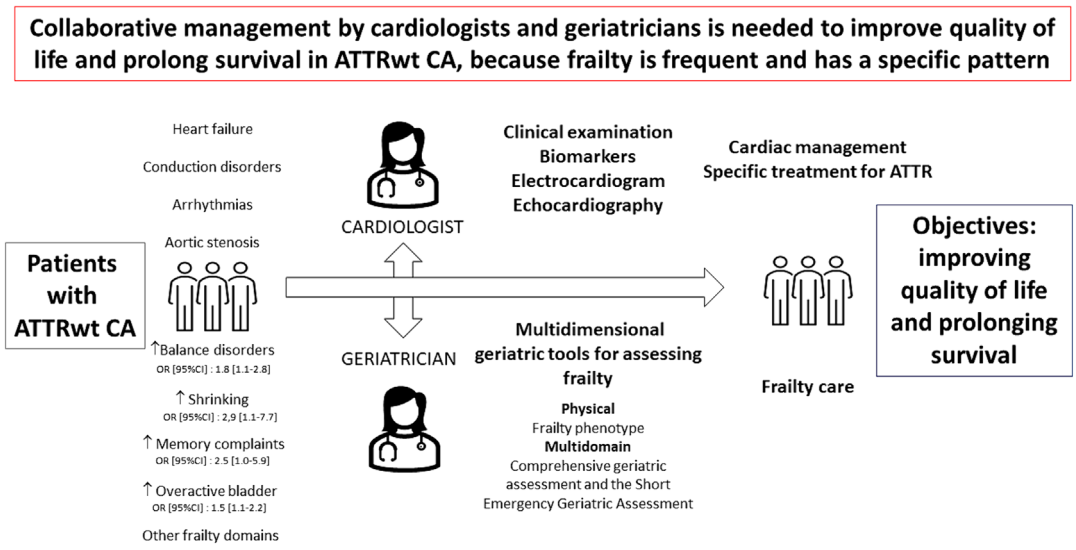
Our study highlighted the importance of screening patients with ATTRwt CA for frailty. Our HF + ATTRwt+ and HF + ATTRwt− groups appeared to have different frailty phenotypes. As suggested by our earlier results, patients who might need to be referred to a geriatrician could be screened in about 10 min by their cardiologist via the Fried phenotype and SEGA.[20] Frailty assessment should be incorporated into the routine clinical evaluation of patients with ATTRwt CA, with a view to improving quality of life, improving risk stratification, and facilitating treatment decisions (*Figure* 3). These benefits have already been observed in older patients with cancer.[37] Moreover, the prognostic impact of frailty on ATTR CA is starting to emerge.[16] Recent data also suggest that transcatheter aortic valve replacement (TAVR) is effective in CA patients with aortic stenosis.[38] A geriatric assessment can therefore have a fundamental influence on the decision to prescribe (or not) these innovative therapies. The results of a geriatric assessment enable us to identify patients who are likely to benefit most from these treatments (particularly TAVR and TTR stabilizers) with an acceptable level of risk. This approach enables the personalized management that is essential in this multisystem disease, with treatment goals being set as a function of the patient's overall condition.

To date, the optimal follow-up schedule for patients with CA includes a six-monthly visit with an electrocardiogram and a battery of blood tests (including NTproBNP and troponin) and yearly cardiac echography and 24 h Holter recording.[21] The specific frailty phenotype in patients with amyloidosis suggest that innovative care pathways are needed to (i) manage the symptoms, signs and complications of the disease, and (ii) attenuate disease progression through the use of ATTR-specific therapies.[39] The guidelines on diagnosis and care published by the French High Authority for Health suggest that the results of a CGA can help to optimize care and maintain autonomy and quality of life.[40] Future research should assess frailty in a larger population of patients with ATTwt-CA and in other subpopulations of patients with CA, receiving TTR stabilizer. Frailty could also be used as an outcome in future Phase III studies involving new therapeutics. Lastly, as the body of literature data on this topic grows, it will be important to develop and validate tools specifically for patients with ATTR CA.

Study limitations

The study's limitations include its single-centre design and the small sample size, which limited the statistical power. Furthermore, the pandemic of coronavirus disease 2019 prevented us from including the originally planned number of control patients. Thus, future studies using multidimensional geriatric tools to assess frailty, in a larger population of patients with ATTRwt CA, and in other subpopulations of patients with CA, are needed to confirm these observations and ensure their generalizability.

Figure 3 Collaborative management by cardiologists and geriatricians. Collaborative management by cardiologists and geriatricians is needed to improve quality of life and prolong survival in ATTRwt CA, because frailty is frequent and have a specific pattern. ATTRwt CA, wild-type transthyretin cardiac amyloidosis; OR, odds ratio.



Conclusion

Frailty is very frequent in patients with ATTRwt CA and forms an integral part of the clinical picture. We identified a specific frailty phenotype in ATTRwt CA: several frailty parameters were significantly associated with the presence of CA, independently of age, sex, NYHA class and diabetes. Patients with ATTRwt CA should be screened for frailty and managed collaboratively by cardiologists and geriatricians, with a view to improving quality of life and assessing the value of TTR stabilizer therapy.

Acknowledgements

We thank all the staff at the French National Reference Centre for Cardiac Amyloidosis (especially Carole Henrion and Isabelle Vallat) for their collaboration and David Fraser (Biotech Communication SARL, Ploudalmézeau, France) for editorial assistance.

Conflict of interest

A. B. has received consultancy fees from Pfizer, Novartis, Vifor Pharma, Boehringer and Astra Zeneca. T. D. has received research grants from Pfizer and Akcea Therapeutics and consultancy fees from Novartis, Vifor Pharma, Pfizer, Alnylam, Akcea and ResMed. S. O. has received consultancy fees from Novartis and Pfizer. M. P., N. L., M. K., C. L., A. Z., A. G., L. H., E. T., J. P. D. and S. B. G. disclose no financial or personal conflicts of interest.

Supporting information

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

Table S1. Logistic regression analyses adjusted for matching variables and diabetes.

References

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003;**349**:583-596. doi:10.1056/NEJMra023144
2. Rapezzi C, Lorenzini M, Longhi S, Milandri A, Gagliardi C, Bartolomei I, *et al*. Cardiac amyloidosis: the great pretender. *Heart Fail Rev* 2015;**20**:117-124. doi:10.1007/s10741-015-9480-0
3. Porcari A, Bussani R, Merlo M, Varrà GG, Pagura L, Rozze D, *et al*. Incidence and characterization of concealed cardiac amyloidosis among unselected elderly patients undergoing post-mortem examination. *Front Cardiovasc Med* 2021;**8**:749523. doi:10.3389/fcvm.2021.749523
4. 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. doi:10.1093/eurheartj/ehv338
5. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, *et al*. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**:2879-2887. doi:10.1093/eurheartj/ehx350
6. Lindmark K, Pilebro B, Sundström T, Lindqvist P. Prevalence of wild type transtyrethin cardiac amyloidosis in a heart failure clinic. *ESC Heart Fail* 2021;**8**:745-749. doi:10.1002/ehf2.13110
7. Brunjes DL, Castano A, Clemons A, Rubin J, Maurer MS. Transthyretin cardiac amyloidosis in older Americans. *J Card Fail* 2016;**22**:996-1003. doi:10.1016/j.cardfail.2016.10.008
8. Yanagisawa A, Ueda M, Sueyoshi T, Okada T, Fujimoto T, Ogi Y, *et al*. Amyloid deposits derived from transthyretin in the ligamentum flavum as related to lumbar spinal canal stenosis. *Mod Pathol Off J U S Can Acad Pathol Inc* 2015;**28**:201-207. doi:10.1038/modpathol.2014.102
9. Bartier S, Bodez D, Kharoubi M, Guellich A, Canouï-Poitrine F, Chatelin V, *et al*. Association between hearing loss and hereditary ATTR amyloidosis. *Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis* 2019;**26**:234-242. doi:10.1080/13506129.2019.1663814
10. Boyle RP, Sharan J, Schwartz G. Carpal tunnel syndrome in transthyretin cardiac amyloidosis: implications and protocol for diagnosis and treatment. *Cureus* 2021;**13**:e14546. doi:10.7759/cureus.14546
11. Kharoubi M, Roche F, Bézard M, Hupin D, Silva S, Oghina S, *et al*. Prevalence and prognostic value of autonomic neuropathy assessed by Sudoscan® in transthyretin wild-type cardiac amyloidosis. *ESC Heart Fail* 2021;**8**:1656-1665. doi:10.1002/ehf2.13131
12. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, *et al*. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail* 2019;**12**:e006075. doi:10.1161/CIRCHEARTFAILURE.119.006075
13. Berthelot E, Broussier A, Hittinger L, Donadio C, Rovani X, Salengro E, *et al*. FINC-94 network. Patients with cardiac amyloidosis are at a greater risk of mortality and hospital readmission after acute heart failure. *ESC Heart Fail* 2023;**10**:2042-2050. doi:10.1002/ehf2.14337
14. Jaramillo-Hidalgo J, Quezada-Feijoó M, Ramos M, Toro R, Gómez-Pavón J, Ayala-Muñoz R. Prevalence of transthyretin cardiac amyloidosis in elderly patients diagnosed with heart failure. *Rev Esp Geriatr Gerontol* 2023;**58**:8-14. doi:10.1016/j.regg.2022.10.005
15. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, *et al*. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018;**39**:2799-2806. doi:10.1093/eurheartj/ehx589
16. Fine NM, McMillan JM. Prevalence and prognostic significance of frailty among patients with transthyretin amyloidosis cardiomyopathy. *Circ Heart Fail* 2021;**14**:e008105. doi:10.1161/CIRCHEARTFAILURE.120.008105
17. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146-M157. doi:10.1093/gerona/56.3.m146

18. Yang X, Lupón J, Vidán MT, Ferguson C, Gastelurrutia P, Newton PJ, *et al*. Impact of frailty on mortality and hospitalization in chronic heart failure: a systematic review and meta-analysis. *J Am Heart Assoc* 2018;**7**:e008251. doi:10.1161/JAHA.117.008251
19. Vitale C, Jankowska E, Hill L, Piepoli M, Doehner W, Anker SD, *et al*. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail* 2019;**21**:1299-1305. doi:10.1002/ejhf.1611
20. Broussier A, David JP, Kharoubi M, Oghina S, Segaux L, Teiger E, *et al*. Frailty in wild-type transthyretin cardiac amyloidosis: the tip of the iceberg. *J Clin Med* 2021;**10**:p3415. doi:10.3390/jcm10153415
21. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, *et al*. 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. doi:10.1093/eurheartj/ehab072
22. Rockwood K, Mogilner A, Mitnitski A. Changes with age in the distribution of a frailty index. *Mech Ageing Dev* 2004;**125**:517-519. doi:10.1016/j.mad.2004.05.003
23. Oubaya N, Dramé M, Novella J-L, Quignard E, Cunin C, Jolly D, *et al*. Screening for frailty in community-dwelling elderly subjects: predictive validity of the modified SEGA instrument. *Arch Gerontol Geriatr* 2017;**73**:177-181. doi:10.1016/j.archger.2017.07.026
24. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;**9**:179-186. doi:10.1093/geront/9.3_Part_1.179
25. Vellas B, Villars H, Abellan G, Soto ME, Rolland Y, Guigoz Y, *et al*. Overview of the MNA—its history and challenges. *J Nutr Health Aging* 2006;**10**:463-465. doi:10.1093/geront/9.3_Part_1.179
26. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, *et al*. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;**49**:M85-M94. doi:10.1093/geronj/49.2.m85
27. Cesari M, Kritchevsky SB, Penninx BWHJ, Nicklas BJ, Simonsick EM, Newman AB, *et al*. Prognostic value of usual gait speed in well-functioning older people-results from the Health, Aging and Body Composition Study. *J Am Geriatr Soc* 2005;**53**:1675-1680. doi:10.1111/j.1532-5415.2005.53501.x
28. Vellas BJ, Wayne SJ, Romero L, Baumgartner RN, Rubenstein LZ, Garry PJ. One-leg balance is an important predictor of injurious falls in older persons. *J Am Geriatr Soc* 1997;**45**:735-738. doi:10.1111/j.1532-5415.1997.tb01479.x
29. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. *Neurology* 2000;**55**:1621-1626. doi:10.1212/wnl.55.11.1621
30. Hyer L, Blount J. Concurrent and discriminant validities of the geriatric depression scale with older psychiatric inpatients. *Psychol Rep* 1984;**54**:611-616. doi:10.2466/pr0.1984.54.2.611
31. Haab F, Richard F, Amarenco G, Coloby P, Arnould B, Benmedjahed K, *et al*. Comprehensive evaluation of bladder and urethral dysfunction symptoms: development and psychometric validation of the Urinary Symptom Profile (USP) questionnaire. *Urology* 2008;**71**:646-656. doi:10.1016/j.urology.2007.11.100
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. doi:10.1016/j.ijcard.2017.01.153
33. Sánchez MB, Dolores Matoso M, Aguirre MA, Mercedes Nucifora E, Marciano S, Cepeda J, *et al*. Prevalence of digestive manifestations in patients with amyloidosis. *Amyloid* 2019;**26**:103-104. doi:10.1080/13506129.2019.1582492
34. Kharoubi M, Bodez D, Bézard M, Zaroui A, Galat A, Guendouz S, *et al*. Describing mode of death in three major cardiac amyloidosis subtypes to improve management and survival. *Amyloid* 2022;**29**:79-91. doi:10.1080/13506129.2021.2013193
35. Poterucha TJ, Kurian D, Raiszadeh F, Teruya S, Elias P, Kogan R, *et al*. Relation of body mass index to transthyretin cardiac amyloidosis particularly in black and Hispanic patients (from the SCAN-MP study). *Am J Cardiol* 2022;**177**:116-120. doi:10.1016/j.amjcard.2022.05.003
36. Eldhagen P, Berg S, Lund LH, Sörensson P, Suhr OB, Westermark P. Transthyretin amyloid deposits in lumbar spinal stenosis and assessment of signs of systemic amyloidosis. *J Intern Med* 2021;**289**:895-905. doi:10.1111/joim.13222
37. Mohile SG, Mohamed MR, Xu H, Culakova E, Loh KP, Magnuson A, *et al*. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. *Lancet* 2021;**398**:1894-1904. doi:10.1016/S0140-6736(21)01789-X
38. Cannata F, Chiarito M, Pinto G, Villaschi A, Sanz-Sánchez J, Fazzari F, *et al*. Transcatheter aortic valve replacement in aortic stenosis and cardiac amyloidosis: a systematic review and meta-analysis. *ESC Heart Fail* 2022;**9**:3188-3197. doi:10.1002/ehf2.13876
39. Irabor B, McMillan JM, Fine NM. Assessment and management of older patients with transthyretin amyloidosis cardiomyopathy: geriatric cardiology, frailty assessment and beyond. *Front Cardiovasc Med* 2022;**9**:863179. doi:10.3389/fcvm.2022.863179
40. HAS santé (2021). Protocole National de Diagnostic et de Soins (PNDS) Amyloses Cardiaques Filière Cardiogen Centre de référence Amyloses Cardiaques 2020–2021. https://www.has-sante.fr/upload/docs/application/pdf/2021-12/pnds_amyloses_cardiaques_v20_version_finale_31082021.pdf. Accessed 6 April 2022.