Circulation: Heart Failure

ORIGINAL ARTICLE

Prognostic Value of Malnutrition, Frailty, and Physical Performance in Transthyretin Cardiac Amyloidosis: Insights From a Prospective Multicenter Cohort Study

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BACKGROUND: The prevalence of transthyretin cardiac amyloidosis among older adults (often octogenarians) is increasing. We aimed to determine whether age and geriatric syndromes bear any impact on the management and outcomes in transthyretin cardiac amyloidosis and assess the risk of ageism.

METHODS: In a prospective, multicenter cohort study, 256 patients diagnosed with transthyretin cardiac amyloidosis from March 2021 to March 2024 underwent comprehensive geriatric assessment (CGA). The study evaluated the prevalence and clinical associations of CGAs across different disease stages (National Amyloidosis Centre stage). Key CGA domains included disability, malnutrition, depression, frailty, Short Physical Performance Battery, and cumulative deficits (sum of the single CGA items). Associations of these measures with disease-modifying therapy and overall mortality were analyzed.

RESULTS: Median age was 82 years (men: n=223 [87%]; variant: n=19 [7.4%]); 129 (50.3%) patients received disease modifiers. Those ≥85 years had significantly lower odds of receiving disease-modifying therapy even after adjusting for disability, frailty, and cumulative deficits. Over 1.9 (interquartile range, 1.0–2.3) years, 45 (17.6%) patients died. After adjustment for National Amyloidosis Centre stage, diuretics and disease modifiers, CGA domains of disability, malnutrition, Short Physical Performance Battery, frailty, and number of deficits, but not age, were significantly associated with mortality. Assessment of CGA domains improved National Amyloidosis Centre prognostic accuracy.

CONCLUSIONS: In a national prospective cohort of patients with transthyretin cardiac amyloidosis, older age was associated with lower prescription of disease modifiers, even among individuals with a low burden of geriatric syndromes. However, when adjusted for geriatric domains, age was not associated with survival, indicating potential ageism. Because some geriatric syndromes may be modifiable, a CGA could enhance risk stratification, reduce age-related bias, and improve outcomes.

Key Words: amyloidosis ■ frailty ■ malnutrition ■ octogenarians ■ prognosis

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.125.012777.
For Sources of Funding and Disclosures, see page XXX.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- This is one of the first prospective, multicenter studies to demonstrate that in transthyretin cardiac amyloidosis, older age alone does not drive prognosis, while geriatric syndromes—particularly frailty, malnutrition, and disability—are independently associated with mortality. Yet older patients were less likely to receive disease-modifying therapy regardless of clinical status, suggesting age-driven treatment bias.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Incorporating a structured comprehensive geriatric assessment into transthyretin cardiac amyloidosis care can enhance risk stratification, uncover modifiable vulnerabilities, and reduce age-related therapeutic inertia. Rather than relying on chronological age, clinicians should assess frailty and functional status to inform treatment decisions and improve care equity in older patients with cardiac amyloidosis.

Nonstandard Abbreviations and Acronyms

ATTR-CA	transthyretin cardiac amyloidosis
CFS	Clinical Frailty Scale
CGA	comprehensive geriatric assessment
HF	heart failure
NAC	National Amyloidosis Centre
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SPPB	Short Physical Performance Battery

Transthyretin cardiac amyloidosis (ATTR-CA) is a common cause of heart failure (HF) among older individuals.[1] It can present in 2 distinct forms (hereditary [v-ATTR-CA] or senile [wild-type]), which are accompanied by different signs and symptoms[2]: the often-nonspecific nature is responsible for a diagnostic delay, which can affect outcome in the long term.[3,4] The epidemiology of ATTR-CA has changed profoundly in the last 2 decades, with patients being diagnosed at an older age (nowadays >80 years), with milder phenotypes, but higher burden of comorbidities.[4] New disease-modifying drugs are now available, but evidence suggests that not all patients may benefit in terms of long-term outcome,[5,6] suggesting that careful candidate selection is mandatory. While a higher number of comorbidities is a known prognosticator of outcome among older adults, geriatric syndromes like frailty, disability, chronic malnutrition, and impaired physical performance have been shown to have excellent discriminatory capabilities for risk stratification. At present, however, whether age and, more specifically, geriatric syndromes bear any impact on the management and prognosis of this challenging condition is poorly understood. In this scenario, a comprehensive geriatric assessment (CGA) aimed at assessing all these syndromes could be a useful tool among patients with ATTR-CA.[7]

Given the present paucity of data on ATTR-CA and CGA, and the unmet need to identify key markers for better patient selection to avoid ageism (withholding therapy according to age alone) or therapeutic futility, we aimed to prospectively determine (1) whether age and geriatric syndromes are associated with disease modifier prescriptions; (2) compare the association of age and geriatric syndromes with outcome, and (3) assess whether a CGA-guided strategy may improve the discriminatory capacity of the National Amyloidosis Centre (NAC) staging system.[8]

METHODS

Data Availability Statement

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

Study Design and Population

This is a prospective, multicenter, observational cohort study. All consecutive patients diagnosed with ATTR-CA from March 2021 to March 2024 were prospectively invited to participate to a CGA screening by trained healthcare personnel (attending physicians or nurses) within the visit or at a CGA outpatient clinic. The diagnosis and risk stratification of ATTR-CA were established based on validated diagnostic and prognostic criteria.[2] Disease stage was defined by the NAC score: Stage I was defined as NT-proBNP (N-terminal pro-B-type natriuretic peptide) ≤3000 ng/L and estimated glomerular filtration rate ≥45 mL/min, stage III was defined as NT-proBNP >3000 ng/L and estimated glomerular filtration rate <45 mL/min, and the remainder were stage II.[8]

Participating centers included: Tuscan Referral Centre for Cardiac Amyloidosis, Careggi University Hospital (Florence, Italy), Turin (University of Turin), Bologna (IRCCS Azienda Ospedaliero–Universitaria di Bologna), Rome (Azienda Ospedaliera Universitaria Sant'Andrea, Sapienza University), the Centre for Rare Diseases, Cardiology Department, AORN Monaldi (Naples, Italy).

The following items were screened in the CGA: basic/instrumental activities of daily living (B/I ADL: disability defined as basic activities of daily living <4 or instrumental activities of daily living <4), malnutrition (Mini Nutritional Assessment–Short Form; risk of malnutrition<10/15), Depression (Geriatric Depression Scale–15 items, positive screening >5/15), cognitive impairment (Pfeiffer test, positive screening >3/10), polypharmacy (defined as chronic use of >5 drugs), Clinical Frailty Scale (CFS, nonfrail: CFS score 1–3 [patients with no impairment in daily living]; mild frailty: CFS score 4–5 [patients with mild functional impairment, from slowing to instrumental activities of daily living impairment]; severe frailty: CFS score 6–9 [progressive impairment of basic activities of daily living][9]),

Short Physical Performance Battery (SPPB, a score ranging from 12 (preserved physical performance) to 0 (not able to perform): low performance: ≤6; intermediate performance: 7–9; high performance 10–12[10]) and a modification of the frailty phenotype[11] (defined as a composite of ≥3 among: weight loss, low physical activity by SPPB, reduced walk time, weakness as referred by the patient during interview, exhaustion derived by the questions in the Geriatric Depression Scale).

Each patient underwent a comprehensive cardiological evaluation standardized at each participating center, including ECG, transthoracic echocardiography, and assessment of laboratory parameters; only patients with ≥6 months of follow-up were included in the present analysis.

The study was conducted according to the Declaration of Helsinki, and informed consent was obtained under the institutional review board policies of the relevant hospital administrations (leading center: Careggi University Hospital Ethics Committee: 22586_oss).

Follow-Up and Clinical Outcomes

All patients underwent 6 to 12 months follow-up visits (or earlier if deemed clinically necessary) per center protocol and in line with current practice.[2] Patients were contacted by telephone to assess live status. The primary outcomes were the association of variables included in the CGA with the prescription of disease-modifying therapy and overall mortality. Furthermore, since patients nowadays are diagnosed at earlier stages of the disease, we aimed to describe the distribution of the items of the CGA according to date of enrollment (year 1: March 2021–April 2022; year 2: April 2022–March 2023; and year 3: April 2023–March 2024).

Statistical Analysis

Continuous variables are reported as medians with interquartile ranges and were compared between groups with nonparametric tests. Categorical variables, reported as counts and percentages, were compared between groups with χ^2 tests (or Fisher exact test when applicable). Kendall Tau correlation was used to correlate the frail phenotype and the CFS.

Logistic regression analysis was used to determine factors associated with prescription of disease-modifying therapy (stabilizers or silencers). Kaplan-Meier curves were constructed to analyze survival in different groups, with statistical significance being assessed with a log-rank test. Cox multivariable regression analysis (variable selection method with backward stepwise elimination) to determine factors associated with all-cause mortality was performed, including all candidate variables (P<0.10 at univariate analysis). Harrell C statistic was calculated to measure the discriminatory capacity of each CGA domain in addition to the NAC staging system. The fitness of each model (NAC versus NAC+CGA domains) was tested with the Likelihood Ratio Test.

A P<0.05 was considered statistically significant. All analyses were performed using SPSS Statistics for Macintosh version 29.0 (Version 29.0; IBM Corp, Armonk, NY), STATA (v. 18.0 StataCorp, 2023. Stata Statistical Software: Release 18; StataCorp LLC, College Station, TX), GraphPad Prism 10.1.1, and the packages epiR, riskRegression, and epitools RStudio 2024.04.1 (R Core Team 2024).

RESULTS

Baseline Clinical Characteristics

Overall, 256 patients were enrolled within the study period (median age, 82 [78–86] years, men: n=223 (87.1%), n=v-ATTR-CA: 19 (7.4%). The main variant was Ile88Leu (n=14), followed by Val142Ile, Phe84Leu and Val50Met. Baseline clinical and instrumental characteristics are summarized in Table 1. Figure S1 summarizes the study cohort derivation.

The median NT-proBNP and estimated glomerular filtration rate were 2642 (1176–4373) and 58 (47–70) mL/min per m^2, respectively. Overall, 50.4% of patients were in NAC stage I, 32.8% in NAC stage II, and 16.8% in NAC stage III. Data on the 6-minute walking distance were available only for 133 patients and are presented in Table 2.

Over the study period, a total of 129 patients (53.0%) were prescribed disease-modifying therapy, including 124 receiving tafamidis and 7 referred to patisiran.

Comprehensive Geriatric Assessment

Prevalence and distribution of the items of the CGA by the NAC Staging system are presented in Table 2. Although the overall number of preserved basic activities of daily living was similarly distributed across the 3 classes, number of instrumental activities of daily living decreased with worsening disease stage, with overt disability being as high as 37.2% among NAC III patients. Risk of malnutrition increased with disease stage.

Polypharmacy, depression, and cognitive decline, which were present in 65.6%, 36.7%, and 14.5% of cases in the overall cohort, did not show distinct prevalence by NAC stage.

Physical performance assessment (SPPB available for 249/256 patients) showed that 27% of patients had a severe reduction of motor capacity (SPPB≤6), with the highest decrease among NAC III patients.

Finally, frailty analysis by frailty phenotype and CFS classified 29.8% and 19.1% patients as frail, respectively. For both tools, worsening disease stage was associated with worsening functional profile. Of note, the correlation of the frail phenotype and the CFS score was only 0.704 (95% CI, 0.630–0.766). Finally, the overall number of deficits increased with higher NAC classes. Clinical and functional baseline characteristics of patients also according to age categories, are summarized in Table S1.

Over the years (from 2021 to 2024), the disease stage at study enrollment had improved. Mirroring this trend, disability, frailty scales, and cumulative deficits showed similar patterns. By contrast, depression, malnutrition, and SPPB were similarly distributed (Figure 1).

Table 1. Baseline Clinical Characteristics of Patients Diagnosed With ATTR-CA

	N=256
Age, y, median [IQR]	82 [78–86]
Men, n (%)	223 (87.1)
Enrollment year, n (%)	
Year 1	49 (19.1)
Year 2	78 (30.5)
Year 3	129 (50.4)
V-ATTR-CA, n (%)*	19 (7.4)
Ile88Leu	14
Val142Ile	2
Phe84Leu	2
Val50Met	1
NYHA class III/IV, n (%)	60 (23.4)
eGFR, median [IQR]	58 [46–71]
NT-proBNP, median [IQR]	2645 [1105–4781]
NAC stage, n (%)	
I	129 (50.4)
II	84 (32.8)
III	43 (16.8)
Atrial fibrillation, n (%)	157 (61.3)
Hypertension, n (%)	129 (50.4)
Type 2 diabetes, n (%)	49 (19.1)
Ischemic heart disease, n (%)	25 (9.8)
Stroke/TIA, n (%)	16 (6.3)
PM, n (%)	26 (10.2)
ICD, n (%)	8 (3.1)
Patients enrolled in clinical trials, n (%)	18 (7.0)
Therapy	
Tafamidis, n (%)	124 (48.4)
Patisiran	7 (3.5)
Beta-blockers, n (%)	106 (41.4)
ACE inhibitor/ARBs, n (%)	52 (20.3)
ARNI, n (%)	4 (1.6)
MRAs, n (%)	26 (10.7)
Loop diuretic, n (%)	185 (72.3)
Diuretic dose, median [IQR]	75 [25–125]
Echocardiographic evaluation	
LAD, mm, median [IQR]	47 [43–50]
LVEF, %, median [IQR]	55 [43–58]
IVS, mm, median [IQR]	17 [15–18]
PW, mm, median [IQR]	16 [15–17]

ACE/ARBs indicates angiotensin converting enzyme inhibitors/angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; ATTR-CA, transthyretin cardiac amyloidosis; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; IVS, interventricular septum; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; MRA, mineralcorticoid receptor antagonist; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; PW, posterior wall; and TIA, transient ischemic attack.

*Information available for 249 patients.

Association of the CGA With Disease-Modifier Prescription

Functional characteristics of patients referred to disease-modifying therapy are summarized in Table S2.

The prescription of disease-modifying drugs in patients with ATTR-CA was reduced in older individuals (≥85 years), regardless of their functional status (Table 3). At multivariable logistic regression analysis, patients over 85 years had significantly lower odds of receiving these treatments compared with those under 80 years, even after adjusting for disability, frailty phenotype, CFS scores, and number of cumulative deficits.

Association of the CGA With Outcome

A total of 45 (17.6%) patients died over a median follow-up of 1.9 (1.0–2.3) years. Cause of death was determined for 29 of 45 (64.4%). Among these, 18 of 29 were cardiac-related and 11 of 29 were noncardiac related.

At Kaplan-Meier analysis, treatment with disease modifiers was associated with improved survival at follow-up (cumulative incidence of overall mortality in patients referred to disease modifiers versus therapy naive: 7.6 per 100 person-years (95% C.I. 4.5-12.6) versus 16.9 per 100 person-years ([95% CI, 11.7–22.6]; P=0.027). Survival analysis by CGA items stratified by referral to disease modifiers showed that disability, risk of malnutrition, physical performance (SPPB), the CFS score, the frailty phenotype, and the cumulative number of deficits were associated with mortality among patients with and without disease-modifying therapy (Figure 2).

At Cox multivariable regression analysis (Table 4, univariable analysis summarized in Table S3), however, age showed a limited impact on all-cause mortality in patients with ATTR-CA, with no significant differences between age categories after multiple adjustments. By contrast, geriatric syndromes demonstrated a significant effect on mortality risk. Disability, risk of malnutrition, mobility, frailty measures, and the overall number of cumulative deficits were, on the other hand, strongly associated with increased mortality.

Discrimination analysis, with the Harrel C statistics and the likelihood ratio tests (Table 5), demonstrated the overall positive restratification impact of CGA items with respect to the NAC staging system on the whole population.

DISCUSSION

The present study assessed for the first time the clinical impact of different CGA items in consecutive patients with ATTR-CA and demonstrated that (1) the prevalence of frailty varied from 19% to 30% depending on the scale

Table 2. Baseline Geriatric Clinical Characteristics of Patients Diagnosed With Transthyretin Cardiac Amyloidosis

	Overall population (N=256)	NAC staging system			*P* value
		I; n=129 (50.4)	II; n=84 (32.8)	III; n=43 (16.8)	
Age, y, median [IQR]	82 [78–86]	79 [75–84]	81 [77–85]	83 [78–85]	0.004
BADL, median [IQR]	6 [5–6]	6 [5–6]	6 [5–6]	5 [3–6]	0.773
IADL, median [IQR]	5 [4–7]	7 [5–8]	6 [3–8]	5 [3–8]	0.009
Overt disability in ADL, n (%)	52 (20.3)	18 (14.0)	18 (21.4)	16 (37.2)	0.001
MNA-SF, median [IQR]	12 [10–14]	13 [10–14]	12 [10–13]	11.5 [8–13]	0.047
Risk of malnutrition, n (%)	97 (37.9)	40 (31.0)	34 (40.5)	23 (53.5)	0.007
Polypharmacy, n (%)	173 (67.6)	80 (62.0)	59 (70.2)	34 (79.1)	0.053
GDS score, median [IQR]	3 [1–7]	3 [1–6]	3 [1–6]	4 [2–8]	0.268
Depression, n (%)	97 (37.9)	43 (33.3)	33 (39.3)	21 (48.8)	0.183
Cognitive decline, n (%)	37 (14.5)	13 (10.1)	15 (17.9)	9 (20.9)	0.120
6-min walking distance, median [IQR]*	335 [277–401]	356 [298–416]	335 [252–399]	266 [187–313]	0.053
SPPB,* median [IQR]	8 [5–10]	9 [7–11]	8 [6–9]	7 [2–9]	<0.001
SPPB≤6, n (%)	68 (27.3)	27 (21.3)	24 (28.9)	17 (43.6)	0.015
Frail phenotype					0.001
Robust, n (%)	83 (32.4)	54 (41.9)	20 (23.8)	9 (20.9)	
Prefrail, n (%)	96 (37.5)	48 (37.2)	36 (42.9)	12 (27.9)	
Frail, n (%)	77 (30.1)	27 (20.9)	28 (33.3)	22 (51.2)	
Clinical Frailty Scale score	3 [2–5]	3 [2–4]	4 [2–5]	5 [3–6]	0.001
1–3, n (%)	139 (54.3)	87 (67.4)	40 (47.6)	12 (27.9)	
4–5, n (%)	68 (26.6)	28 (21.7)	25 (29.8)	15 (34.9)	<0.001
≥6, n (%)	49 (19.1)	14 (10.9)	19 (22.6)	16 (37.2)	
Cumulative deficits					<0.001
0–1, n (%)	145 (56.6)	86 (66.7)	44 (52.4)	15 (34.9)	
2–3, n (%)	61 (23.8)	27 (20.9)	24 (28.6)	10 (23.2)	
>4, n (%)	50 (19.5)	16 (12.4)	16 (19.0)	18 (41.9)	

For categorical variables, *P* values reflect global χ^2. SPPB is determined in 249 patients. ADL indicates activities of daily living; BADL, basic activities of daily living; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; IQR, interquartile range; MNA-SF, Mini Nutritional Assessment Short Form; NAC, National Amyloidosis Centre; and SPPB, Short Physical Performance Battery.

*Available for 133 patients.

adopted; over the 3 years of enrollment, the prevalence of malnutrition, depression, and impaired physical performance remained stable, whereas the prevalence of frailty, disability, and cumulative deficits declined, mirroring a significant improvement in NAC stage; (2) patients aged over 85 years had significantly lower odds of receiving disease-modifying treatments compared with those aged under 80 years, even after adjusting for disability, frailty, and cumulative deficits. This reduction persisted across different models, indicating that age was a key factor influencing the decision to prescribe disease-modifying drugs; and (3) at a median of 1.9 years, disability, risk of malnutrition, physical performance, frailty and an increasing number of deficits were associated with increased risk of mortality in both patients with and without disease modifiers and even after adjustment for multiple known prognosticators; CGA domains enhanced the predictive value of the NAC staging system for all-cause mortality. Age, by contrast, had no impact on survival, suggesting that there is a non-negligible risk for ageism (withholding effective treatments based on age alone) in ATTR-CA.

These findings provide insight into the changing epidemiology and management of older patients with ATTR-CA. Over the past 2 decades, patients have been presenting at older ages with earlier-stage disease but greater comorbidity and competing risks.[4] Data from trials and registries have shown variable benefits of disease-modifying therapy in octogenarians,[5,6,12] suggesting that careful patient selection may improve outcomes.[13] In this context, routine assessment of key geriatric prognostic factors could help refine risk stratification and guide individualized interventions.

The significantly lower use of disease-modifying therapy in older patients raises important clinical and ethical considerations. Although advanced disease stage and comorbidities may justify nonprescription in some cases, our findings suggest that age alone influenced treatment decisions, even in functionally preserved individuals. This

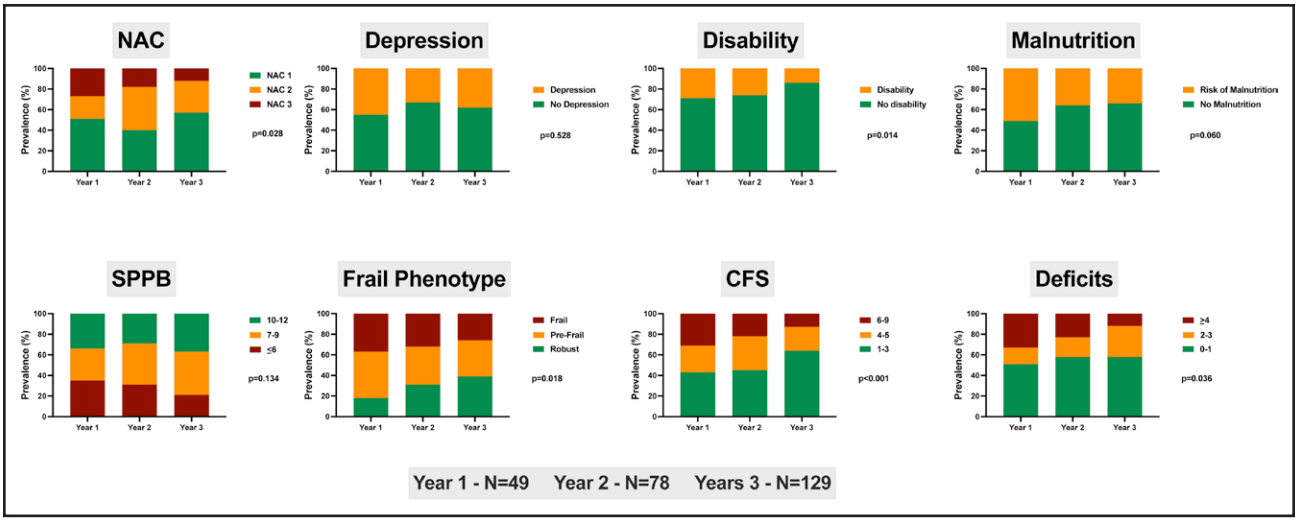

Figure 1. Prevalence of comprehensive geriatric assessment items by year at enrollment.
CFS indicates Clinical Frailty Scale; NAC, National Amyloidosis Centre; and SPPB: Short Physical Performance Battery. Years have been divided as follows: year 1: March 2021–April 2022; year 2: April 2022–March 2023; and year 3: April 2023–March 2024.

trend may reflect therapeutic inertia or age-related bias, both recognized in geriatric care. In Italy, where access to Tafamidis is governed by public reimbursement based on national (Italian Drug Agency [Agenzia Italiana del Farmaco www.aifa.gov.it]) and subsequent regional criteria taken from Phase III Trials, age may indirectly limit eligibility. These factors, combined with physician perception, likely contribute to reduced prescribing in older adults.

Although patients aged >85 years had a higher prevalence of advanced NAC stages, age itself was not independently associated with increased mortality after adjustment for clinical and geriatric variables. This apparent paradox likely reflects the multifactorial nature of vulnerability in older adults. Geriatric syndromes—particularly frailty, disability, and malnutrition—were more common in the oldest group and emerged as stronger predictors of mortality than age alone. In addition, reduced use of disease-modifying therapy in older patients, even among those without significant functional impairment, may have influenced the relationship between age and survival. These findings support the notion that chronological age is an imperfect surrogate for biological risk and highlight the value of CGA in refining prognostic stratification and guiding treatment decisions in ATTR-CA.

Frailty was recently associated with quality of life,[14] caregiver relationship quality,[15] and disease duration and severity[16] in ATTR-CA, and preliminary evidence suggest that it is also associated with outcome beyond the NAC Stage and HF symptoms.[17,18] Although frailty prevalence varied by assessment tool, it was consistent with a previous ATTR-CA cohort,[17] and slightly lower than other HF cohorts >65 years old.[19]

In the present study, the prevalence of disability was high (21%), but this was not unexpected, given the average older age at evaluation. The increased mortality risk among ATTR-CA patients with disability warrants further study, particularly regarding the influence of social factors, such as the role of caregivers, on the long-term care of these patients. These findings highlight the importance of evaluating functional status and social support when planning long-term care.

Nutritional status, though often overlooked, is also key in older care. Risk of malnutrition was present in 39% of individuals, similar to other HF contexts.[20,21] Given its overlap with HF pathophysiology, malnutrition is associated with worse outcome.[22–24] Because this may be a potentially reversible condition if addressed early, active screening should be pursued whenever possible. Preliminary trials combining nutrition and exercise in older HF patients suggest that early intervention may improve physical reserve[25] with similar approaches being tested in adjacent settings such as cardiac surgery (eg, Steinmetz et al[26] and URL: https://www.clinicaltrials.gov; Unique identifier: NCT03571906).

From a biological perspective, malnutrition and sarcopenia contribute to reduced physical performance, frailty, and disability.[11] In this study, SPPB <6 was associated with a 2-fold increase in mortality risk. The SPPB may be a feasible alternative to the 6-minute walk test in frail or resource-limited contexts. Recently, the SPPB was compared with the 6-minute walking test in older patients hospitalized for acute HF: those patients with limited performance (ie, <6/12) had a similar prognosis as those who walked <242 m.[27] Given that the 6-minute walk test can refine risk stratification beyond traditional prognosticators in ATTR-CA[28] but may sometimes be difficult to perform, future studies may determine whether the SPPB could be a feasible option in resource-limited settings for patients with ATTR-CA.

Table 3. Clinical Factors Associated With Prescription of Disease Modifiers

	Univariable analysis			Adjusted for disability			Adjusted for frail phenotype			Adjusted for CFS			Adjusted for deficits		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age category, y (vs 80 y)															
80–84	0.612	0.367–1.281	0.238	0.791	0.407–1.539	0.491	0.782	0.392–1.560	0.487	0.915	0.459–1.827	0.803	0.812	0.401–1.591	0.545
≥85	0.173	0.091–0.331	<0.001	0.256	0.130–0.507	<0.001	0.237	0.112–0.480	<0.001	0.321	0.156–0.660	<0.001	0.286	0.134–0.537	<0.001
Gender (men)	1.931	0.906–4.888	0.088	1.641	0.706–3.818	0.250	1.590	0.704–3.276	0.241	1.546	0.657–3.636	0.318	1.627	0.697–3.811	0.267
NYHA class III/IV	0.297	0.015–0.556	<0.001	0.560	0.266–1.187	0.130	1.003	0.406–3.244	0.947	0.749	0.335–1.679	0.483	0.555	0.265–1.129	0.143
Disability	0.195	0.095–0.402	<0.001	0.408	0.171–0.966	0.039	…	…	…	…	…	…	…	…	…
Risk of malnutrition	0.363	0.215–0.514	<0.001	0.547	0.299–1.001	0.051	0.687	0.326–1.452	0.332	0.641	0.347–1.222	0.178	0.849	0.790–1.789	0.667
Polypharmacy	0.690	0.407–1.179	0.168	…	…	…	…	…	…	…	…	…	…	…	…
Depression	0.551	0.330–0.921	0.023	1.236	0.645–2.356	0.527	1.191	0.306–1.745	0.155	1.384	0.719–2.705	0.399	1.769	0.790–3.961	0.165
Cognitive decline	1.348	0.668–2.721	0.571	…	…	…	…	…	…	…	…	…	…	…	…
SPPB (vs 6)															
6–9	3.891	2.004–7.554	<0.001	…	…	…	…	…	…	…	…	…	…	…	…
≥10	3.360	1.704–6.621	<0.001	…	…	…	…	…	…	…	…	…	…	…	…
Frail phenotype (vs robust)															
Prefrail	1.387	0.754–2.553	0.292	…	…	…	1.584	0.717–3.497	0.234	…	…	…	…	…	…
Frail	0.182	0.090–0.367	<0.001	…	…	…	0.182	0.047–0.881	0.033	…	…	…	…	…	…
CFS score (vs 1–3)							…	…	…						
4–5	0.296	0.161–0.542	<0.001	…	…	…	…	…	…	0.441	0.216–0.901	0.025	…	…	…
6–9	0.107	0.048–0.241	<0.001	…	…	…	…	…	…	0.208	0.081–0.603	0.004	…	…	…
Cumulative deficits (vs 0–1)							…	…	…						
2–3	0.388	0.210–0.716	<0.001	…	…	…	…	…	…	…	…	…	0.489	0.190–1.233	0.124
≥4	0.157	0.074–0.334	<0.001	…	…	…	…	…	…	…	…	…	0.219	0.064–0.781	0.019

The prescription of disease-modifying drugs in transthyretin cardiac amyloidosis was reduced in older individuals, regardless of their functional status. These findings suggest that older age, rather than functional status alone, played a crucial role in limiting the use of these therapies in clinical practice. CFS indicates Clinical Frailty Scale; NYHA, New York Heart Association; OR, odds ratio; and SPPB, Short Physical Performance Battery.

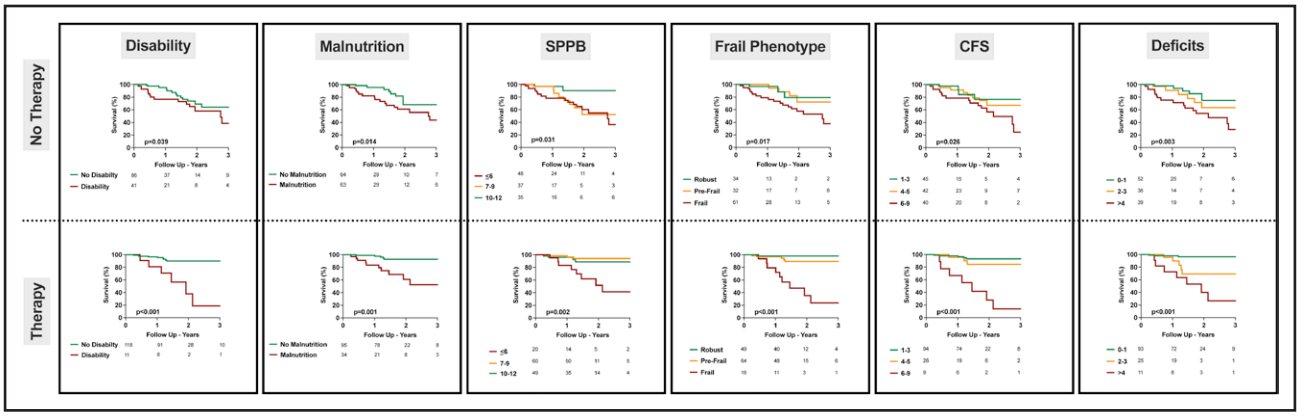

Figure 2. Survival Analysis of patients diagnosed with transthyretin cardiac amyloidosis referred to a comprehensive geriatric assessment according to the presence or absence of disease-modifying therapy.
CFS indicates Clinical Frailty Scale; and SPPB, Short Physical Performance Battery.

Finally, frail individuals had >4× higher risk of death at follow-up when compared with robust ones after adjustment for NAC Stage and therapy. The correlation between the 2 scales was moderate, suggesting that different tools explore different domains: this is expected as the CFS is a rapid eyeball exam that explores only a limited range of geriatric aspects while the other is performance-based. However, despite the different dimensions recorded by the 2 tools, frail status seems to have a class effect over the long-term prognosis, similar to other HF contexts.[29]

Our findings suggest that patients with advanced geriatric syndromes, particularly those with severe frailty, malnutrition, and disability, had worse outcomes despite receiving disease-modifying therapy. Although this may reflect a degree of therapeutic futility in highly compromised individuals, it also highlights the importance of early referral and treatment initiation before irreversible functional decline occurs, leaving room for prehabilitation. Given the substantial cost of disease-specific therapies and their growing use in older populations, these observations underscore the need for careful, multidimensional patient evaluation. Rather than relying on rigid exclusion criteria, we advocate for a multidisciplinary, individualized approach that incorporates CGA into therapeutic decision-making. This strategy can help identify patients who are most likely to benefit, support responsible resource allocation, and avoid both under- and over-treatment in vulnerable populations.

Recently, data from a multicenter cohort study showed that most diagnoses in ATTR-CA were driven by HF, with patients being older and most comorbid, thus representing a subgroup with an overall reduced survival probability and less likely to benefit from disease modifiers.[30] Given the present expansion of these class of drugs (with one medication registered and others shown to be beneficial in phase III[6,31,32]), identification and treatment of geriatric syndromes beyond age and reversible risk factors (eg, via prehabilitation) could improve the odds for therapy success, reduce the risk of ageism, and possibly identify subjects who do not benefit from disease-modifying therapy.

Limitations

This is an observational study, where only associations and not causality could be determined for therapy prescription and outcome. Only 7% of the study cohort had v-ATTR-CA: this may limit the generalizability of the study results to genetic forms of the disease. However, given that some mutations carry intrinsic neuropathy or gastrointestinal syndromes (like malabsorption), it is reasonable to hypothesize that variants belonging to the non–p.Val142Ile could be at higher risk for geriatric syndromes. By study design, patients evaluated at referral centers were in different stages of the disease: adjustment by disease duration or diagnostic delay (which are known factors associated with outcome[3]) was not possible as this information was not available for all enrolled patients. Data on 6-minute walking distance were not available for all patients in our real-world cohort. However, the SPPB, a validated tool widely used in geriatric practice, was employed within the CGA to describe both motor capacity and frailty, as it is feasible even in patients unable to complete longer distances due to frailty or other orthopedic or neurological impairments. Although we could not systematically identify orthopedic or neurological causes of walking limitation, we think their impact is captured through SPPB scores and the number of preserved basic activities of daily living. All healthcare providers (nurses, geriatricians, and cardiologists) received a formal training; however, interobserver and intraobserver variability could not be determined. Furthermore, a modified Frailty Phenotype was used to assess frailty. Finally, data on hospitalizations were not collected for survival analysis.

Table 4. Multivariable Cox Regression Analysis to Determine the Association of the Items of the Comprehensive Geriatric Assessment With All-Cause Mortality

	Adjusted for disability			Adjusted for malnutrition			Adjusted for SPPB			Adjusted for frail phenotype			Adjusted for CFS			Adjusted for deficits		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age category, y (vs 80)																		
80–84	1.800	0.749–4.325	0.170	1.660	0.669–4.120	0.275	1.559	0.630–3.856	0.338	1.626	0.652–4.053	0.297	1.883	0.413–4.771	0.182	1.436	0.578–3.568	0.436
≥85	1.365	0.623–2.994	0.374	1.446	0.613–3.408	0.339	1.358	0.568–3.248	0.491	1.306	0.522–3.091	0.543	1.403	0.570–3.452	0.461	1.083	0.463–2.535	0.855
Gender (men)	…	…	…	…	…	…				…	…	…	…	…	…	…	…	…
Diuretic therapy	1.002	1.000–1.004	0.084	1.003	1.001–1.006	0.004	1.002	1.001–1.005	0.027	1.002	0.999–1.005	0.075	1.002	1.000–1.004	0.121	1.002	1.000–1.004	0.074
NAC staging system																		
2 vs 1	1.965	0.827–4.670	0.126	2.115	1.909–9.980	0.089	1.886	0.877–4.574	0.160	2.050	0.870–4.830	0.101	1.869	0.789–4.425	0.388	1.942	0.819–4.603	0.132
3 vs 1	5.421	2.189–12.838	0.001	4.558	1.898–7.712	0.001	4.497	1.853–10.899	0.001	6.236	2.801–13.830	<0.001	6.285	2.812–14.049	0.001	4.195	1.750–10.051	0.001
Disease modifiers	0.981	0.454–2.186	0.963	1.037	0.476–2.256	0.928	0.887	0.432–2.068	0.945	0.992	0.552–2.997	0.963	0.910	0.486–2.105	0.644	0.988	0.503–2.354	0.830
Disability	2.482	1.306–4.717	0.006	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Risk of malnutrition	…	…	…	3.862	1.898–7.142	<0.001	…	…	…	…	…	…	…	…	…	…	…	…
Polytherapy	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Depression	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Cognitive decline	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
SPPB (vs 6)																		
6–9	…	…	…	…	…	…	0.416	0.200–0.867	0.019	…	…	…	…	…	…	…	…	…
≥10	…	…	…	…	…	…	0.363	0.140.922	0.033	…	…	…	…	…	…	…	…	…
Frail phenotype (vs robust)																		
Prefrail	…	…	…	…	…	…	…	…	…	1.307	0.396–4.311	0.661	…	…	…	…	…	…
Frail	…	…	…	…	…	…	…	…	…	5.702	1.971–16.500	0.001	…	…	…	…	…	…
CFS score (vs 1–3)	…	…	…	…	…	…	…	…	…	…	…	…						
4–5	…	…	…	…	…	…	…	…	…	…	…	…	1.584	0.644–3.883	0.315	…	…	…
6–9	…	…	…	…	…	…	…	…	…	…	…	…	5.087	2.308–11.213	<0.001	…	…	…
Cumulative deficits (vs 0–1)	…	…	…	…	…	…	…	…	…	…	…	…						
2–3	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	3.176	1.262–7.989	0.014
≥4	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	6.115	2.658–14.071	<0.001

CFS indicates Clinical Frailty Scale; HR, hazard ratio; NAC, National Amyloidosis Centre; and SPPB, Short Physical Performance Battery.

Table 5. Effect of the Addition of the Items of the CGA on the Overall Predictivity of the NAC Staging System

	HR (95% CI)	*P* value	Harrel C statistic	Likelihood ratio test
NAC staging system			0.734	Reference
2 vs 1	2.55 (0.96–6.74)	0.059	…	…
3 vs 1	8.34 (3.49–20.21)	<0.001	…	…
Predictivity of CGA items when added to the NAC staging system				
Disability	2.32 (1.20–4.73)	0.010	0.759	χ^2=5.85, *P*=0.015
Risk of malnutrition	3.07 (1.47–6.26)	<0.001	0.812	χ^2=9,78, *P*=0.001
Depression	2.84 (1.41–5.85)	0.004	0.769	χ^2: 9.92, *P*=0.002
SPPB≤6	2.39 (1.12–4.53)	0.022	0.778	χ^2=5.24, *P*=0.021
Frail phenotype	2.68 (1.42–4.27)	<0.001	0.781	χ^2=11.89, *P*<0.001
CFS score	3.27 (1.72–6.21)	0.001	0.770	χ^2=12.07, *P*<0.001
Cumulative deficits	2.39 (1.52–3.40)	<0.001	0.783	χ^2=17.44, *P*<0.001

CFS indicates Clinical Frailty Scale; CGA, comprehensive geriatric assessment; HR, hazard ratio; NAC, National Amyloidosis Centre; and SPPB, Short Physical Performance Battery.

Conclusions

In a prospective cohort of ATTR-CA patients, older age was associated with limited access to disease-modifier therapy, even among nonfrail individuals. However, when survival was assessed with multiple models adjusting for CGA items, age was not a determining factor for worse outcome, suggesting a non-negligible risk of ageism (discrimination based on age alone). Because some geriatric syndromes may be modifiable, a CGA could enhance risk stratification, reduce age-related bias, and improve outcomes.

by the Italian Ministry of Health, RC-2024-2789983 project, and the European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD-Heart. Dr Olivotto is supported by grants for Respect, StratifyHF, and SmashHCM and has received grants from Bayer, MyoKardia Inc, which is a wholly owned subsidiary of Bristol Myers Squibb, Sanofi Genzyme, and Shire, which is now part of Takeda; personal fees from Bayer, Sanofi Genzyme, and Shire/Takeda; and payments as a consultant from MyoKardia Inc. Dr Perfetto has received honoraria for advisory board participation from Pfizer, Alnylam, and Akcea. Dr Ungar is supported by Piano Nazionale di Ripresa e Resilienza grants. F. Cappelli has received consultant fees from Pfizer, Alnylam, AstraZeneca, BridgeBio, Daiichi Sankyo, and NovoNordisk. The other authors report no conflicts.

Supplemental Material

Tables S1–S3
Figure S1
STROBE Checklist

ARTICLE INFORMATION

Received January 1, 2025; accepted June 9, 2025.

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Sources of Funding

None.

Disclosures

MM is supported by grants from the National Institutes of Health (R01HL139671 and R01AG081582-01); grants and personal fees from Alnylam, Pfizer, Eidos, Prothena, and Ionis; and personal fees from AstraZeneca, Akcea, Intellia, and Novo Nordisk. Dr Fontana is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/18/21/33447). RF is supported by Programmi di Ricerca Scientifica di Rilevante Interesse Nazionale (scientific research programs of high national interest; no. 2020LM8WNW). Dr Longhi is supported

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