

The NT-proBNP/hs-cTnT Ratio Identifies Distinct Hemodynamic Phenotypes in Wild-type Transthyretin Cardiac Amyloidosis: a multicenter Italian study

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Abstract

Background

Wild-type transthyretin cardiac amyloidosis (ATTRwt-CA) is a progressive pseudo-hypertrophic cardiomyopathy and an increasingly recognized cause of heart failure in elderly patients.

Methods

Seventy patients with confirmed ATTRwt-CA from three Italian tertiary centers were included in this hypothesis-generating analysis. Per-patient median values across available visits were used to define phenotypic profiles. Patients were stratified into tertiles of the NT-proBNP/hs-cTnT ratio, and group differences were assessed using age-, sex-, NT-proBNP-, and hs-cTnT-adjusted models.

Results

Median age was 80.5 years (IQR 76.5–85.0), and 88% were male. Ratio tertiles were < 29.9 (T1), 29.9–51.0 (T2), and > 51.0 (T3). hs-cTnT was similar across tertiles ($p = 0.639$), whereas NT-proBNP progressively increased (1258, 4301, 7118 pg/mL; $p < 0.001$). T1 showed preserved ejection fraction, better renal function, and lower atrial fibrillation prevalence. T2 displayed reduced renal function and markedly higher atrial fibrillation and device implantation prevalence. T3 showed reduced ejection fraction, impaired longitudinal strain, right ventricular dysfunction, and the lowest eGFR.

Conclusions

The NT-proBNP/hs-cTnT ratio identifies three distinct ATTRwt-CA phenotypes. Prospective validation in larger cohorts is warranted.

Introduction

Transthyretin (TTR) cardiac amyloidosis (ATTR-CA) is an infiltrative cardiomyopathy with a hypertrophic phenotype, characterized by extracellular accumulation of insoluble fibrils of misfolded TTR oligomers within the myocardium [1]. This pseudo-hypertrophy distinguishes ATTR-CA from sarcomeric hypertrophic cardiomyopathy (HCM), whose primary defect lies in myofibrillar disarray [2], and lysosomal storage diseases (LSDs), such as Anderson-Fabry disease (OMIM #) and Pompe disease (OMIM #), in which intracellular deposits accumulate within myocytes [3]. ATTR-CA encompasses both wild-type (ATTRwt) and hereditary variants (ATTRv). ATTRv results from pathogenic variants in the TTR gene and may present with prominent extracardiac manifestations, with neurological and gastrointestinal features predominating at onset [4]. ATTRwt-CA, by contrast, has no genetic basis. It arises from an age-related degenerative process in which structurally normal TTR misfolds and forms extracellular amyloid deposits predominantly within the heart [1].

Beyond clinical and electrocardiographic features, the diagnostic suspicion of ATTRwt-CA is most frequently raised by echocardiographic “red flags”: left ventricular (LV) hypertrophy (LVH), a “granular sparkling” appearance of the myocardium, preserved or mildly reduced LV ejection fraction (LVEF) with diastolic dysfunction, valvular thickening, and pericardial effusion [5]. Moreover, advanced echocardiographic parameters such as global longitudinal strain (GLS) and

the relative apical sparing (AS) pattern may support the distinction of ATTR-CA from other forms of increased LV wall thickness [5].

When ATTRwt-CA is suspected, biochemical testing [e.g., serum free light chain (FLC) assay, serum and urine protein electrophoresis (SPIE and UPIE) with immunofixation] and bone scintigraphy with ^{99m}Tc-labelled tracers, applying Perugini scoring, allow diagnostic confirmation and serve to rule out light-chain cardiac amyloidosis (AL-CA) [6].

Early diagnosis is imperative, as disease-specific therapies are capable of significantly slowing disease progression and improving the prognosis, otherwise burdened by a high early mortality rate [7].

Although the mechanisms underlying TTR misfolding and amyloid deposition in ATTRwt-CA remain incompletely understood, the determinants of disease severity and progression toward overt heart failure are likewise poorly defined. Moreover, currently available staging systems may not fully capture the hemodynamic heterogeneity observed among individual patients. Therefore, the present study aimed to characterize clinical phenotypes across different degrees of disease severity in a cohort of patients with ATTRwt-CA, focusing on variables capable of delineating the transition between distinct disease stages. The roles of natriuretic peptides and troponin as biomarkers of disease progression were investigated.

Methods

Study cohort

This is a multicenter, non-interventional observational study conducted in three specialized centers with expertise in infiltrative cardiomyopathies: the Division of Cardiology and the Division of Internal Medicine and Metabolic Rare Diseases at the “Paolo Giaccone” University Hospital of Palermo, and the Cardiology Unit of “Papardo” University Hospital of Messina. Data were collected from patients with ATTRwt-CA attending the outpatient clinics between 2021 and 2025.

Inclusion criteria: patients with ATTRwt-CA aged > 18 years, with available N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) values measured concurrently in one or more assessments.

Exclusion criteria: patients with other forms of cardiac amyloidosis (AL, ATTRv, etc.); lack of available paired NT-proBNP and hs-cTnT values.

Each patient was followed from the diagnosis of ATTRwt-CA and the beginning of disease-modifying therapy (tafamidis for all patients) until the last visit in 2025, with a maximum interval of one year between visits. Diagnosis of ATTRwt-CA was established according to biochemical examinations, ^{99m}Tc-labelled tracer bone scintigraphy with Perugini scoring, and genetic testing. In doubtful cases, myocardial biopsy was required to confirm the diagnosis [6].

The initial cohort comprised 82 patients. Twelve were excluded because of the absence of paired NT-proBNP and hs-cTnT values. The final cohort therefore consisted of 70 patients.

Data collected included baseline clinical characteristics, amyloid-compatible clinical signs such as carpal tunnel syndrome and polyneuropathy, cardiovascular risk factors, NYHA class, biochemical examinations assessing thyroid, hepatic, and renal function [GFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation], cardiac biomarkers (NT-proBNP and hs-cTnT), therapy, and outcomes (annual number of hospital admissions and mortality from cardiovascular and non-cardiovascular causes).

NT-proBNP (ng/L) was measured using an electrochemiluminescence sandwich immunoassay on the Elecsys 2010 system (Roche Diagnostics). hs-cTnT (ng/L) was measured using a second-generation assay. Prognostic scores included the NAC score and Mayo score [8, 9]. The Kansas City Cardiomyopathy Questionnaire (KCCQ) score was also assessed to evaluate patients' quality of life [10].

Each patient underwent at least one 12-lead electrocardiography (ECG) and comprehensive transthoracic echocardiography, including color Doppler, tissue Doppler, and speckle tracking analysis. Echocardiographic parameters were evaluated according to the guidelines of the American Society of Echocardiography (ASE) [11].

Combined ECG-echocardiographic variables according to the ACTIVE study were also recorded [12].

For each patient, these clinical and imaging data were collected before and after the beginning of disease-modifying therapy (tafamidis for all patients) at every follow-up visit [13].

Echocardiography: Standard transthoracic echocardiography was performed by physicians experienced in cardiac imaging using a Canon Aplio i700 ultrasound system, with off-line analysis on a Vitrea workstation (Canon), and a General Electric (GE) Vivid E95 ultrasound system with a 4Vc-D (1.4–5.2 MHz) transducer. Echocardiographic data were digitally stored.

LV mass (LVM) was determined using the ASE-corrected cube formula and was indexed

(LVMI) to body surface area (BSA—m²). LVH was defined as IVST $\geq$ 12 mm and/or

LVMI $\geq$ 115 g/m² in men and $\geq$ 95 g/m² in women, according to the 2018 ESH/ESC

Guidelines [11]. RWT was calculated as the ratio between the sum of interventricular septum wall thickness plus posterior wall thickness over the LV-end-diastolic diameter [(IVSWT + PWT)/LVEDD]. LVEF% was assessed by biplane modified Simpson method in apical 4- and 2-chamber views. Clinical heart failure (HF) phenotype was classified according to the most recent guidelines as HF with reduced ejection fraction (HFrEF; LVEF < 50%) or HF with preserved ejection fraction (HFpEF; LVEF $\geq$ 50% together with appropriate evidence of structural and/or functional cardiac abnormalities and/or elevated filling pressures) [14].

LV and left atrium volumes were indexed over BSA. Diastolic function was evaluated using mitral inflow and tissue Doppler echocardiography, according to ASE recommendations. Mitral inflow was assessed in the apical 4-chamber view, using pulsed wave Doppler echocardiography, with the Doppler beam aligned parallel to the direction of flow and the sample volume at the leaflet tips. Mitral inflow early (E) and late diastolic (A) velocities, E/A ratio, and deceleration time of E-wave (DT-E) were measured. Tissue Doppler imaging of the lateral and septal mitral valve annulus was obtained from the apical 4-chamber to evaluate the mean early diastolic myocardial velocity (e'). The E/e' ratio was derived as diastolic function variable. Right ventricular function was defined by assessing the tricuspid annular plane systolic excursion (TAPSE) acquired by the pulse-wave tissue Doppler [11].

LV global longitudinal strain (GLS) variables and the AS pattern (calculated as the apical-to-basal ratio of systolic longitudinal strain > 2.9) were assessed by 2D speckle-tracking and measured in apical 4-, 2- and 3-chamber views [15].

After image acquisition, all images were stored in DICOM format. A random sample of 10 recorded exams was selected to evaluate the variability within and between observers. Two experienced ultrasound physicians independently evaluated the two-dimensional images and measures.

To assess measurement reproducibility, a random sample of 10 echocardiographic examinations was independently reviewed by two experienced echocardiographers. For intra-observer assessment, one observer repeated the

measurements after a 2-week interval. Inter-observer variability was assessed by comparing measurements obtained independently by the two observers. Intra- and inter-observer correlation coefficients were considered satisfactory. All patient data were anonymized. Each patient was informed about data collection and provided informed consent for publication of anonymized data. The study was approved by the Ethics Committee of each participating center.

Statistics

Per-patient median values were computed for NT-proBNP (ng/L) and hs-cTnT (ng/L) across all available visits; the NT-proBNP /TnT ratio was derived from these medians. Of 82 patients, 70 had both biomarkers recorded in at least one visit and constituted the analytical cohort. Patients were stratified into three groups according to the empirical tertiles of the NT-proBNP /TnT ratio distribution (T1: <29.9 n = 23; T2: 29.9–51.0 n = 23; T3: >51.0 n = 24).

Continuous variables were compared across tertiles by ANCOVA (lm(), R), adjusting for age, sex, NT-proBNP, and hs-cTnT; results are expressed as mean $\pm$ SD. Binary variables were analyzed by adjusted logistic regression (glm(), binomial family), with the same covariate set and T1 as the reference category; odds ratios (OR) are reported with 95% confidence intervals. Both biomarkers were retained as covariates to isolate the independent contribution of their ratio beyond individual biomarker levels. Given the exploratory nature of the analysis, no correction for multiple comparisons was applied ($p < 0.05$ significant; $p < 0.10$ noted as trend).

Changes in circulating biomarkers (NT-proBNP, hs-cTnT, and the NT-proBNP/hs-cTnT ratio) before and after tafamidis treatment were assessed using paired within-patient analyses using the measurements obtained at treatment initiation (Tf0) and the last measurement obtained during tafamidis treatment (Tf1). Absolute changes were calculated as Tf1 minus Tf0. Paired Student's t-tests were used for the primary within-patient comparisons, with Wilcoxon signed-rank tests performed as sensitivity analyses. To account for differences in treatment duration, individual biomarker changes were additionally modelled as a function of months of tafamidis therapy using linear regression with heteroskedasticity-robust standard errors. Analyses were also performed separately within each NT-proBNP/hs-cTnT ratio tertile. Pre/post-treatment comparisons were repeated stratifying for each tertiles, using the Kruskal-Wallis test, followed by Bonferroni-adjusted pairwise comparisons.

A heatmap was constructed using the binary and continuous variables. Group-level medians (continuous variables) or proportions (binary variables) were standardized row-wise to z-scores. Variables in which lower values indicated worse prognosis (LVEF, TAPSE, eGFR, KCCQ score) were sign-inverted prior to standardization, so that darker shading consistently denoted worse clinical status. Hierarchical clustering (Ward's D2 linkage, Euclidean distance) was applied to rows.

All analyses were performed in R (v4.3, R Foundation for Statistical Computing, Vienna, Austria); figures were generated using the ggplot2 and heatmap packages.

Results

Clinical, biochemical, and instrumental characteristics of the study cohort according to gender are reported in Table 1. The study cohort comprised 70 patients (62 males, 8 females; median age 81 years), followed for a mean of 14 ± 12.4 months. No significant differences were observed between males and females across the majority of clinical, biochemical, or echocardiographic parameters. Notably, carpal tunnel syndrome was significantly more prevalent in females (88% vs. 35%, $p = 0.017$), as was the LV overload pattern on ECG (56% vs. 21%, $p = 0.044$).

Table 1
Clinical, biochemical and instrumental characteristics of the study cohort according to gender.

CLINICAL CHARACTERISTICS	Males (n = 62)	Females (n = 8)	p-value*
Age at visit (years)	81.0 [76.1–85.0]	81.2 [80.5–83.5]	0.698
Age at diagnosis (years)	80.0 [76.0–84.0]	80.5 [79.0–81.2]	0.285
Age at symptom onset (years)	78.0 [74.0–82.0]	79.0 [74.5–80.5]	0.072
BMI (kg/m ²)	25.9 [22.9–29.0]	26.2 [24.0–31.2]	0.562
NYHA class	2.0 [2.0–2.0]	2.0 [2.0–3.0]	1.000
Survival rate (n/N (%))	54/62 (87%)	8/8 (100%)	0.999
CV death (n/N (%))	7/62 (11%)	0/8 (0%)	0.994
KCCQ score (points)	62.0 [48.0–88.5]	49.7 [33.6–63.2]	0.593
NAC score (points)	2.0 [1.0–2.4]	1.0 [1.0–3.1]	0.302
Mayo score (points)	2.0 [1.0–3.0]	1.5 [1.0–3.0]	0.385
Hypertension (n/N (%))	52/62 (84%)	7/8 (88%)	0.825
Type 2 diabetes (n/N (%))	18/62 (29%)	2/8 (25%)	0.867
Ischemic heart disease (n/N (%))	12/62 (19%)	2/8 (25%)	0.695
Cerebrovascular disease (n/N (%))	6/62 (10%)	1/8 (12%)	0.672
Systolic HF (n/N (%))	31/62 (50%)	5/8 (62%)	0.524
Diastolic HF (n/N (%))	59/62 (96%)	8/8 (100%)	0.999
Atrial fibrillation (n/N (%))	37/62 (60%)	6/8 (75%)	0.447
Carpal tunnel syndrome (n/N (%))	21/62 (35%)	7/8 (88%)	0.017
Perugini score	2.0 [2.0–3.0]	2.5 [2.0–3.0]	0.086
THERAPY			
Loop diuretic use (n/N (%))	44/62 (72%)	6/8 (75%)	0.986
Beta-blocker (n/N (%))	33/61 (55%)	4/8 (50%)	0.932
ACEi/ARNi (n/N (%))	40/61 (66%)	5/8 (62%)	0.894
MRA (n/N (%))	21/61 (34%)	3/8 (38%)	0.834
SGLT2 inhibitor (n/N (%))	22/61 (36%)	4/8 (50%)	0.503
DOAC (n/N (%))	36/61 (60%)	5/8 (62%)	0.956

* Continuous variables: quantile regression (median, $\tau = 0.5$) adjusted for age; p-value for sex effect. Binary variables: logistic regression adjusted for age; p-value for sex effect. Unadjusted Mann Whitney test for Age at visit. NE: p not estimable. BMI body mass index; KCCQ Kansas City Cardiomyopathy Questionnaire; NAC National Amyloidosis Centre; PM/ICD pacemaker/implantable cardioverter-defibrillator; MRA mineralocorticoid receptor antagonist; SGLT2i sodium-glucose cotransporter-2 inhibitor; DOAC direct oral anticoagulant; NT-proBNP N-terminal pro-B-type natriuretic peptide; eGFR estimated glomerular filtration rate (CKD-EPI); IVS interventricular septum; LV left ventricle; LVEF LV ejection fraction; GLS global longitudinal strain; TAPSE tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure; MR mitral regurgitation; TR tricuspid regurgitation; RBBB right bundle branch block; LBBB left bundle branch block.

CLINICAL CHARACTERISTICS	Males (n = 62)	Females (n = 8)	p-value*
Tafamidis duration (months)	3.0 [0.0–7.8]	6.5 [5.6–8.0]	0.153
BIOCHEMICAL PARAMETERS			
NT-proBNP (pg/mL)	2305.5 [1292–5729]	2823.2 [2195–9270]	0.852
High-sensitivity troponin (ng/L)	73.5 [45.2–100.0]	59.2 [51.3–73.3]	0.736
eGFR (CKD-EPI) (mL/min/1.73m ²)	60.0 [39.5–79.2]	38.4 [34.8–74.8]	0.344
C-reactive protein (mg/L)	0.6 [0.1–3.0]	0.1 [0.1–1.3]	0.612
LDL cholesterol (mg/dL)	69.3 [51.5–90.8]	72.0 [68.5–95.0]	0.897
TSH (mU/L)	1.6 [1.1–2.1]	2.0 [1.5–2.7]	0.561
HbA1c (%)	5.9 [5.2–6.9]	5.7 [5.5–6.3]	0.860
ECHOCARDIOGRAPHY			
IVS thickness (mm)	17.0 [16.0–19.0]	17.0 [16.8–18.2]	0.713
Posterior wall thickness (mm)	16.0 [14.0–17.0]	14.5 [13.8–16.2]	0.613
LV wall thickness (mm)	17.0 [16.0–19.0]	17.0 [16.8–18.2]	0.523
LV mass index (g/m ²)	178.0 [153.0–201.5]	177.5 [157.2–211.4]	0.949
Relative wall thickness	0.7 [0.6–0.8]	0.7 [0.6–0.8]	0.799
LV end-diastolic diameter (mm)	45.0 [42.0–48.0]	43.0 [35.8–45.2]	0.437
LVEF (%)	50.0 [42.9–55.0]	51.0 [48.8–55.5]	0.646
GLS (average) [missing n = 11] (%)	-11.5 [-15.0--9.9]	-12.0 [-13.6--11.2]	0.825
GLS 4-chamber [missing n = 32] (%)	-12.7 [-15.4--10.0]	-10.7 [-11.8--10.5]	0.633
Apical sparing pattern (GLS) (n/N (%))	48/57 (85%)	6/7 (86%)	0.945
TAPSE (mm)	17.0 [15.9–20.0]	16.5 [14.8–18.0]	0.876
E/e' ratio	16.0 [13.5–21.0]	18.0 [14.3–25.0]	1.000
Left atrial volume (mL)	47.0 [40.5–62.0]	52.0 [43.8–53.2]	0.552
Estimated PASP (mmHg)	35.0 [27.0–44.5]	43.5 [30.0–50.8]	0.555
Aortic valve disease (n/N (%))	24/62 (39%)	2/8 (25%)	0.468
Mod-severe MR (n/N (%))	21/62 (35%)	4/8 (50%)	0.429
Mod-severe TR (n/N (%))	24/62 (39%)	4/8 (50%)	0.581

* Continuous variables: quantile regression (median, $\tau = 0.5$) adjusted for age; p-value for sex effect. Binary variables: logistic regression adjusted for age; p-value for sex effect. Unadjusted Mann Whitney test for Age at visit. NE: p not estimable. BMI body mass index; KCCQ Kansas City Cardiomyopathy Questionnaire; NAC National Amyloidosis Centre; PM/ICD pacemaker/implantable cardioverter-defibrillator; MRA mineralocorticoid receptor antagonist; SGLT2i sodium-glucose cotransporter-2 inhibitor; DOAC direct oral anticoagulant; NT-proBNP N-terminal pro-B-type natriuretic peptide; eGFR estimated glomerular filtration rate (CKD-EPI); IVS interventricular septum; LV left ventricle; LVEF LV ejection fraction; GLS global longitudinal strain; TAPSE tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure; MR mitral regurgitation; TR tricuspid regurgitation; RBBB right bundle branch block; LBBB left bundle branch block.

CLINICAL CHARACTERISTICS	Males (n = 62)	Females (n = 8)	p-value*
ECG			
PR interval (ms)	200.0 [160.0–240.0]	185.0 [147.5–208.8]	0.585
Sokolow index (mm)	15.0 [12.2–21.7]	11.0 [9.2–14.2]	0.469
Low peripheral voltages (ECG) (n/N (%))	23/61 (39%)	2/8 (25%)	0.425
LV overload pattern (ECG) (n/N (%))	13/62 (21%)	4/8 (56%)	0.044
RBBB (n/N (%))	24/62 (39%)	1/8 (12%)	NE
LBBB (n/N (%))	9/62 (15%)	2/8 (25%)	0.494
* Continuous variables: quantile regression (median, $\tau = 0.5$) adjusted for age; p-value for sex effect. Binary variables: logistic regression adjusted for age; p-value for sex effect. Unadjusted Mann Whitney test for Age at visit. NE: p not estimable. BMI body mass index; KCCQ Kansas City Cardiomyopathy Questionnaire; NAC National Amyloidosis Centre; PM/ICD pacemaker/implantable cardioverter-defibrillator; MRA mineralocorticoid receptor antagonist; SGLT2i sodium-glucose cotransporter-2 inhibitor; DOAC direct oral anticoagulant; NT-proBNP N-terminal pro-B-type natriuretic peptide; eGFR estimated glomerular filtration rate (CKD-EPI); IVS interventricular septum; LV left ventricle; LVEF LV ejection fraction; GLS global longitudinal strain; TAPSE tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure; MR mitral regurgitation; TR tricuspid regurgitation; RBBB right bundle branch block; LBBB left bundle branch block.			

Figure 1 shows the distribution of per-patient median NT-proBNP versus median hs-cTnT values across the three tertiles of the NT-proBNP/hs-cTnT ratio (T1: ratio < 29.9, n = 23; T2: 29.9–51, n = 23; T3: >51, n = 24) in the patients with both biomarkers available. Error bars represent ± 1 bootstrap standard error of the median; two outlier patients are not shown. Tertile boundaries were empirically defined on the observed distribution of per-patient median ratio values.

The distribution of continuous parameters across the identified tertiles is shown in Table 2. NT-proBNP significantly differed with an increasing trend from T1 to T3 ($1,258 \pm 922$ vs. $4,301 \pm 3,481$ vs. $7,118 \pm 4,316$ pg/mL; $p < 0.001$). Disease severity scores rose accordingly (NAC score: 1.2 vs. 2.0 vs. 2.4, $p < 0.001$; Mayo score: 1.7 vs. 2.1 vs. 2.5, $p = 0.001$). Markers of LV systolic function declined progressively across tertiles: LVEF (52.9 vs. 48.3 vs. 45.8%, $p = 0.006$), average GLS (-13.7 vs. -12.2 vs. -10.9% , $p = 0.007$), and TAPSE (18.6 vs. 17.9 vs. 15.8 mm, $p = 0.017$). Renal function was significantly impaired in higher tertiles (eGFR: 69.7 vs. 54.0 vs. 52.8 mL/min/1.73m², $p = 0.009$). TSH levels were higher in T3 compared with T1 and T2 (2.6 vs. 1.4 vs. 1.6 mU/L, $p = 0.021$). In contrast, structural parameters – IVS thickness, LV mass index, and wall thickness – did not differ significantly across tertiles, nor did high-sensitivity troponin levels ($p = 0.639$).

Table 2
Continuous variables according to the tertiles of the NT-proBNP/hs-cTnT ratio

Variables	T1 NT/T: ≤29.9	T2 NT/T > 29.9 ≤ 51.0	T3 NT/T: >51.0	p-value
No. of patients	23	23	24	-
CLINICAL CHARACTERISTICS				
Age at diagnosis (years)	78.9 ± 5.9	78.6 ± 6.5	79.8 ± 5.8	0.096
Age at symptom onset (years)	76.9 ± 6.5	76.7 ± 7.0	77.9 ± 6.7	0.278
Years from symptoms to diagnosis	1,7 ± 3.0	1.7 ± 2.6	1,9 ± 3.4	0.962
BMI (kg/m ²)	26.7 ± 3.5	23.7 ± 6.9	25.7 ± 6.4	0.595
KCCQ score (points)	67.3 ± 26.3	63.3 ± 24.6	58.1 ± 26.0	0.236
NAC score (points)	1.2 ± 0.4	2.0 ± 1.1	2.4 ± 0.9	< 0.001
Mayo score (points)	1.7 ± 0.6	2.1 ± 0.9	2.5 ± 0.8	0.001
Days survived from 1 visit (dead)	689 ± 416	334 ± 259	264 ± 115	0.09
THERAPY				
Tafamidis duration (months)	5.0 ± 9.3	8.6 ± 11.9	6.6 ± 8.4	0.601
BIOCHEMICAL PARAMETERS				
NT-proBNP (ng/L)	1258.4 ± 921.5	4300.8 ± 3480.7	7118.2 ± 4315.5	< 0.001
Hs-cTnT (ng/L)	80.8 ± 75.4	106.4 ± 88.9	71.5 ± 32.4	0.639
eGFR CKD-EPI (mL/min/1.73m ²)	69.7 ± 21.8	54.0 ± 22.9	52.8 ± 19.3	0.009
C-reactive protein (mg/L)	0.6 ± 0.6	2.2 ± 4.3	2.5 ± 2.9	0.263
LDL cholesterol (mg/dL)	70.2 ± 26.2	82.7 ± 27.6	70.9 ± 16.3	0.945
TSH (mU/L)	1.4 ± 0.9	1.6 ± 1.0	2.6 ± 1.6	0.021
HbA1c (%)	6.2 ± 1.1	6.6 ± 1.4	5.6 ± 0.9	0.303
ECHOCARDIOGRAPHY				
IVS thickness (mm)	17.3 ± 2.6	17.5 ± 2.3	17.4 ± 2.2	0.889
Posterior wall thickness (mm)	14.6 ± 2.5	15.4 ± 2.3	15.8 ± 2.7	0.088
Data are expressed as mean ± SD. Between-group comparisons were performed using one-way ANCOVA with tertile group as the main factor, adjusted for age, sex, NT-proBNP, and hs-cTnT. T1, T2, and T3 represent the first, second, and third tertile of the NT-proBNP/hs-cTnT ratio (patient-level median values; T1: ratio < 29.9; T2: ratio 29.9–51; T3: ratio > 51). A two-tailed p-value < 0.05 was considered statistically significant. † p < 0.10; * p < 0.05; ** p < 0.01; *** p < 0.001.				
BMI: body mass index; KCCQ: Kansas City Cardiomyopathy Questionnaire; NAC score: National Amyloidosis Centre score; NT-proBNP: N-terminal pro-B-type natriuretic peptide; Hs-cTnT: high sensitivity Troponin T; eGFR: estimated glomerular filtration rate (CKD-EPI equation); TSH: thyroid-stimulating hormone; IVS: interventricular septum; LV: left ventricle; LVEF: LV ejection fraction; GLS: global longitudinal strain; TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure.				

Variables	T1 NT/T: ≤29.9	T2 NT/T > 29.9 ≤ 51.0	T3 NT/T: >51.0	p-value
No. of patients	23	23	24	-
CLINICAL CHARACTERISTICS				
LV mass index (g/m ²)	173.5 ± 34	178.3 ± 42	185.9 ± 45	0.297
Relative wall thickness	0.69 ± 0.13	0.70 ± 0.15	0.75 ± 0.18	0.187
LV end-diastolic diameter (mm)	45.0 ± 4.0	43.7 ± 4.7	44.8 ± 6.2	0.856
LVEF (%)	52.9 ± 6.7	48.3 ± 9.1	45.8 ± 9.2	0.006
GLS average (%)	-13.7 ± 3.3	-12.2 ± 3.1	-10.9 ± 2.9	0.007
GLS 4-chamber (%)	-13.5 ± 2.6	-12.8 ± 3.3	-11.2 ± 3.6	0.07
TAPSE (mm)	18.6 ± 3.5	17.9 ± 4.1	15.8 ± 3.7	0.017
E/e' ratio	17.1 ± 6.0	17.0 ± 6.1	18.8 ± 6.8	0.381
Left atrial volume (mL)	52.5 ± 11.6	50.9 ± 16.0	51.6 ± 18.0	0.837
PASP (mmHg)	35.7 ± 11.8	34.0 ± 11.3	41.6 ± 14.0	0.122
ECG				
PR interval (ms)	205.2 ± 56	184.3 ± 43	214.1 ± 91	0.755
Sokolow index (mm)	16.5 ± 10.1	18.8 ± 8.1	14.1 ± 5.9	0.349
Data are expressed as mean ± SD. Between-group comparisons were performed using one-way ANCOVA with tertile group as the main factor, adjusted for age, sex, NT-proBNP, and hs-cTnT. T1, T2, and T3 represent the first, second, and third tertile of the NT-proBNP/hs-cTnT ratio (patient-level median values; T1: ratio < 29.9; T2: ratio 29.9–51; T3: ratio > 51). A two-tailed p-value < 0.05 was considered statistically significant. † p < 0.10; * p < 0.05; ** p < 0.01; *** p < 0.001.				
BMI: body mass index; KCCQ: Kansas City Cardiomyopathy Questionnaire; NAC score: National Amyloidosis Centre score; NT-proBNP: N-terminal pro-B-type natriuretic peptide; Hs-cTnT: high sensitivity Troponin T; eGFR: estimated glomerular filtration rate (CKD-EPI equation); TSH: thyroid-stimulating hormone; IVS: interventricular septum; LV: left ventricle; LVEF: LV ejection fraction; GLS: global longitudinal strain; TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure.				

The distribution of binary variables according to tertile group is reported in Table 3. Atrial fibrillation (AF) was markedly more prevalent in T2 and T3 compared with T1 (81.8% and 78.3% vs. 30.4%; OR T2 vs. T1: 10.54 [95% CI 2.78–48.64]; OR T3 vs. T1: 8.01 [2.20–33.94]; $p < 0.001$). DOAC use closely paralleled AF prevalence across tertiles (81.8%, 72.7% vs. 30.4%; $p = 0.001$). Loop diuretic use increased, but not significantly, across tertiles (60.9% vs. 72.7% vs. 91.3%; $p = 0.078$). No significant differences were observed for other binary variables, including survival, LV overload pattern, low peripheral voltages, pacemaker/ICD implantation, or AS pattern.

Table 3
Binary variables according to the tertiles of the NT-proBNP/hs-cTnT ratio

Variable	T1 (%) NT/T: ≤29.9	T2 (%) NT/T > 29.9 ≤ 51.0	T3 (%) NT/T: >51.0	OR T2 vs T1 [95% CI]	OR T3 vs T1 [95% CI]	Global <i>p-value</i>
CLINICAL CHARACTERISTICS						
Survival rate	87	90.9	87	1.72 [0.24– 15.18]	1.02 [0.16– 6.39]	0.829
CV death	13	9.1	8.7	0.59 [0.07– 4.13]	0.62 [0.07– 4.25]	0.833
Hypertension	91.3	77.3	82.6	0.32 [0.04– 1.73]	0.41 [0.05– 2.43]	0.4
Type 2 diabetes	26.1	45.5	17.4	2.45 [0.70– 9.22]	0.62 [0.13– 2.65]	0.126
Ischemic heart disease	17.4	27.3	17.4	1.88 [0.45– 8.64]	0.96 [0.19– 4.79]	0.597
Cerebrovascular disease	4.3	9.1	17.4	3.25 [0.22– 99.57]	6.11 [0.53– 190.47]	0.367
Systolic Heart Failure	47.8	54.5	60.9	1.39 [0.42– 4.64]	1.63 [0.49– 5.54]	0.714
Diastolic Heart Failure	95.7	100	95.7	NA	0.97 [0.03– 26.61]	0.403
Atrial fibrillation	30.4	81.8	78.3	10.54 [2.78– 48.64]	8.01 [2.20– 33.94]	< 0.001
Carpal tunnel syndrome	47.8	27.3	47.8	0.42 [0.11– 1.50]	0.97 [0.28– 3.36]	0.335
NYHA class (I 2 3 4)	13.6 68.2 13.6 4.5	4.5 68.2 27.3 0	8.3 62.5 25 4.2	1.69 [0.4– 7.07]	1.85 [0.47– 7.48]	0.790
NYHA class (I-II III-IV)	72.7 27.3	68.2 31.8	58.3 41.7	1.24 [0.34– 4.56]	1.90 [0.55– 6.59]	0.571
Perugini score (1 2 3)	0 65.2 34.8	0 56.5 43.5	0 43.5 50	1.44 [0.44– 4.74]	1.88 [0.58– 6.06]	0.572
THERAPY						
Loop diuretic	60.9	72.7	91.3	1.76 [0.49– 6.79]	5.96 [1.25– 44.09]	0.078

Variable	T1 (%) NT/T: ≤29.9	T2 (%) NT/T > 29.9 ≤ 51.0	T3 (%) NT/T: >51.0	OR T2 vs T1 [95% CI]	OR T3 vs T1 [95% CI]	Global <i>p</i> -value
CLINICAL CHARACTERISTICS						
Beta-blockers	43.5	54.5	68.2	1.54 [0.47–5.22]	3.23 [0.94–12.09]	0.175
ACEi/ARNi	65.2	54.5	77.3	0.59 [0.17–2.01]	2.29 [0.59–9.83]	0.146
MRA	26.1	27.3	45.5	1.04 [0.27–3.99]	2.51 [0.71–9.53]	0.279
SGLT2i	21.7	50	54.5	3.94 [1.06–16.64]	4.03 [1.09–16.79]	0.058
DOAC	30.4	81.8	72.7	10.41 [2.73–48.53]	5.99 [1.68–24.30]	0.001
ECHOCARDIOGRAPHY						
Apical sparing pattern (GLS)	81.8	90	85	2.01 [0.34–16.08]	1.49 [0.27–8.97]	0.741
Aortic valve disease	43.5	40.9	26.1	0.90 [0.27–2.97]	0.44 [0.12–1.55]	0.402
Mod-severe MR	30.4	36.4	47.8	1.36 [0.39–4.89]	1.89 [0.56–6.69]	0.596
Mod-severe TR	39.1	45.5	43.5	1.31 [0.40–4.40]	1.14 [0.34–3.82]	0.904
ECG						
Low peripheral voltages	40.9	36.4	39.1	0.82 [0.23–2.87]	0.83 [0.24–2.87]	0.938
LV overload pattern	13	27.3	39.1	3.32 [0.68–20.87]	4.35 [0.94–26.36]	0.146
RBBB	21.7	31.8	17.4	1.60 [0.42–6.49]	0.78 [0.17–3.50]	0.596
LBBB	8.7	9.1	30.4	1.09 [0.12–9.89]	4.02 [0.81–30.09]	0.156
Pacemaker / ICD	21.7	31.8	30.4	1.63 [0.42–6.63]	1.56 [0.40–6.38]	0.734

Variable	T1 (%) NT/T: ≤29.9	T2 (%) NT/T > 29.9 ≤ 51.0	T3 (%) NT/T: >51.0	OR T2 vs T1 [95% CI]	OR T3 vs T1 [95% CI]	Global <i>p</i> -value
CLINICAL CHARACTERISTICS						
Data are expressed as percentage of patients in each tertile group. Between-group comparisons were performed using binary logistic regression with tertile group entered as a categorical factor (T1 as reference), adjusted for age, sex, NT-proBNP, and hs-cTnT. Odds ratios (OR) are reported separately for T2 vs T1 and T3 vs T1; global <i>p</i> -value reflects the omnibus likelihood ratio test (Type II, car: Anova) for the overall group effect. A two-tailed <i>p</i> -value < 0.05 was considered statistically significant. † <i>p</i> < 0.10; * <i>p</i> < 0.05; ** <i>p</i> < 0.01; *** <i>p</i> < 0.001.						
NA: OR not estimable due to complete separation (100% prevalence in T2); wide confidence intervals for cerebrovascular disease reflect the small number of events (<i>n</i> ≤ 4 per group) and should be interpreted with caution. DOAC use closely parallels atrial fibrillation prevalence across tertiles, consistent with anticoagulation prescribed for rhythm control in this cohort.						
HF: heart failure; ACEi: angiotensin-converting enzyme inhibitor; ARNi: angiotensin receptor-neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium-glucose cotransporter-2 inhibitors; DOAC: direct oral anticoagulant; GLS: global longitudinal strain; MR mitral regurgitation; TR: tricuspid regurgitation; LV: left ventricle; RBBB: right bundle branch block; LBBB: left bundle branch block; PM/ICD: pacemaker/implantable cardioverter-defibrillator.						

No significant pre-/post-treatment changes in NT-proBNP or hs-cTnT were observed in the overall cohort or within individual tertiles, with the exception of a near-significant difference in the NT-proBNP/hs-cTnT ratio, which was higher after treatment in the T3 group (pre: 80.3 ± 37.6 vs. post: 95.1 ± 62.3) than in T1 (pre: 22.5 ± 24.1 vs. post: 22.0 ± 21.9) and T2 (pre: 53.5 ± 39.1 vs. post: 40.8 ± 16.9) groups (*p* = 0.052) (see Table 4).

Table 4
Circulating cardiac biomarkers before and after tafamidis therapy

Variables	All patients		<i>p</i> -value#	T1		T2		T3		<i>p</i> -value#
N = 70	Tf0	Tf1		Tf0	Tf1	Tf0	Tf1	Tf0	Tf1	
NT-proBNP	4.201 ± 4.368	5.188 ± 6.906	0.505	1634.1 ± 1781.3	3170.7 ± 8079.0	5469.9 ± 6027.8	4872.8 ± 6295.6	5434.2 ± 3572.0	7156.6 ± 5980.0	0.231
Hs-cTnT	101.8 ± 134.3	100.8 ± 129.3	0.656	131.3 ± 209.4	134.1 ± 206.0	109.3 ± 104.0	101.1 ± 89.8	70.7 ± 37.8	72.0 ± 33.8	0.892
NT-proBNP/hs-cTnT	53.6 ± 41.6	55.4 ± 52.1	0.451	22.5 ± 24.1	22.0 ± 21.9	53.5 ± 39.1	40.8 ± 16.9	80.3 ± 37.6	95.1 ± 62.3	0.052
NT-proBNP, hs-cTnT, and the NT-proBNP/hs-cTnT ratio were compared between treatment initiation (Tf0) and follow-up during tafamidis therapy (Tf1), both in the overall cohort and across ratio tertiles. Within-patient comparisons were assessed using paired analyses, with additional adjustment for tafamidis treatment duration. Between-tertile differences in biomarker changes were evaluated using the Kruskal–Wallis test with post-hoc pairwise comparisons. NT-proBNP: N-terminal pro-B-type natriuretic peptide; Hs-cTnT: high sensitivity Troponin T.										

Figure 2 shows the phenotypic characterization of the cohort according to tertile group. Each row represents one clinical variable; color intensity reflects the row z-score computed from group medians or proportions, with sign inversion applied to LVEF, eGFR, TAPSE, and KCCQ score so that darker shading consistently indicates worse clinical status (see Figure legend). Row ordering was determined by hierarchical clustering. The heatmap confirms a progressive gradient of hemodynamic compromise from T1 to T3, involving systolic and right ventricular function, renal function, and disease severity scores. Structural infiltration markers (IVS thickness, LV mass index, LV wall thickness)

and hs-cTnT levels show a uniform distribution across tertiles, indicating a common morphological substrate irrespective of tertile assignment. Survival among the three groups was comparable (87% and 90.9% vs. 87%; OR T2 vs. T1: 1.72 [95% CI 0.24–15.18]; OR T3 vs. T1: 1.02 [0.16–6.39]; $p = 0.8$). In T3, cardiovascular death occurred earlier than in T1 and T2. Overall, most cardiovascular events occurred within 18 months after tafamidis treatment initiation.

Discussion

Transthyretin cardiac amyloidosis is an established cause of HF, with progressive clinical deterioration if left untreated with disease-modifying therapy [16]. Circulating biomarkers of myocardial stretch and injury, such as NT-proBNP and hs-cTnT, respectively, support diagnosis, prognostic assessment, and evaluation of treatment response [17].

The present study stratifies a cohort of patients with ATTRwt-CA into three tertiles (T1, T2, T3) according to the NT-proBNP/hs-cTnT ratio, identifying three phenotypes of clinical severity that are not fully explained by differences in age, sex, or the absolute levels of either biomarker alone.

The low-ratio phenotype (T1) was characterized by relatively low NT-proBNP levels despite persistently elevated hs-cTnT, together with preserved or only mildly reduced LVEF, less impaired GLS, preserved TAPSE, better renal function, and the lowest prevalence of atrial fibrillation. This phenotype should not be interpreted as the absence of cardiac disease. On the contrary, the presence of increased wall thickness, abnormal strain, positive scintigraphy findings, and elevated hs-cTnT confirms established amyloid cardiomyopathy but with a compensated hemodynamic response. The relatively high prevalence of carpal tunnel syndrome in this group is also consistent with the recognized extracardiac prodromal phase of transthyretin amyloidosis, in which amyloid deposition in tenosynovial tissues may precede overt cardiac manifestations by several years [18].

The intermediate-ratio phenotype (T2) was distinguished less by further deterioration in LV systolic function than by a striking increase in atrial fibrillation (AF) prevalence (~80%). Atrial infiltration, stiffness, and enlargement due to amyloid deposition provide the substrate for AF [19]. In patients with ATTRwt-CA, AF is common, occurring in nearly 70% of cases, whereas its prevalence in non-amyloid heart failure (HF) cohorts is remarkably lower (range 13%–27%) [20]. Of note, while AF is an independent mortality risk factor in non-amyloid HF [19], other studies demonstrate that in patients with ATTRwt-CA it is not associated with worse prognosis [21], as observed in the T2 group. The combination of higher NT-proBNP levels without a corresponding increase in hs-cTnT is compatible with an arrhythmic-hemodynamic transition, in which AF implies congestion on a pre-existing infiltrated ventricular substrate.

The high-ratio phenotype (T3) showed the most advanced disease. Compared with T1 and T2, T3 was associated with lower LVEF, more impaired GLS, reduced TAPSE, greater pulmonary pressure, worse renal function, higher disease severity scores (Mayo and NAC scores), and fewer days of survival from Visit 1 (see Table 2). Multi-drug therapy for HF [e.g., loop diuretics, ACE inhibitors, sodium-glucose cotransporter-2 inhibitors (SGLT2i)] and NYHA classes III–IV were more frequently observed in this group. Quality of life was perceived as lower in this group according to the KCCQ.

It should be stated that these three groups of patients did not differ in age, and no apparent transition between tertiles was observed during the mean 14-month follow-up or after treatment initiation. However, the relatively short observation period limits any inference regarding longitudinal phenotypic transitions. Longer follow-up will be required to determine whether these groups represent stable pathophysiological phenotypes or different stages along a continuum of ATTRwt-CA progression.

hs-cTnT levels did not differ significantly across tertiles. Troponin elevation in cardiac amyloidosis is not merely a marker of acute ischemic injury but rather reflects chronic myocyte damage related to amyloid infiltration, interstitial expansion, and microvascular dysfunction [22]. Altered interstitial and microvascular myocardial environments and

mechanical stress secondary to diastolic dysfunction produce prolonged troponin release. Chronic troponin elevation may precede myocardial hypertrophy by many years and is therefore used in the evaluation of patients with suspected ATTR. hs-cTnT and hs-cTnI are both used in this setting. A cut-off of hs-cTnI > 80 ng/L has also been demonstrated to independently predict mortality in ATTRwt-CA [23].

The comparable hs-cTnT values and LV echocardiographic structural parameters (e.g., IVS, LVMI, RWT) among the three groups suggest similar cardiomyocyte injury but a gradient of worsening hemodynamic impairment. In this setting, markedly elevated NT-proBNP and lower eGFR values may reflect increased LV filling pressures and impaired kidney function as the substrate of a cardiorenal syndrome.

The central observations of this study rely on the concepts that ATTRwt-CA progression is not fully captured by a linear increase in both NT-proBNP and hs-cTnT. An increasing NT-proBNP/hs-cTnT ratio does not simply reflect a greater amyloid infiltration or a direct cardiomyocyte injury, but rather the hemodynamic consequences generated by the infiltrative myocardial substrate. Within this framework, the intermediate-ratio group may represent a transitional phenotype in which arrhythmic involvement—particularly AF—contributes to progression from relative hemodynamic compensation toward overt HF. This interpretation is reminiscent of the pathophysiological model previously described, in which cardiac amyloidosis progresses from a presymptomatic stage—already marked by amyloid-related morpho-structural myocardial abnormalities—to a symptomatic phase, with arrhythmogenic alterations acting as a key transitional mechanism [24].

Moreover, the present data suggest that NT-proBNP and hs-cTnT individually do not capture these pathophysiological mechanisms, as already demonstrated in the current literature [8].

In our cohort, biomarker levels remained stable before and after treatment, consistent with previous reports showing stabilization of NT-proBNP and troponin during the first year of tafamidis therapy [25]. The NT-proBNP/hs-cTnT ratio appeared to follow the same trend, except in the T3 group, in which the ratio increased after treatment initiation. This finding should not be interpreted as evidence of treatment failure, particularly given the exploratory nature of the analysis. Indeed, the duration of treatment and the time from HF symptoms to therapy initiation were similar among the groups and do not appear to have affected these results.

Current prognostic models in ATTR-CM, including the NAC and Mayo staging systems, incorporate circulating biomarkers such as NT-proBNP, cardiac troponin, and renal function to stratify mortality risk [8, 9]. These systems are clinically useful, reproducible, and remain essential for baseline risk assessment. Nevertheless, they generally treat biomarkers as additive or threshold-based predictors rather than evaluating their proportional relationship.

Study limitations should be acknowledged. The NT-proBNP/hs-cTnT ratio reflects disease severity but is not a mortality predictor. Mortality occurred earlier in T3 than in T1 and T2 (Table 2), although this difference did not reach statistical significance. Most cardiovascular events occurred within 18 months of tafamidis initiation [26]. However, the majority of deceased patients were excluded from the study because paired NT-proBNP and hs-cTnT values were lacking; therefore, the small sample and limited number of events reduce statistical power.

Moreover, the retrospective observational design precludes causal inference and does not allow definitive assessment of tertiles as chronologically ordered disease stages. These data require confirmation in a larger sample, and future studies should aim to standardize biomarker measurement in order to determine the clinical utility of these findings.

In conclusion, the NT-proBNP/hs-cTnT ratio identifies three distinct hemodynamic phenotypes in patients with ATTRwt-CA that share a broadly similar structural myocardial substrate but differ in functional impairment. These findings suggest that an easily derived variable may capture a proportional relationship between wall-stress signaling and

myocardial injury. Further prospective studies are needed to confirm our results and validate thresholds for the NT-proBNP/hs-cTnT ratio among the groups.

Abbreviations

ACEi	
angiotensin-converting enzyme inhibitor	
AF	
atrial fibrillation	
AL-CA	
light-chain cardiac amyloidosis	
ARNi	
angiotensin receptor–neprilysin inhibitor	
AS	
apical sparing	
ATTR-CA	
transthyretin cardiac amyloidosis	
ATTRv	
variant transthyretin amyloidosis	
ATTRwt-CA	
wild-type transthyretin cardiac amyloidosis	
BMI	
body mass index	
BSA	
body surface area	
CKD-EPI	
Chronic Kidney Disease Epidemiology Collaboration	
DOAC	
direct oral anticoagulant	
ECG	
electrocardiogram	
eGFR	
estimated glomerular filtration rate	
FLC	
free light chain	
GLS	
global longitudinal strain	
HF	
heart failure	
HFpEF	
heart failure with preserved ejection fraction	
HFrEF	
heart failure with reduced ejection fraction	
hs-cTnT	
high-sensitivity cardiac troponin T	
ICD	

implantable cardioverter-defibrillator
IVS
interventricular septum
KCCQ
Kansas City Cardiomyopathy Questionnaire
LBBB
left bundle branch block
LV
left ventricle
LVEDD
left ventricular end-diastolic diameter
LVEF
left ventricular ejection fraction
LVH
left ventricular hypertrophy
LVM
left ventricular mass
LVMI
left ventricular mass index
MR
mitral regurgitation
MRA
mineralocorticoid receptor antagonist
NAC
National Amyloidosis Centre
NT-proBNP
N-terminal pro-B-type natriuretic peptide
NYHA
New York Heart Association
PASP
pulmonary artery systolic pressure
PM
pacemaker
RBBB
right bundle branch block
RWT
relative wall thickness
SGLT2i
sodium-glucose cotransporter-2 inhibitor
TAPSE
tricuspid annular plane systolic excursion
TR
tricuspid regurgitation
TSH
thyroid-stimulating hormone
TTR

Declarations

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Competing interests

The authors declare that they have no competing interests.

Data availability

Data will be available from the corresponding authors on reasonable request.

Author contributions

Bellini F and Di Lisi D: writing – original draft, writing – review and editing, investigation. Nardi E: writing – review and editing, investigation. Gagliardo CM: writing – original draft, investigation. Giammanco A, Di Gesaro G, Macaione F, Licordari R, Colarusso L, Teresi L: investigation. Cefalù AB: writing – review and editing, methodology. Di Bella G, Novo G and Noto D: conceptualization, data curation, formal analysis, investigation, methodology.

Ethics approval

The study was approved by the Ethics Committee of each participating center.

Consent to participate and publication

Each patient was informed about data collection and provided informed consent for publication of anonymized data.

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Figures

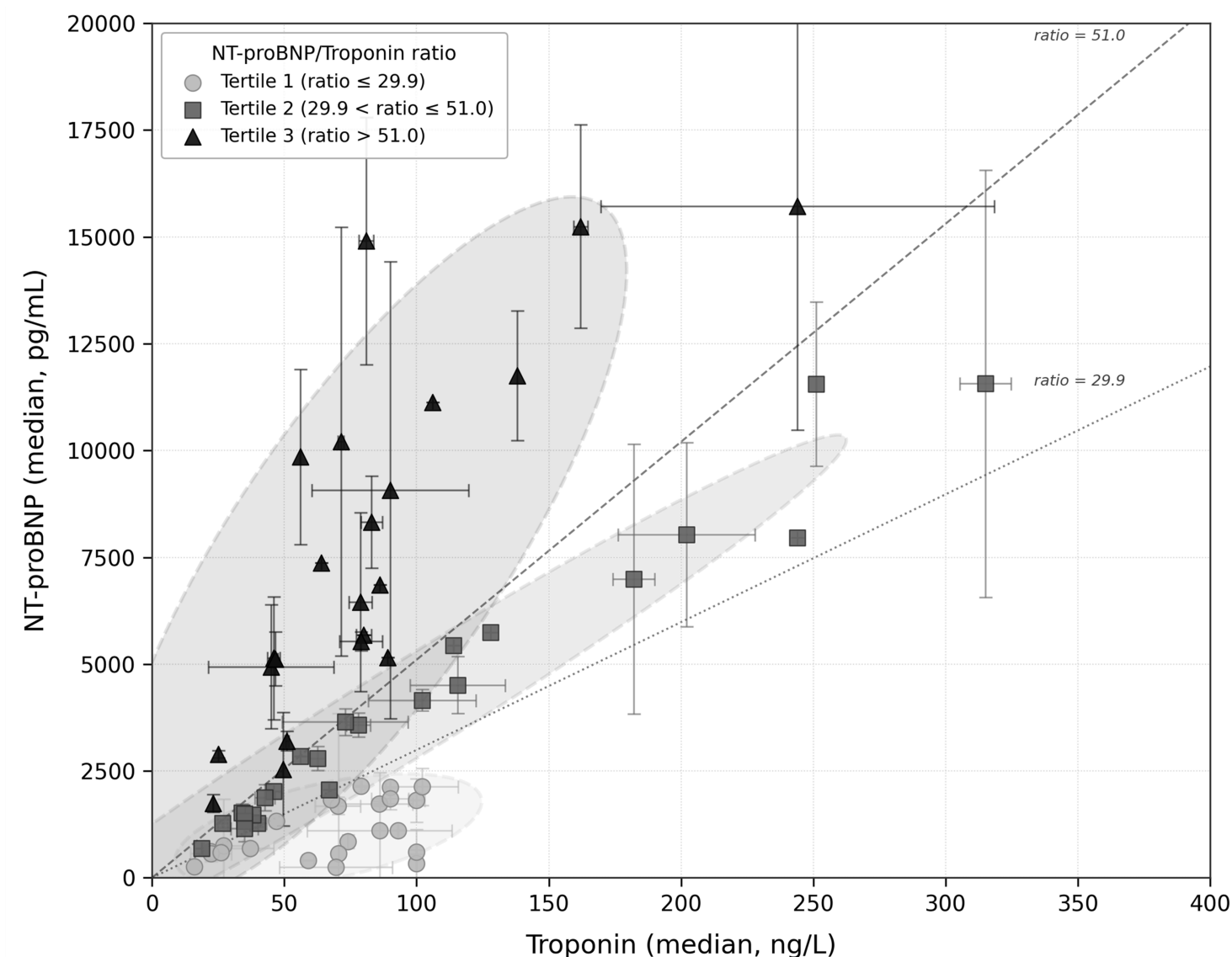


Figure 1

Scatterplot of hs-cTnT vs. NT-proBNP values

Scatter plot of per-patient median NT-proBNP (ng/L) versus median high-sensitivity troponin (hs-cTnT, ng/L) in 70 patients with ATTR-CA. Median values across all available visits for an individual patient. Patients are shown by tertiles of the NT-proBNP/hs-cTnT ratio. Error bars represent ± 1 bootstrap standard error of the median, estimated from 2,000 resamples without distributional assumptions; outliers were excluded using Tukey's fences ($Q1 - 1.5 \times IQR$, $Q3 + 1.5 \times IQR$) prior to resampling, Dashed lines indicate tertile boundaries while ellipses represent 95% confidence regions under a bivariate normal approximation. Two outliers are not shown. IQR: interquartile range; SE: standard error.

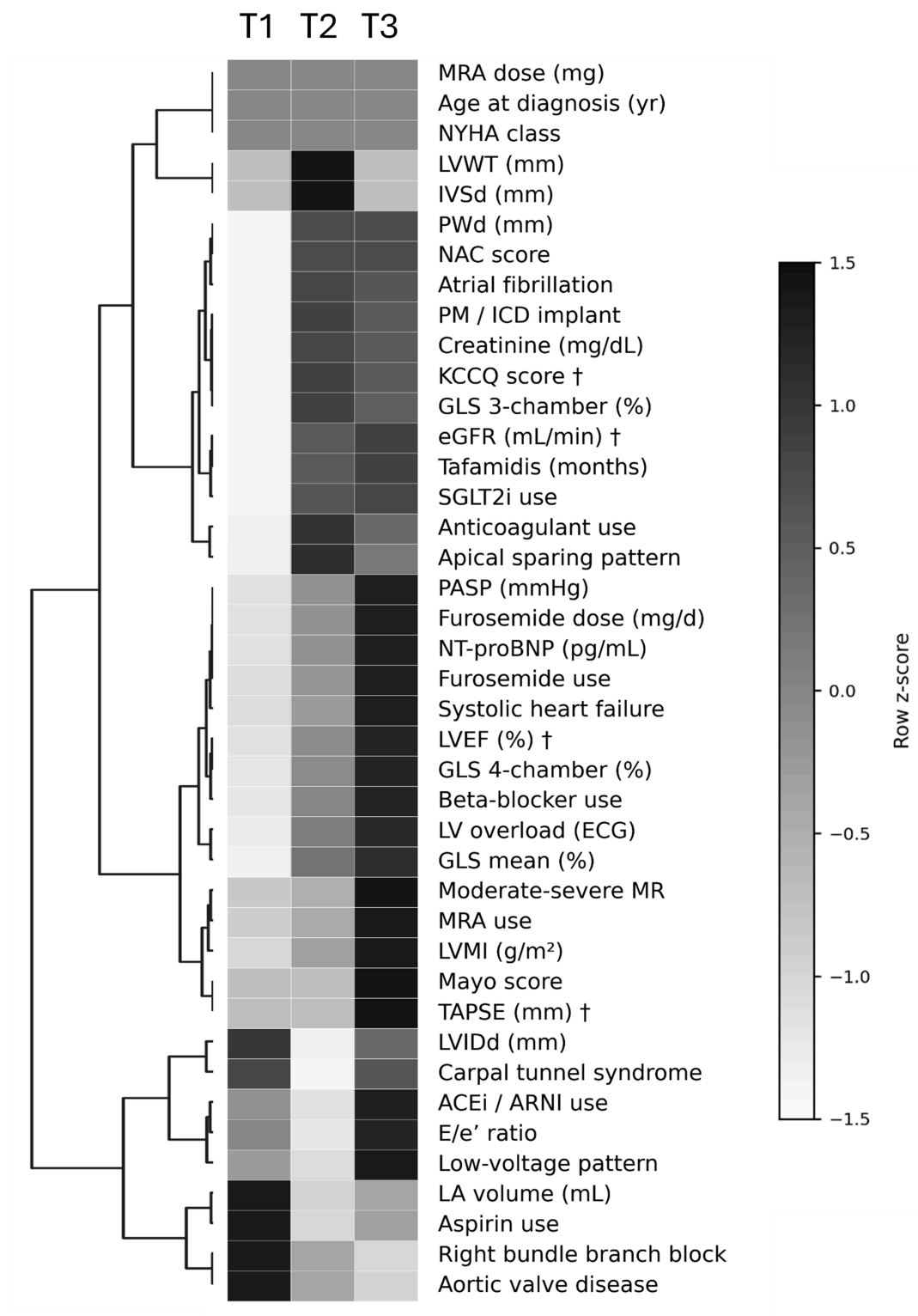


Figure 2

Phenotypic characterization of ATTRwt-CA patients according to NT-proBNP/hs-cTnT ratio tertiles

Each row represents one clinical variable; columns represent the three tertile groups (T1, T2, T3). Color intensity reflects the row z-score computed from group medians (continuous variables) or group proportions (binary variables), normalized for each row. Row ordering was determined by hierarchical clustering. The left vertical stripe shows continuous variables (light grey) and binary variables (dark grey). † Variables with sign-inverted z-score so that darker

shading consistently indicates worse clinical status: left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), tricuspid annular plane systolic excursion (TAPSE), and Kansas City Cardiomyopathy Questionnaire (KCCQ) score.