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ORIGINAL ARTICLE

A new staging system for hereditary transthyretin amyloidosis in the era of specific amyloidosis therapies

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Abstract

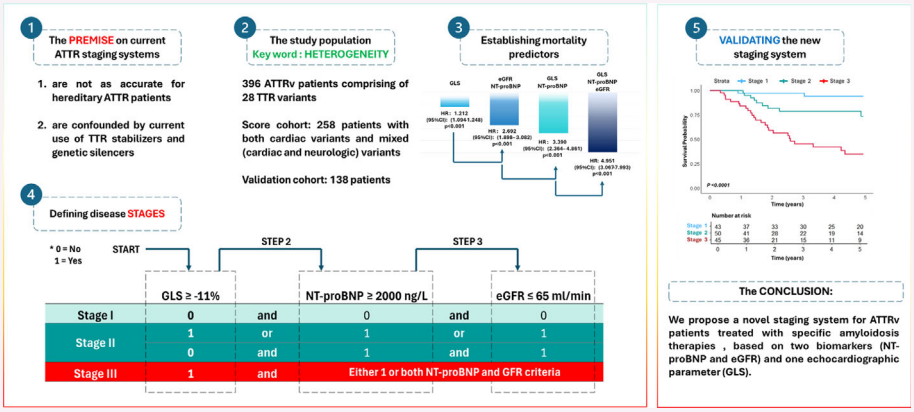
Objectives Currently, there are two prognosis staging systems validated for transthyretin amyloidosis (ATTR). We sought to develop a new staging system dedicated to hereditary transthyretin amyloidosis (ATTRv) patients on specific treatments.

Methods and Results A total of 258 patients diagnosed with ATTRv from two cardiac amyloidosis reference centres in France and Romania were stratified into three disease stages based on NT-proBNP, estimated glomerular filtration rate (eGFR) and global longitudinal strain (GLS). A staging system was created using the following criteria: GLS $\geq -11\%$, NT-proBNP ≥ 2000 ng/L and eGFR ≤ 65 mL/min. Stage I was defined as the presence of none of the criteria. Stage III was defined as GLS $\geq -11\%$ and either one or both NT-proBNP and eGFR criteria, while the remaining patients were defined as Stage II. Stage I patients had a 98.5% (95% CI 94.8–100) 5-year survival rate, Stage II patients 75.1% (95% CI 64.8–87.1) and Stage III patients a 29.4% (95% CI 18.6–46.5) 5-year survival rate (Stage I vs. Stage II, $P = 0.001$; Stage II vs. Stage III, $P < 0.001$). After age is adjusted for, compared to Stage I, the hazard ratio (HR) for death was 9.9 (95% CI 1.28–76.27, $P = 0.02$) for Stage II and 39.75 (95% CI 5.28–299.54, $P < 0.001$) for Stage III patients. HRs and statistical significance were maintained across different ATTR genotypes. The staging system was validated in a cohort of 138 patients.

Conclusions We propose a novel staging system for ATTRv patients on specific treatment, based on two biological markers and one echocardiographic parameter, common in clinical practice.

Graphical Abstract

The aim of our study was to develop a more accurate staging system for hereditary ATTR patients currently receiving specific treatment. A staging system was created using as criteria: GLS $\leq -11\%$, NT-proBNP $\leq 2{,}000$ ng/L, and eGFR ≤ 65 mL/min. We managed to accurately stratify patients into three disease stages, significantly different in terms of prognosis. This novel staging system maintained its statistical significance across different ATTR genotypes, including some with mixed phenotype, even after adjusting for age.



Keywords amyloidosis; ATTRv; cardiomyopathy; phenotype; prognosis; mortality; staging

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Introduction

Transthyretin (TTR) amyloidosis (ATTR) is a progressive systemic disease resulting from the deposition of TTR amyloid, mainly in the heart and peripheral and autonomic nervous systems.[1,2] Based on the accumulation of either variant or wild-type transthyretin, there are two different subpopulations of ATTR: hereditary or variant ATTR (ATTRv) and wild-type ATTR (ATTRwt formerly known as senile systemic amyloidosis).[3]

ATTRwt occurs through the process of ageing and manifests predominantly as cardiac involvement, but with specific extracardiac features such as carpal tunnel syndrome or spinal stenosis.[4]

ATTRv on the other hand results from single base variants in the TTR gene, resulting in varied phenotypes.[5] Val30Met is the most common variant worldwide, with higher prevalence in endemic areas such as Portugal, Scandinavia and Japan.[6] This distribution is important as different phenotypes have been described for the Val30Met variant: an early onset neurologic disease in endemic regions and a late-onset, mainly cardiac, in the non-endemic regions, with better outcomes.[7,8] In the United States, on the other hand, the most common variant is Val122Ile, resulting in a cardiac phenotype with late onset and lower penetrance.[5]

In France, according to the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry, the Val30Met variant was the most prevalent.[9] However, in recent years, an increase in the prevalence of Val122Ile was observed and explained through immigration practices.[10] In Romania, on the other hand, the Glu54Gln variant originally reported in the north-east region of the country is the most prevalent, leading to a mixed and aggressive phenotype, but other variants such as Glu89Lys and Ile107Val were also described.[11]

Currently, there are two staging systems proposed for ATTR. The Mayo staging system developed by Grogan et al. based on cardiac biomarkers, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT),[12] and the UK National Amyloidosis Centre (NAC) staging based on NT-proBNP and glomerular filtration rate (GFR).[13] The Mayo staging system was developed on a population of ATTRwt, and the NAC one on a mixed population of ATTRwt and ATTRv, but with a higher proportion of ATTRwt. However, in both cases, the study populations were of untreated patients. We hypothesize these staging systems are confounded by current worldwide use of specific ATTR treatments. Moreover, given the diverse phenotypes of ATTRv, we sought to investigate a staging system not only for ATTRv cardiomyopathy but also for ATTRv with mixed phenotypes. By merging the two vastly different populations

of ATTRv from France and Romania, we sought to create one of the most heterogeneous cohorts in terms of genetic variants, improving the applicability of our staging system.

Methods

A retrospective review of all patients with a diagnosis of hereditary ATTR from two cardiac amyloidosis reference centres in France and Romania between 2004 and late 2023 and between 2017 and late 2023, respectively, was performed.

The institutional review board from each centre approved the study. Data were recorded electronically in the Henri Mondor Amyloidosis Network registry according to the authorization given by the French CNIL (Commission National de l'Informatique et des Libertés).

Data on clinical presentation including demographics, cardiac and extracardiac symptoms, and family history were collected at diagnosis. Laboratory findings including genotyping, as well as imaging studies with advanced echocardiography were assessed.

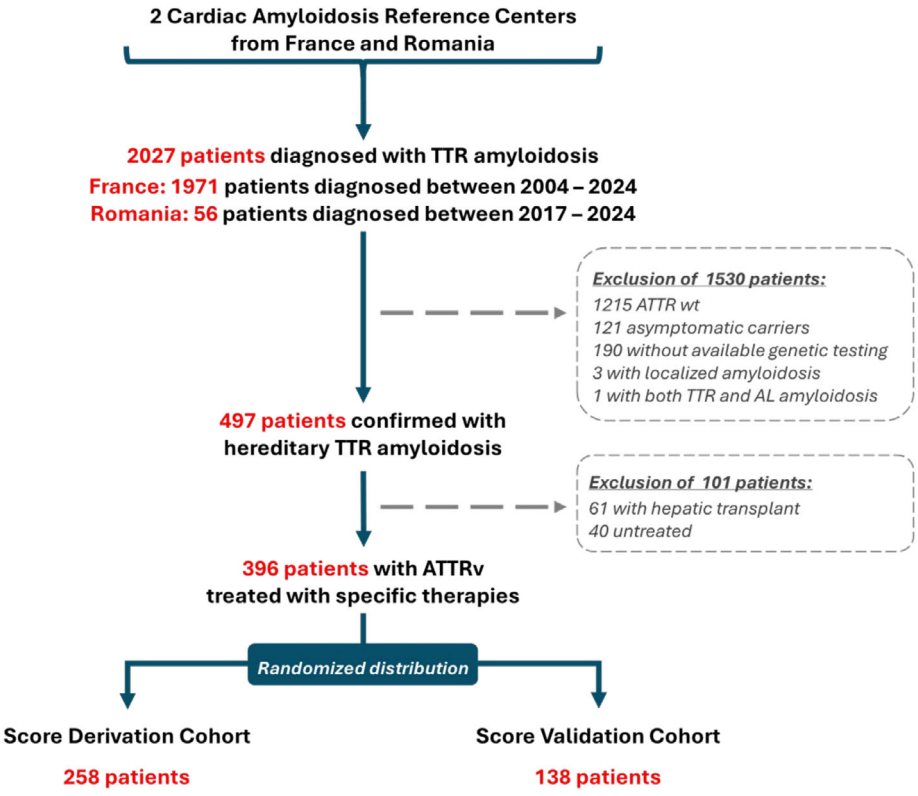
Information on vital status was determined with use of the clinical record, specific services in France and Romania (Service Public and CNAS, respectively), and yearly phone calls to patients and was collected until June 2024.

Patients

Patients were included based on the following criteria: (1) positive diagnosis of ATTR; either histology confirmed or established on non-biopsy diagnostic criteria[14] and (2) presence of a pathogenic TTR gene variant.

We excluded patients without genetic testing, ATTRwt, as well as asymptomatic carriers of ATTRv (*Figure 1*). Asymptomatic carriers were defined by the presence of a pathogenic variant of the TTR gene but no clinical manifestations of the disease based on clinical data, cardiac biomarkers and imaging through bone scintigraphy and when available cardiac magnetic resonance. All patients benefited from specific amyloidosis treatment with either a TTR stabilizer or genetic silencers during the follow-up period, as well as patients who underwent treatment regimen changes such as switching from TTR stabilizers to genetic silencers. Patients who underwent hepatic or heart transplantation as well as untreated patients were excluded from the study.

Figure 1 Patient selection flowchart. Legend: ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; AL: light chain amyloidosis.



We defined TTR variants based on the predominant manifestations, according to data published from the THAOS[15] and provided by the Online Registry for Mutations in Hereditary Amyloidosis.[16] A randomization process was used to divide the population in a 65% to 35% ratio in a score derivation cohort and internal validation cohort.

Biomarkers

All enrolled patients had a complete blood count and basic biochemistry analysis, including serum creatinine performed within a 24-hour interval from diagnosis. Glomerular filtration rate was estimated (eGFR) according to the standard CKD-EPI formula (including the correction for race). Cardiac biomarkers N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-cTnT), and I (hs-cTnI) respectively, were also assessed.

Echocardiography

All patients had a comprehensive echocardiographic exam performed using a Vivid E95 or S70 scanner with all conventional and advanced analysis packages (GE Vingmed Ultrasound, Horten, Norway).[17] Conventional views were analysed offline using dedicated software based on the European Association for Cardiovascular Imaging standardization documents[17] (EchoPAC PC version v203; GE Medical Systems, Milwaukee, WI, United States). We calculated left ventricular ejection fraction (LVEF) through the application of Simpson's formula, based on the four- and two-chamber views. Using

Table 1 Baseline characteristics of the Score Derivation Cohort and the Validation Cohort

Variables	Score Derivation Cohort (n = 258)	Validation Cohort (n = 138)	P
Demographic data			
Age at diagnosis, years	69.9 [59.4–77.1]	69.5 [57.6–77.0]	0.740
Men, n (%)	170 (65.9)	88 (63.8)	0.673
Homozygous, n (%)	16 (6.2)	10 (7.2)	0.689
Body mass index, kg/m^2	24.5 [21.7–27.4]	25.3 [22.3–27.7]	0.127
Clinical data			
Main phenotype			0.385
Cardiac	147 (56.9)	80 (58.0)	
Cardiac and Neurologic	94 (36.4)	45 (32.6)	
Neurologic	17 (6.6)	13 (9.4)	
Heart failure symptoms at diagnosis	112 (43.4)	61 (44.2)	0.880
NYHA class III-IV	55 (21.3)	21 (15.2)	0.142
Autonomic dysfunction	100 (38.8)	51 (37.0)	0.725
Biological data			
NT-proBNP, ng/L	1528.5 [610.0–3352.7]	1633.0 [871.5–2875.2]	0.846
hs-TnT, ng/L	48.5 [27.7–76.0]	46.0 [24.5–78.0]	0.686
eGFR (CKD-EPI), mL/min/1.73 m^2	60.5 [44.6–87.1]	65.8 [47.7–90.3]	0.213
AST, U/L	28.5 [24.0–39.0]	30.0 [23.7–44.2]	0.300
ALT, U/L	24.0 [19.0–32.7]	25.5 [21.0–37.5]	0.346
GGT, UI/L	57.5 [28.0–142.5]	42.5 [27.0–151.2]	0.508
Haemoglobin, g/dL	13.1 [12.2–13.9]	12.8 [11.8–14.3]	0.675
NAC Stage			
I	159 (61.6)	88 (63.8)	0.675
II	62 (24.0)	39 (28.3)	0.357
III	37 (14.3)	11 (8.0)	0.065
Treatment initiation delay			
prior to 2018 (months)	11.1 [2.8–32.8]	9.1 [3.9–20.7]	0.464
after 2018 (months)	1.5 [0.3–5.6]	1.4 [0.3–6.5]	0.888
Echocardiographic features			
Interventricular septum thickness, mm	16.0 [14.0–19.0]	16.0 [13.0–19.0]	0.200
LV mass index, g/m^2	149.4 [121.5–184.4]	157.8 [108.2–190.6]	0.683
LV end diastolic volume, mL	77.0 [59.8–98.2]	80.0 [63.0–101.2]	0.165
LV ejection fraction, %	54.0 [41.0–61.0]	54.0 [40.0–62.0]	0.669
LV global longitudinal strain, %	−11.6 [−8.9 to −15.7]	−11.7 [−8.2 to - 16.4]	0.958
TAPSE, mm	17.0 [14.0–21.0]	16.0 [13.0–21.0]	0.615
LAVi, mL/m^2	44.4 [34.1–57.6]	45.6 [32.5–57.6]	0.691
Pericardial effusion	85 (32.9)	38 (27.5)	0.268

2D speckle tracking in all the three apical views, we assessed the global longitudinal strain (GLS) of the left ventricle.

Statistical methods

The baseline characteristics of the study population are presented by number and percentage or median and interquartile range (IQR) for continuous variables. Characteristics were compared between groups using the Student T test or Mann–Whitney when appropriate, for continuous variables. For the categorical variables, the Pearson chi-square test was used. Missing data were addressed by imputation. Around 18% of troponin T data were missing, while NT-proBNP, eGFR, and GLS had less than 5% missing values.

The mortality endpoint was defined either as time to death for deceased subjects or time to last known follow-up for those last known to be alive. Follow-up time was censored after 5 years. Survival analysis was performed using Kaplan–Meier methods to plot survival by time, while the log-rank test was used to assess for differences between groups. Association between baseline variables and mortality was evaluated by Cox proportional hazards regression. The results of the Cox models were presented as hazard ratios (HRs) and 95% confidence intervals (CI). The results of the age-adjusted models were reported through HRs with their 95% confidence intervals (CI). The discriminatory capacity of each model was determined by calculating Harrell's c-statistic.

To define the staging system, optimal cut points for relevant variables were determined using the approach of Contal and O'Quigley.[18] The sensitivity of cut-off points to individual data points was evaluated, and a representative cut-off point was chosen and reported. Decision support hierarchical models were utilized to facilitate the definition of each disease stage. The staging system was internally validated using a cohort of 138 patients.

All analyses were performed using R statistics v.4.1.1 and RStudio IDE (Posit, PBC); two-sided tests were used, and $P < 0.05$ was considered significant. Where applicable, significance values have been adjusted by the Bonferroni correction for multiple tests. GraphPad Prism v.10 and IBM SPSS v.29 were used for graphic design.

Results

Study population

The total study population consisted of 396 patients with a median age of 69.9 years [58.9–77.1], 65.2% men, 56.1% with cardiac TTR variants. This cohort was divided through a randomized process into a Score Derivation Cohort (n = 258 patients; 65% of total population; median age 69.9 [59.4–77.1], 65.9% men, 55.0% prevalence of cardiac variants) and an Internal Validation Cohort (n = 138; 35% of total population, median age 69.5 [57.6–77.0], 63.8% men, 58.0% prevalence of cardiac variants). A comparison of the baseline characteristics of the Score Derivation Cohort and the Validation Cohort is available in *Table 1*. More detailed baseline characteristics of the Score Derivation Cohort are available in *Table 2* and *Table 3*. The Score Derivation Cohort consisted of 22 different ATTR variants (Table S1), associated with cardiac (n = 147) or mixed phenotypes (n = 94). In a smaller proportion, our cohort consisted of TTR variants associated with mainly neurological involvement (n = 17). This last group had significantly lower NT-proBNP values of 862.0 ng/L [313.0–3034.5], $P < 0.001$, and interventricular septal thickness of 11.0 mm [9.0–15.0], $P < 0.001$, but did present a degree of longitudinal dysfunction (GLS -17.2 [−14.3 to −19.0]) and heart failure symptoms, with almost 18% having a NAC stage II or III. The most frequent variant was Val122Ile (52.33%) followed by Val30Met (16.67%) and Glu54Gln (7.75%).

Regarding specific treatment, a total of 252 patients (97.7%) had tafamidis as the first line of treatment: 144 (56.0%) were started on a 20 mg dose, 68 (26.5%) on a 61 mg dose and 39 (15.2) on an 80 mg dose. Four (1.6%) patients were started on patisiran and 2 (0.8%) were treated initially with diflunisal. For the 95 patients diagnosed before 2018 when treatment became more available, the delay to treatment initiation was significantly higher (11.1 months [2.8–32.8] vs 1.5 [0.3–5.6], $P < 0.001$). There was no statistically significant difference in survival prior to or after 2018. The survival rates at 5 years were 50.5% (95% CI 43.2–58.6%) before 2018 vs 55.8% (95% CI 46.6–66.7%) after 2018, log-rank test P = 0.16 (Figure S4).

UK National Amyloidosis Centre staging system for hereditary transthyretin amyloidosis with cardiac amyloidosis

The NAC[13] score was applied to the score cohort. One hundred fifty-nine patients (61.6%) were Stage I, 62 (24.1%) were Stage II, and 37 (14.3%) were Stage III. Almost 54% of patients with a mainly cardiac phenotype were Stage I, 25.9% Stage II, and 20.4% were Stage III. In contrast, only 5.3% of mixed phenotype patients were Stage II, and 70.2 % were Stage I. Moreover, 82.4% of the mainly neurological phenotype patients were Stage I. Survival probabilities by Kaplan–Meier analysis stratified by stage for the score cohort are shown in *Figure 2*. Stage II and Stage III patients had similar survival rates at 5 years: 52.2% (95% CI 38.3–71.0) vs 55.2% (95% CI 37.4–81.6); Stage I patients had a survival rate of 74.4% (95% CI 66.4–83.4) (log-rank test; Stage I vs. Stage II, P = 0.003; Stage II vs. Stage III, P = 0.743). Cox proportional hazards regression analysis showed that compared with Stage I, the HR for death was 2.33 (95% CI 1.32–4.12, P = 0.003)

Table 2 Baseline characteristics of the Score Derivation Cohort: total population and stratified by phenotype subgroups

Variables	Total population (n = 258)	Main phenotype			P
		Cardiac (n = 147)	Cardiac and Neurologic (n = 94)	Neurologic (n = 17)	
Demographic data					
Age at diagnosis, years	69.9 [59.4–77.1]	74.7 [69.5–79.1] *†	60.5 [52.0–69.7]	41.9 [38.0–49.3]	<0.001
Ethnicity, *n*(%)					
Caucasian	108 (41.9)	24 (16.9)	80 (80.8)	4 (23.5)	
African descent	129 (50.0)	115 (81.0)	13 (13.1)	1 (5.9)	
Portuguese	18 (7.0)	2 (1.4)	5 (5.1)	11 (64.7)	
Asian descent	3 (1.2)	1 (0.7)	1 (1.0)	1 (5.9)	
Men, *n* (%)	170 (65.9)	104 (73.2) †	58 (58.6)	8 (47.1)	0.015
Homozygous, *n* (%)	16 (6.2)	16 (11.3)	0	0	0.014
Body mass index, kg/m^2	24.5 [21.7–27.4]	24.6 [22.5–28.2]	24.5 [21.0–26.7]	22.5 [18.7–27.2]	0.078
Clinical data					
Heart failure symptoms at diagnosis	112 (43.4)	76 (53.5)	34 (34.3)	2 (11.8)	<0.001
NYHA class III-IV	55 (21.3)	40 (28.2)	15 (15.2)	0 (0)	0.004
Autonomic dysfunction	100 (38.8)	34 (23.9) *	58 (58.6)	8 (47.1)	<0.001
Systolic blood pressure, mmHg	126.5 [114.0–140.0]	129.0 [115.0–143.2]	121.0 [110.0–139.0]	125.0 [110.0–145.0]	0.169
Diastolic blood pressure, mmHg	75.0 [66.0–85.0]	75.5 [58.5–84.2]	75.0 [64.0–86.0]	69.0 [66.5–86.0]	0.683
Heart rate, beats per minute	75.0 [66.7–84.0]	75.0 [67.7–86.0]	76.0 [66.0–83.0]	70.0 [60.5–75.0]	0.054
Biological data					
NT-proBNP, ng/L	1528.5 [610.0–3352.7]	2068.0 [922.0–4055.0] *†	1200.0 [223.0–2380.0] †	862.0 [313.0–3034.5]	<0.001
hs-TnT, ng/L	48.5 [27.7–76.0]	62.0 [43.0–87.2] *†	37.0 [23.0–55.7] †	25.0 [20.0–43.5]	<0.001
eGFR (CKD-EPI), mL/min/1.73 m^2	60.5 [44.6–87.1]	52.5 [40.4–66.7] *†	83.7 [54.2–100.0]	99.5 [56.4–114.6]	<0.001
AST, U/L	28.5 [24.0–39.0]	29.5 [25.7–41.0]	26.0 [21.0–31.0]	26.0 [20.5–34.0]	0.628
ALT, U/L	24.0 [19.0–32.7]	23.0 [18.0–33.2] †	24.0 [18.0–33.0] †	33.0 [14.5–42.0]	<0.001
GGT, UI/L	57.5 [28.0–142.5]	80.5 [38.7–161.7] *†	31.0 [18.0–62.0]	30.0 [14.5–36.0]	<0.001
Albumin, g/L	39.5 [36.0–42.0]	39.0 [35.5–41.0]	40.6 [39.0–43.7]	31.0 [30.0–35.0]	0.172
Haemoglobin, g/dL	13.1 [12.2–13.9]	13.0 [11.8–14.0]	13.1 [12.9–13.8]	13.2 [13.1–14.5]	0.700
CRP, mg/L	2.6 [1.0–6.6]	3.1 [1.1–7.4]	1.8 [1.0–3.2]	5.7 [3.2–19.6]	0.232
Prognosis - NAC stage					
I	159 (61.6)	79 (53.7)	66 (70.2)	14 (82.4)	0.014
II	62 (24.0)	38 (25.8)	23 (24.4)	1 (5.9)	0.193
III	37 (14.3)	30 (20.4)	5 (5.3)	2 (11.8)	0.007
Events					
Terminal events (5 years follow-up)	60 (23.3)	46 (31.3)	11 (11.7)	3 (17.6)	0.002
HF hospitalization (5 years follow-up)	120 (46.5)	94 (63.9)	25 (26.6)	1 (5.9)	<0.001

*$P < 0.05$ when compared to 'cardiac and neurologic' phenotype.
†$P < 0.05$ when compared to 'neurologic' phenotype.

for Stage II and 2.04 (95% CI 1.02–4.12, P = 0.045) for Stage III patients. Harrell's c-statistic was 0.598.

A new staging system definition for all hereditary transthyretin amyloidosis patients

Univariate and multivariate analyses of factors associated with death in our cohort are shown in *Table 4*. By Cox regression analysis models, we determined that the discriminatory capacity and association to death of a mixed model consisting of GLS, NT-proBNP, and eGFR were significantly ameliorated when compared to a one-variable model or two-variable model (*Figure 3*).

For NT-proBNP, the optimal cut-off point was 2045 ng/L, which gave a sensitivity of 71.7% and specificity of 67.7%. The optimal cut point for eGFR was 68.6 mL/min/1.73 m^2 (sensitivity 50%, specificity 83.3%), for GLS was −10.8% (sensitivity 68.7%, specificity 75.5%). After comparing the sensitivity of cut-off points to individual data points, we established that NT-proBNP with a cut-off point of 2000 ng/L (sensitivity 71.7%, specificity 65.2%), eGFR with a cut-off point of 65 mL/min/1.73 m^2 (sensitivity 52%, specificity 73.3%), and GLS with a cut-off point of −11% (sensitivity 67.2%, specificity 78.3%.) were significantly associated with death (log-rank test, $P < 0.0001$; *Figure 4*).

A staging system was created using these cut-offs as criteria. Stage I was defined as the presence of none of these criteria. Stage III was defined by the presence of the GLS criterion (GLS ≥ −11%) and either one or both NT-proBNP and eGFR criteria, while the remaining patients were defined as Stage II.

Sixty-eight (26.4%) patients were classified as Stage I, 103 (39.9%) patients were Stage II, and 87 (33.7%) patients were Stage III. Survival probabilities by Kaplan–Meier analysis strat-

Table 3 Echocardiographic features of the Score Derivation Cohort: total population and stratified by phenotype subgroups

Variables	Total population (n = 258)	Main phenotype			
		Cardiac (n = 147)	Cardiac and Neurologic (n = 94)	Neurologic (n = 17)	P
Interventricular septum thickness, mm	16.0 [14.0–19.0]	17.0 [15.0–19.0] †	16.0 [13.0–19.0] †	11.0 [9.0–15.0]	<0.001
Posterior wall thickness, mm	15.0 [12.0–17.0]	16.0 [13.0–18.0] †	14.0 [12.0–17.0] †	11.0 [8.0–14.0]	<0.001
LV mass index, g/m^2	149.4 [121.5–184.4]	155.9 [135.8–186.0] †	145.2 [110.5–184.6] †	107.0 [68.5–139.7]	<0.001
LV end diastolic volume, mL	77.0 [59.8–98.2]	79.5 [61.0–96.5]	74.0 [60.0–101.0]	75.0 [53.5–85.5]	0.630
LV end systolic volume, mL	35.5 [26.0–48.0]	40.0 [29.0–53.0] * †	31.0 [24.0–44.0]	30.0 [20.0–34.5]	<0.001
LV ejection fraction, %	54.0 [41.0–61.0]	48.0 [37.0–58.0] *	59.0 [49.5–63.0]	63.0 [58.0–70.0]	<0.001
LV global longitudinal strain, %	−11.6 [−8.9 to −15.7]	−10.1 [−7.7 to −13.0] * †	−12.6 [−10.2 to - 16.7] †	- 17.2 [− 14.3 to - 19.0]	<0.001
Stroke volume index, mL/m^2	31.5 [25.1–39.0]	30.0 [24.3–36.3] †	34.0 [26.4–40.4] †	40.3 [29.2–62.2]	<0.001
E wave velocity, cm/s	80.0 [63.7–98.0]	80.0 [65.0–97.2]	78.0 [61.0–99.0]	70.0 [60.0–100.0]	0.748
E/A ratio	1.5 [0.9–2.7]	2.0 [1.1–3.1]	1.2 [0.8–2.3]	1.3 [1.0–1.6]	<0.001
E/e' ratio	15.1 [10.7–20.8]	16.5 [12.8–22.1] †	13.0 [8.3–20.2]	8.7 [6.7–13.2]	<0.001
TAPSE, mm	17.0 [14.0–21.0]	16.5 [14.0–20.0] *	19.0 [16.0–22.0]	20.0 [17.0–23.0]	0.005
RV S wave velocity, cm/s	10.0 [8.8–12.0]	10.0 [8.0–12.0] †	11.0 [9.0–13.0]	13.0 [9.5–15.0]	<0.001
PA systolic pressure, mmHg	35.0 [25.5–41.9]	37.0 [28.8–46.7] †	31.6 [23.1–37.8	25.5 [17.5–45.8]	0.008
LA A-P diameter, mm	43.0 [37.0–48.2]	45.5 [39.0–49.2]	42.5 [38.0–47.0]	42.5 [32.0–50.5]	0.019
LAVi, mL/m^2	44.4 [34.1–57.6]	49.5 [38.9–60.5] †	41.2 [33.5–58.9]	35.3 [29.2–47.7]	<0.001
Pericardial effusion, n (%)	85 (32.9)	47 (32.6)	34 (36.1)	4 (23.5)	0.618

*$P < 0.05$ when compared to 'cardiac and neurologic' phenotype;
†$P < 0.05$ when compared to 'neurologic' phenotype

ified by stage for the Score Derivation Cohort are shown in *Figure 5*. Stage I patients had a 98.5% (95% CI 94.8–100) survival rate at 5 years, Stage II patients had a 75.1% (95% CI 64.8–87.1) survival rate, and Stage III patients had a 29.4% (95% CI 18.6–46.5) survival rate, log-rank test; Stage I vs. Stage II, P = 0.001; Stage II vs. Stage III, $P < 0.001$. Median survival for Stage III patients was 3.61 years (95% CI 3.011–4.211). By Cox proportional hazards regression analysis, compared with Stage I, the HR for death was 13.47 (95% CI 1.79–101.67, P = 0.001) for Stage II and 54.3 (95% CI 7.45–396.04, $P < 0.001$) for Stage III patients.

In our analysis, age was a prognostic factor associated with death, with a HR of 11.43 (95% CI 4.13–31.61) for a cut-off point of 65 years. After adjusting for age, compared with Stage I, the HR for death was 9.9 (95% CI 1.28–76.27, P = 0.02) for Stage II and 39.75 (95% CI 5.28–299.54, $P < 0.001$) for Stage III patients. The HR for death in patients with Stage III compared with Stage II was 4.03 (95% CI 2.25–7.19, $P < 0.001$). Harrell's c-statistic was 0.733 (*Table 5*).

To formally assess the difference in prognostic discrimination between the NAC model and our staging system, we performed DeLong's test for two correlated ROC curves. The AUC for the NAC model was 0.653, while the AUC for the new staging system was 0.804. This difference was statistically significant, Z = −4.63 (95% CI -0.215 to −0.087), $P < 0.00001$.

Validation

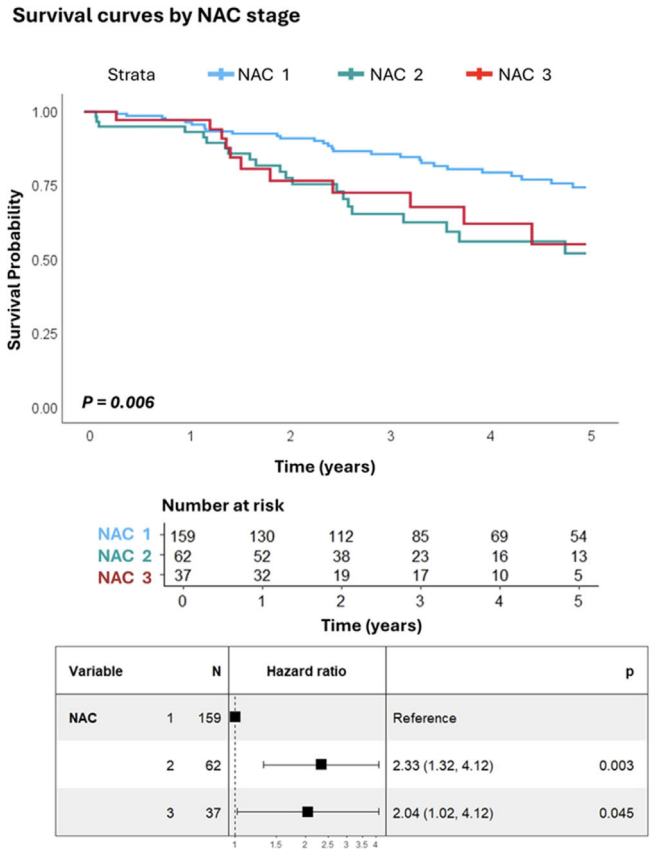
The staging system was applied to the validation cohort of 138 patients with hereditary ATTR; this cohort consisted of 80 patients with cardiac variant (58.0%) and 58 (42.0%) with cardiac and neurologic variants. The baseline characteristics of the validation cohort are shown in *Table 1*. Despite the randomized selection of the validation cohort, baseline characteristics are consistent with those of the score cohort. Forty-two (30.4%) patients were classified as Stage I, 38 (27.5%) patients were Stage II, and 45 (32.6%) patients were Stage III. Survival by Kaplan–Meier analysis stratified by stage is shown in *Figure 6*. Results from Cox proportional hazards regression analysis adjusted for age are shown in *Table 5*. Stage I patients had a 5-year survival rate of 94.1% (95% CI 86.5–100), Stage II 76.2% (95% CI 60.5–96.0) and Stage III 38.4% (95% CI 25.8–57.1), log-rank test; Stage I vs. Stage II, P = 0.027; Stage II vs. Stage III, $P < 0.001$. Median survival time for Stage III patients was 2.6 years (95% CI 1.6–3.6). Cox proportional hazards regression analysis showed that compared with Stage I, the HR for death was 9.26 (95% CI 1.14–75.26, P = 0.04) for Stage III and 30.18 (95% CI 4.10–222.43, $P < 0.001$) for Stage III patients. Harrell's c-statistic was 0.747.

A Cox proportional hazard analysis comparing the accuracy of the staging systems for cardiac phenotype variants and mixed (cardiac and neurologic) phenotype variants is available in Table S2.

Discussion

Our study focused on ATTRv patients from two cardiac amyloidosis reference centres in France and Romania. Combining GLS, renal and cardiac biomarkers, we stratified patients in

Figure 2 Kaplan–Meier curves showing survival probabilities in 258 patients with ATTRv stratified by NAC stage: Stage II and Stage III patients had similar survival rates at 5 years 52.2% (95% CI 38.3–71.0) vs 55.2% (95% CI 37.4–81.6); Stage I patients had a survival rate of 74.4% (95% CI 66.4–83.4) (log-rank test; Stage I vs. Stage II, $P = 0.003$; Stage II vs. Stage III, $P = 0.743$). Cox proportional hazards regression analysis showed that compared with Stage I, the HR for death was 2.33 (95% CI 1.32–4.12, $P = 0.003$) for Stage II and 2.04 (95% CI 1.02–4.12, $P = 0.045$) for Stage III patients. Harrell's *c*-statistic was 0.598.



three disease stages. The staging system was adjusted for age and then validated in a second group of ATTRv patients. This new staging system will help physicians to better stratify the prognosis of ATTRv patients treated with specific drugs against amyloidosis.

Staging systems in transthyretin amyloidosis cardiac amyloidosis

ATTR has been increasingly diagnosed, as awareness for this disease increases. While ATTRwt is a disease of the heart, extracardiac symptoms are milder and usually consist of carpal tunnel syndrome,[2] for ATTRv the phenotype and onset age can be highly variable depending on the pathogenic variant.[5] The THAOS registry has allowed a detailed description of the most frequent variants in terms of symptoms and prognostic.[9] Until now, two different scoring systems have been developed for ATTR amyloidosis. In 2016, Grogan et al developed a staging system based on cardiac biomarkers (NT-proBNP with a cut-off point of 3000 ng/L and troponin T with a cut-off point of 50 ng/L) to stratify the risk in wild-type ATTR.[12]

Later, in 2018, a second prognostic score was developed by the UK National Amyloidosis Centre and validated on a population from the Mondor Amyloidosis Center.[13] The test population in this study, however, consisted of almost 64% ATTRwt; only 13.2% of patients were non-Val122Ile hereditary ATTR, and Val30Met ATTRv was excluded from the analysis. Furthermore, this population did not benefit from specific amyloidosis treatment. Our results partially validate the NAC staging system, particularly its ability to discriminate lower risk patients from those with more advanced stages of disease. However, it had low discriminatory capacity between Stage II and III patients in our population. Establishing an accurate risk stratification for the latter category requires a more complex approach.

Table 4 Univariate and multivariate predictors of mortality in the Score Derivation Cohort

Univariate	HR	95% CI	*P*
Age (years)	1.088	1.056–1.120	<0.001
< 65	1 (Ref)	-	-
≥ 65	11.436	4.132–31.610	<0.001
NYHA III-IV functional class at diagnosis	2.452	1.445–4.161	<0.001
NT-proBNP	1.002	1.001–1.003	<0.001
hs-TnT, ng/L	1.008	1.005–1.011	<0.001
eGFR (CKD-EPI), mL/min/1.73 m^2	1.025	1.013–1.034	<0.002
GGT, UI/L	1.003	1.001–1.005	<0.001
Interventricular septum thickness, mm	1.126	1.054–1.202	<0.001
LV global longitudinal strain, %	1.276	1.156–1.271	<0.001
TAPSE, mm	1.152	1.085–1.176	<0.001
Pericardial effusion	1.843	1.111–3.060	0.018
Multivariate			
NT-proBNP ng/L	1.002	1.001–1.003	0.028
eGFR (CKD-EPI), mL/min/1.73 m^2	1.012	1.001–1.024	0.044
GLS %	1.210	1.094–1.248	<0.001

Considered correlations between predictors: NYHA III-IV functional class at diagnosis and NT-proBNP ($P < 0.001$, Cramér's V $\chi^2 = 6.641$); eGFR (CKD-EPI) and age ($P < 0.001$, Pearson's $R = 0.605$)

Survival in the era of specific treatments

Both the UK National Amyloidosis Centre staging system and the Mayo staging system for ATTRwt were developed before specific treatments were approved for ATTR cardiomyopathy. The first molecule to be approved for both ATTR neuropathy and cardiomyopathy was tafamidis, a TTR tetramer stabilizer.[19–21] Recent data from the THAOS registry comparing patients treated with tafamidis and untreated patients clearly showed important differences in survival at 30 and 42 months respectively, 84.4% (95% CI 80.5–87.7) and 76.8% (95% CI 70.9–81.7) in tafamidis-treated patients, and 70.0% (95% CI 66.4–73.2) and 59.3% (95% CI 55.2–63.0) in tafamidis-untreated patients.[22]

Our study population consisted of treated patients. We include in our analysis patients who received any dosage of tafamidis, providing an accurate representation of the real-world management of ATTRv. Differences in tafamidis dose may be due to differences in drug availability at the time of diagnosis and local practices. The ninety-five patients diagnosed before 2018 had access to tafamidis, either 20 mg or 80 mg, through clinical trials. After 2018, based on the data from the ATTR-ACT clinical study and the long-term extension study, treatment was more readily available for ATTRv with both cardiac and mixed phenotypes.[23,24] However, as other treatment options, such as genetic silencers, became available,[25,26] a large part of the population had changed treatment. This is in line with data from the THAOS registry, almost 20% of patients in both the tafamidis-treated and tafamidis-untreated groups being enrolled in other clinical trials during the follow-up period.[22]

A new staging system

We sought to establish through our study a new staging system for hereditary ATTR, easily applicable in clinical practice for both cardiac dominant phenotypes and mixed phenotypes. Based on Cox proportional hazards regression analysis and decision support hierarchical models, we defined a staging system based on 2 biomarkers, NT-proBNP and eGFR, already established as predictors of mortality and 1 echocardiographic parameter, GLS. In recent years, GLS has proven valuable both in disease monitoring and as a mortality predictor in both AL and ATTR amyloidosis.[27,28] Furthermore, a recent post-hoc analysis of the ATTR-ACT population showed in a comprehensive stepwise model including 23 covariates that blood urea nitrogen and NT-proBNP, 6-minute walk test distance, genotype (wild-type vs hereditary), treatment, and GLS had prognostic value.[29]

The proposed staging system discriminates between 3 groups of patients based on 5 years survival rates: notably between Stage I patients with a survival rate of 98.5% (95% CI 94.8–100) and the more severe Stage II patients with a 75.1% (95% CI 64.8–87.1) survival rate and Stage III: 29.4% (95% CI1 18.6–46.5) survival rate. The global survival rate at 5 years was 76.7% in our population, similar to that recently reported from the THAOS registry, respectively, a survival rate of 76.8% at 42 months in tafamidis-treated patients.[22]

Regarding the NT-proBNP and eGFR correlation, this was addressed when the NAC staging system was developed. We should point out that our cut-off point of 2000 ng/L, although lower than that of NAC staging, remains higher than that expected in patients without significant cardiac disease, even in the context of end stage renal disease in both Caucasian and African American populations.[30,31]

Age and genotype as confounding factors

In the multivariate analysis, age, notably above 65 years, was a factor associated with mortality. We note that there is a correlation between age and eGFR in the general population as well as between NT-proBNP concentration and eGFR. When adjusting our model for age, we demonstrated good discriminatory capacity and accuracy for both patients below and above 65 years.

It is well established that disease onset is highly variable for hereditary ATTR. We categorized the ATTRv into cardiac variants and cardiac and neurologic variants,[9] classification based on which we further validated our model. Our staging system proved a good discriminatory capacity and accuracy in stratifying the risks in both populations. In the cardiac phenotype group, there was a higher proportion of Stage III patients. If this distribution is due to disease severity or delay in diagnosis is difficult to establish. On a subset analysis between the Val122Ile variant, late-onset Val30Met, and

Figure 3 By Cox regression analysis, we compared different models to GLS only as predictors of mortality. Our data showed that a two-variable model of NT-proBNP and GFR had a HR of 2.69 (95% CI 1.89–3.08), superior to GLS only as a predictor of mortality, but was inferior when compared to GLS containing models. The GLS + NTproBNP model had a HR for death of 3.39 (95% CI 2.36–4.81), $P < 0.001$ and a χ^2 of 55.9, while the three-variable model (GLS + NTproBNP + GFR) had a HR of 4.95 (95% CI 3.06–7.99), $P < 0.001$, $\chi^2 = 74.4$.

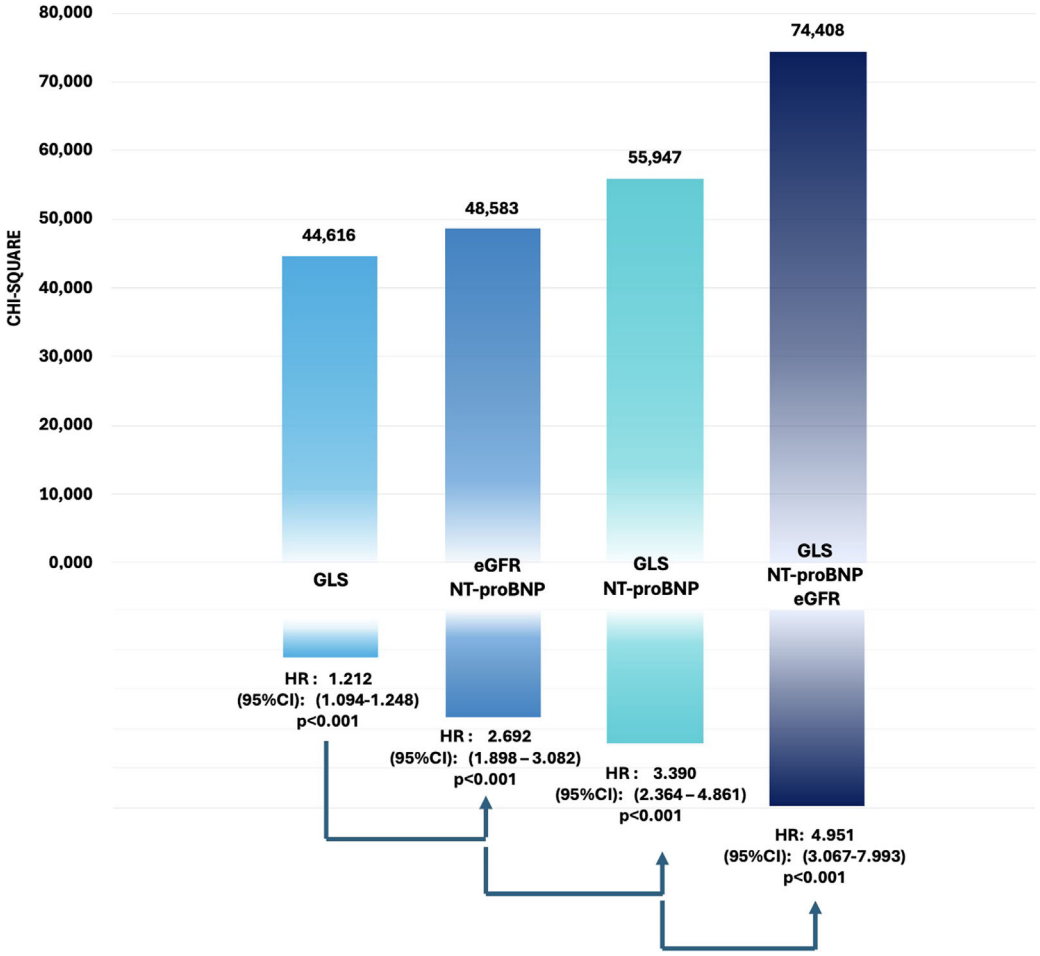


Figure 4 Kaplan–Meier curves showing survival probabilities in 258 patients with ATTRv stratified by optimal cut-off points for eGFR, NT-proBNP and GLS. Cut-off points were established using the approach of Contal and O'Quigley.

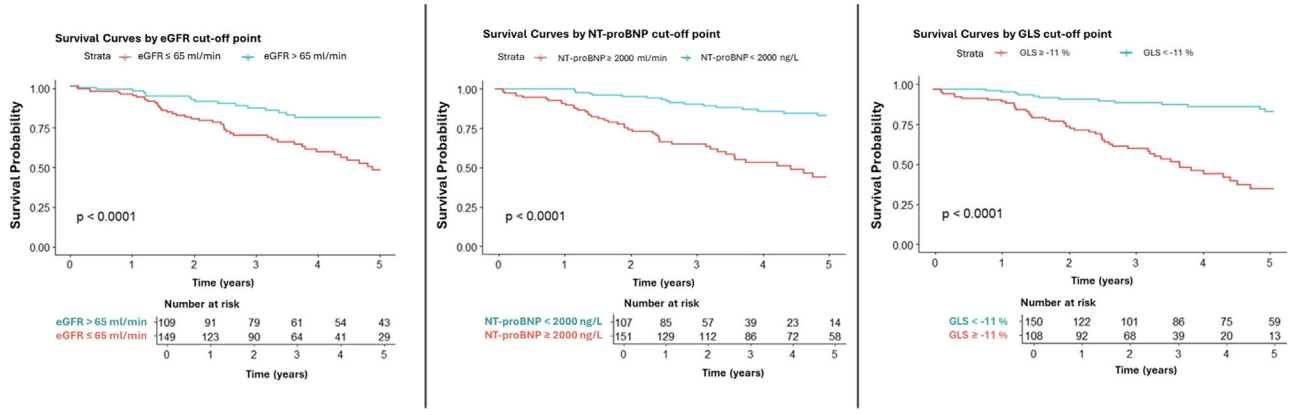


Figure 5 **A.** Kaplan–Meier curves showing survival probabilities in 258 patients with ATTRv stratified by disease stage (log-rank test; Stage 1 vs. Stage 2, $P = 0.001$; Stage 2 vs. Stage 3, $P < 0.001$). Median survival for Stage 3 patients was 3.6 years (95% CI 3.0–4.2 years) **B.** Definition of disease stages based on the 3 criteria: GLS ≥ −11%, NT-proBNP ≥ 2000 ng/L and eGFR ≤65 mL/min/1.73 m^2 **C.** By Cox proportional hazards regression analysis, compared with Stage 1, the HR for death was 13.47 (95% CI 1.79–101.67, $P = 0.001$) for Stage 2 and 54.3 (95% CI 7.45–396.04, $P < 0.001$) for Stage 3 patients. Harrell's *c*-statistic was 0.752. Schoenfeld Residuals were used to assess goodness of fit, $P = 0.406$.

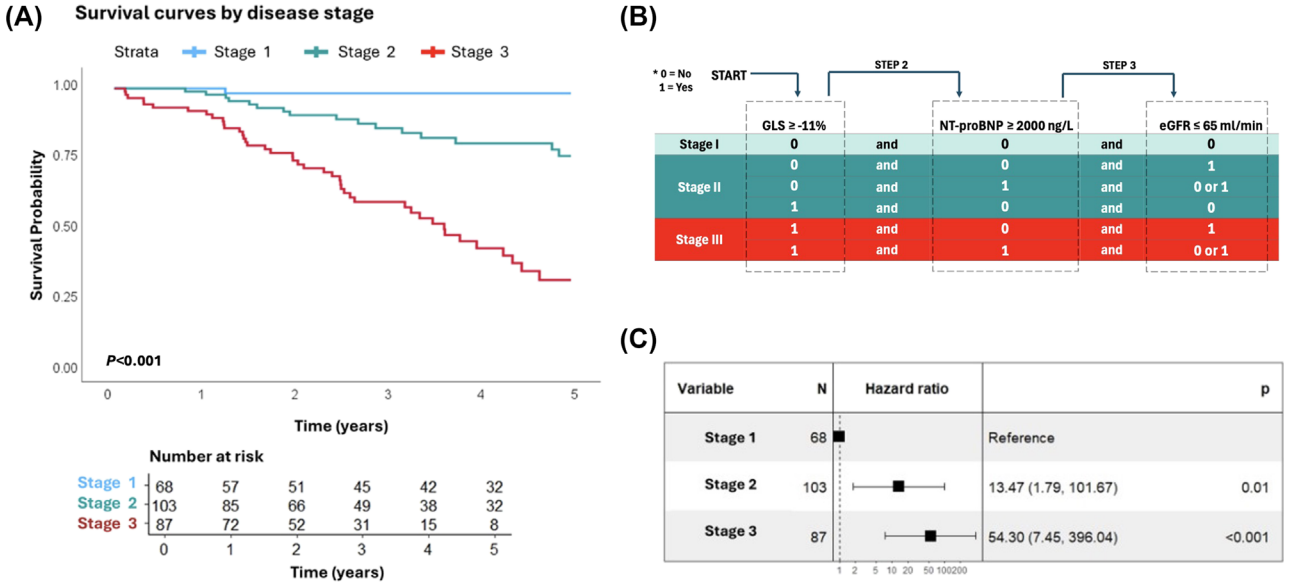


Table 5 Cox proportional hazards regression analysis of staging system, adjusted for age

Model		Results	
		Score derivation cohort	Validation cohort
Stage 1 vs. Stage 2	HR (95% CI)	9.9 (1.28–76.27)	7.61 (0.98–59.08)
	P	0.02	0.052
Stage 1 vs. Stage 3	HR (95% CI)	39.75 (5.28–299.54)	23.31 (3.36–161.21)
	P	<0.001	0.001
Stage 2 vs. Stage 3	HR (95% CI)	4.03 (2.25–7.19)	3.26 (1.34–6.97)
	P	<0.001	0.007

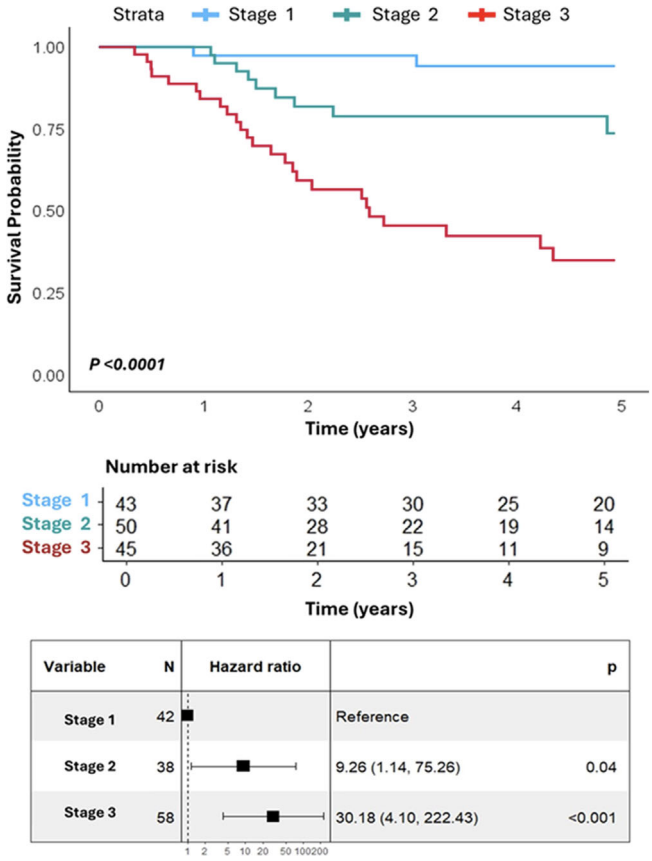
Glu54Gln, the median delay from cardiovascular symptom onset to diagnosis was 18 months [3–120], 8 months [2-20] and 8 months [2-24] respectively. The poor prognosis of cardiac phenotype patients might reflect a more aggressive disease phenotype rather than excessive delay in diagnosis.

Moreover, there is little available data on large cohorts of hereditary patients with mixed or neurological phenotypes related to predictors of mortality in this subset of patients. A single-centre study on a population of 29 patients (10 different variants, 82% prevalence of mixed phenotype) showed that the cardiac involvement and particularly a more advanced NYHA functional class at diagnosis tended to predict a poor prognosis, while phenotype, genotype, and PND score as a measure of severity of peripheral neuropathy had no predictive value.[32]

Study limitations

Our study comprised the largest cohort of hereditary ATTR; 258 patients were included in our score derivation cohort and 138 in the validation cohort, superior to the most recent analysis from THAOS where the ATTRv population consisted of 186 patients. Even so, our study has its limitations due to the relatively small number of patients when compared to other studies on mortality and prognosis, as well as the lack of an external validation cohort. Moreover, given the more advanced age of the cardiac phenotype group, the presence of other comorbidities should also have been taken into account, as well as the use of heart failure treatments when stratifying risk. Furthermore, due to the retrospective nature of our analysis, longitudinal data on the progression

Figure 6 Kaplan–Meier curves showing survival probabilities in 138 patients with ATTRv from the Validation Cohort stratified by disease stage (log-rank test; Stage 1 vs. Stage 2, $P = 0.027$; Stage 2 vs. Stage 3, $P < 0.001$). Stage III patients had a median survival of 2.6 years (95% CI 1.63–3.60 years). Separate analyses were performed before and after the time at which the curves cross (before 1 year: log-rank test; Stage I vs. Stage II, $P = 0.083$; Stage II vs. Stage III, $P = 0.04$. After 1 year: log-rank test; Stage I vs. Stage II, $P = 0.013$; Stage II vs. Stage III, $P = 0.009$). Cox proportional hazards regression analysis showed that compared with Stage 1, the HR for death was 9.26 (95% CI 1.14–75.26, $P = 0.04$) for Stage 2 and 30.18 (95% CI 4.10–222.43, $P < 0.001$) for Stage 3 patients. Harrell's *c*-statistic was 0.747.



of disease under treatment were not available. Although data on biomarkers could have been obtained, in the absence of accurate clinical context, increases in NT-proBNP or decreases in eGFR should be interpreted with caution. Confounding factors for upstaging patients could include the onset of atrial fibrillation, acute kidney injury due to causes unrelated to ATTRv or infectious disease, only to name a few.

Second, our staging system, although created on a population of patients with both cardiac and neurologic involvement, failed to establish the prognostic value of the latter. Although it was hypothesized that autonomic dysfunction might be a predictor of mortality, either through vasoplegia, cardiac denervation, or cachexia due to digestive symptoms,[33] our study failed to demonstrate that. Given that this was a retrospective analysis, there was no established definition of vascular or digestive dysautonomia apart from that of orthostatic hypotension. To avoid bias due to interobserver variability, the neurological component was not considered in this study.

Third, treatment outside the well-curated design of a clinical trial will always represent a limitation when evaluating prognostic factors. Our study population consisted only of treated patients. However, the type of ATTR treatment, duration, dosing, delay from diagnosis to second line treatment, all represent variables that were not taken into consideration. Based on the method of Contal and O'Quigley, we established a cut-off point of 2 years for the delay to treatment, providing a sensitivity of 66.7% and a specificity of 55.3%. Although our staging system maintained its statistical power for patients with a diagnosis to treatment delay both lower and higher than 2 years, our analysis showed a better prognosis in patients with early access to treatment. We analysed survival probabilities in 216 patients with ATTRv having a diagnosis to treatment delay of $\leq$2 years (log-rank test; Stage 1 vs. Stage 2, $P < 0.001$; Stage 2 vs. Stage 3, $P < 0.001$) and in 42 patients with ATTRv having a diagnosis to treatment delay $>$2 years (log-rank test; Stage 1 vs. Stage 2, $P = 0.107$; Stage 2 vs. Stage 3, $P = 0.048$). Median survival for Stage 3 pa-

tients who had early access to treatment was 4.1 years (95% CI 2.26–4.97 years) while for Stage 3 patients that had more than 2 years of delay, the median survival was 2.5 years (95% CI 1.41–3.66 years) (Figure S5).

Conclusions

We propose a novel staging system for treated ATTRv patients, based on two biological markers and one echocardiographic parameter which is commonly assessed in clinical practice. Our work was based on already existing staging systems and illustrates the ever-changing field of TTR amyloidosis. This staging system will be of importance for clinicians in need of a risk quantification tool not only for ATTRv cardiomyopathy but also for patients with both cardiac and neurologic involvement receiving specific treatment against amyloidosis.

Author contributions

GN: conceptualization, methodology, original draft outline, reviewing and editing AZ: conceptualization, methodology, supervision; MK: investigation, data curation, reviewing draft manuscript; RA: investigation, data curation, reviewing and editing the draft manuscript; DC: reviewing the final manuscript; RJ: supervision and reviewing the final manuscript; TD: conceptualization, methodology, supervision, reviewing and editing;

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Disclosure statement

RA and RJ received speaker fees and unrestricted educational grants from Pfizer. T.D. has served on the scientific board of, and received funding from, Pfizer, Alnylam, Akcea, Prothena, and GSK. The remaining authors have no relevant conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (GN) upon reasonable request.

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Supporting information

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

Table S1. Distribution of ATTR variants, phenotype and ethnicity across the Score derivation cohort.
Figure S1. ATTR variants frequency in the total population (A), Score Derivation Cohort (B) and Validation Cohort (C).
Figure S2. First and second line treatment options in the Score Derivation Cohort A total of 39 patients (15.4%) were switched on genetic silencer (38 on patisiran and one on vutrisiran, three also receiving concomitant treatment with tafamidis), after having spent a period of 25.0 months [12.5–39.4] on tafamidis. Out of the 144 patients initially on tafamidis 20 mg, 43 (29.8%) received the 61 mg dose and 32 (22.2%) the 80 mg dose after a delay of 11.0 months [5.5–17.6] and 18.4 months [12.0–23.7] respectively. Seven (2.7%) patients were treated with inotersen as a second line treatment.
Figure S3. Delay in months between first- and second-line treatment options when patients were switched from Tafamidis 20 mg to **A.** Patisiran **B.** Tafamidis 61 mg and **C**. Tafamidis 80 mg.
Table S2. Cox proportional hazards regression analysis, comparison of staging system according to ATTRv phenotype ('neurologic' and 'cardiac and neurologic' phenotypes were analysed together).
Figure S4. Kaplan–Meier curves showing survival probabilities in 258 patients with ATTRv stratified by moment of diagnosis. Log rank test Before 2018 vs After 2018 P = 0.16. Survival rates at 5 years were 50.5% (95% CI 43.2–58.6%) before 2018 vs 55.8% (95% CI 46.6–66.7%) after 2018.
Figure S5. Kaplan–Meier curves showing survival probabilities

in 258 patients with ATTRv stratified by disease stage: **A.** survival probabilities in 216 patients with ATTRv having a diagnosis to treatment delay ≤2 years (log-rank test; Stage 1 vs. Stage 2, $P < 0.001$; Stage 2 vs. Stage 3, $P < 0.001$). Median survival for Stage 3 patients was 4.1 years (95% CI 2.26–4.97 years). **B.** survival probabilities in 42 patients with ATTRv having a diagnosis to treatment delay >2 years (log-rank test; Stage 1 vs. Stage 2, $P = 0.107$; Stage 2 vs. Stage 3, $P = 0.048$). Median survival for Stage 3 patients was 2.83 years (95% CI 1.41–3.66 years).

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