Development of TTRACK Study Diagnostic Scores to Identify Elevated Risk of Transthyretin Amyloid Cardiomyopathy in Older Patients With Unexplained Hypertrophic Cardiomyopathy

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INTRODUCTION

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and fatal condition caused by the misfolding of transthyretin (TTR) protein forming amyloid fibrils that deposit in the heart and other organs.[1,2]
- Delayed diagnosis and misdiagnosis of ATTR-CM are common at least partly due to clinically heterogeneous manifestations overlapping with other more common diseases.[3]
  - Increased left ventricular (LV) wall thickness, a common sign of ATTR-CM, may be mistaken for sarcomeric hypertrophic cardiomyopathy (HCM) in patients with undiagnosed cardiac amyloidosis (CA).[4]
- Diagnosis at an early stage of ATTR-CM and prompt initiation of disease-modifying treatment improves clinical outcomes.[1,3]
  - Non-invasive nuclear imaging techniques and monoclonal protein testing, in appropriate clinical situations, could be used to accurately diagnose ATTR-CM.[1,4]
  - Diagnostic algorithms or machine-learning models have been developed to facilitate the identification of patients with increased ATTR-CM risk who may need further clinical evaluation.[5-7]
- We created new ATTR-CM diagnostic scores to help identify patients at high disease risk who may benefit from further screening using data from older patients with unexplained HCM who participated in the TTRACK study (NCT03842163).

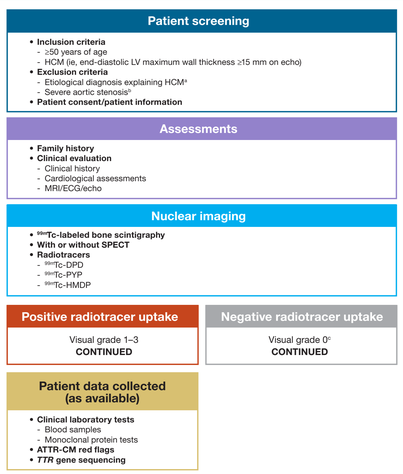
OBJECTIVE

- To describe the development, validation, and potential usefulness of these new diagnostic scores in predicting increased ATTR-CM risk in the TTRACK study population.

METHODS

- TTRACK was a non-interventional, cross-sectional, epidemiologic study (**Figure 1**) across 20 centers in 11 countries.[8]
  - Study period: July 2018–October 2022.

Figure 1: TTRACK study flow



[a] Genetic hypertropic cardiomyopathy, Fabry disease, sarcoidosis, any type of amyloidosis.
[b] Aortic valve area <1.0 cm².
[c] Visual grade 0 / 1 / 2 / 3 = absent / low / moderate / high radiotracer uptake.
99mTc-DPD / HMDP / PYP=technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid / hydroxymethylene diphosphonate / pyrophosphate; ATTR-CM=transthyretin amyloid cardiomyopathy; ECG=electrocardiogram; echo=echocardiogram; HCM=hypertrophic cardiomyopathy; LV=left ventricular; MRI=magnetic resonance imaging; SPECT=single photon emission computed tomography; *TTR*=transthyretin

- Eligible patients (aged ≥50 years) had HCM (LV maximum wall thickness ≥15 mm on echocardiogram [echo]) of unknown etiology and technetium-99m-DPD/-PYP/-HMDP–labeled bone scintigraphy scans.
- Nuclear image grading was based on cardiac vs bone radiotracer uptake using the Perugini system: grade 0=no cardiac uptake, 1=low (cardiac uptake < bone), 2=moderate (cardiac uptake equal to bone), 3=high (cardiac uptake > bone).[9]
  - Patients with moderate or high cardiac uptake had CA.
  - Patients with moderate or high cardiac uptake without monoclonal protein abnormalities had ATTR-CM.
- Patients with no cardiac uptake (grade 0) on scans and patients with ATTR-CM were randomly assigned to derivation or validation cohorts.
- Candidate predictive variables were analyzed by univariate logistic regression, with significant variables (P<0.05) included in a multivariate logistic model.
  - In the derivation cohort, variables independently associated with ATTR-CM were identified using sequential backward elimination. Weighted risk prediction scores were built using variable β estimates in the final model.
  - In the validation cohort, area under the receiver operating characteristic curves (AUROC) were created. Optimal high risk score cutoffs were determined based on sensitivity and specificity. Final scores were assessed in the validation cohort.
  - Performance of the new TTRACK scores was compared with the Mayo score.[5]

RESULTS

Patient Disposition

- Of 445 patients in the derivation cohort, 348 (78.2%) had a grade 0 uptake and 97 (21.8%) had ATTR-CM.
- Of 220 patients in the validation cohort, 173 (78.6%) had a grade 0 uptake and 47 (21.4%) had ATTR-CM.

ATTR-CM Predictors and TTRACK Diagnostic Scores in the Derivation Cohort

- Predictors of ATTR-CM based on univariate and multivariate regression analyses in the derivation cohort are shown in **Figure 2**.
  - The strongest predictor of ATTR-CM was carpal tunnel syndrome (CTS; odds ratio [95% CI], univariate regression 36.08 [18.99–68.52], P<0.001; multivariate regression 136.22 [42.31–438.58], P<0.001).

Table 1: Description of the diagnostic scores by scoring system

Mayo score[5] (range –1 to 10)		TTRACK overall score (range 0–6.5)		TTRACK simple score (range 0–4)	
Variable	**Points**	**Variable**	**Points**	**Variable**	**Points**
Age, years		Age, years		Age, years	
60–69	+2	>72	+1	>72	+1
70–79	+3				
≥80	+4				
Male sex	+2	Male sex	+1	Male sex	+1
Diagnosed hypertension	–1	Carpal tunnel syndrome[b]	+2	Carpal tunnel syndrome[b]	+2
LVEF <60%	+1	LVEF <60%	+0.5		
Posterior wall thickness ≥12 mm	+1	Posterior wall thickness ≥12 mm	+1		
Relative wall thickness[a] >0.57	+2	Relative wall thickness[a] >0.7	+1		

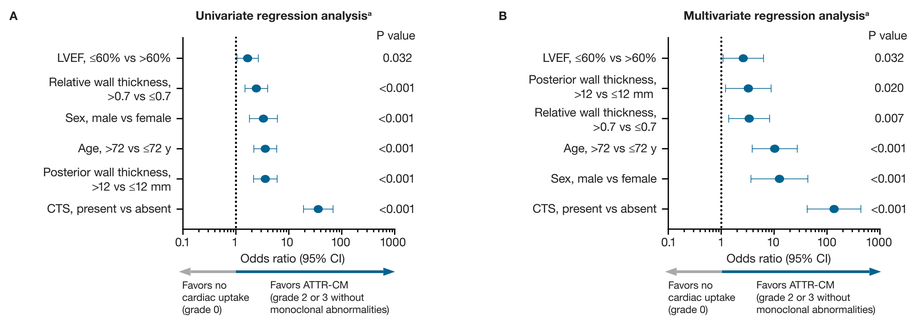
[a] Septal + posterior wall thickness/left ventricular end diastolic diameter.
[b] Unilateral or bilateral carpal tunnel syndrome.
LVEF=left ventricular ejection fraction

- Two diagnostic scores were developed in the TTRACK derivation cohort (**Table 1**):
  - A 6-variable overall score (range 0–6.5), including age >72 years, male sex, CTS, LV maximum posterior wall thickness >12 mm (echo), relative wall thickness >0.7 (echo), and LV ejection fraction <60%, *and*
  - A 3-variable simple score (range 0–4), including age >72 years, male sex, and CTS.

ATTR-CM Risk Prediction With TTRACK and Mayo Scores in the Validation Cohort

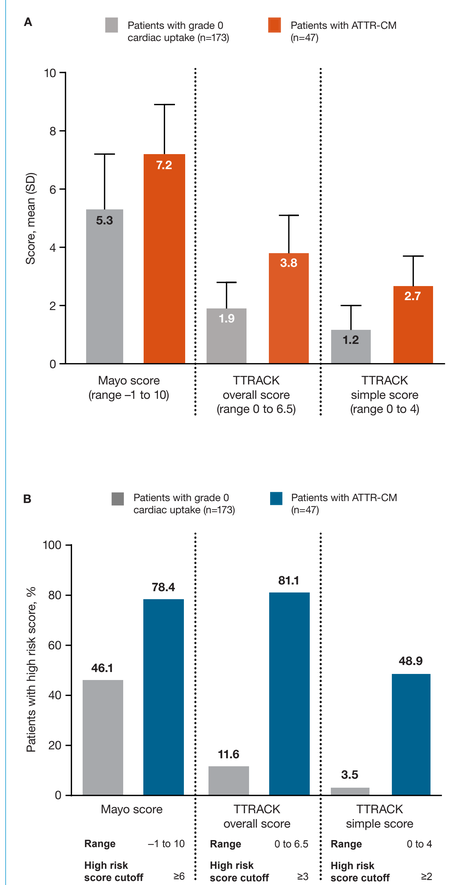
- The mean (SD) TTRACK diagnostic scores were ≥2x higher (overall 3.8 [1.3] vs 1.9 [0.9]; simple 2.7 [1.0] vs 1.2 [0.8]) and the Mayo score was 1.4x higher (7.2 [1.7] vs 5.3 [1.9]) in patients with ATTR-CM vs those with no cardiac uptake (**Figure 3A**).
- When high risk score cutoffs ≥3 and ≥2 were applied with the TTRACK overall and simple scores, respectively, 81.1% (n=30/37) and 48.9% (n=23/47) of patients with ATTR-CM were identified as high risk for the disease vs 11.6% (18/155) and 3.5% (6/173) of patients with no cardiac uptake (**Figure 3B**).
  - When a high risk score cutoff ≥6 was applied with the Mayo score, 78.4% (n=29/37) of patients with ATTR-CM were identified as high risk for the disease vs 46.1% (n=70/152) of patients with no cardiac uptake.
- The TTRACK overall high risk score performed better in identifying patients at risk for ATTR-CM than the Mayo score: AUROC (95% CI) 0.88 (0.81–0.95) vs 0.78 (0.70–0.87), P<0.001 (**Figure 4**).
  - Performance of the TTRACK simple high risk score was not significantly different from the Mayo score: AUROC (95% CI) 0.87 (0.81–0.92) vs 0.78 (0.70–0.87); P=0.639.

Figure 2: Predictors of ATTR-CM based on (A) univariate and (B) multivariate analysis in the derivation cohort



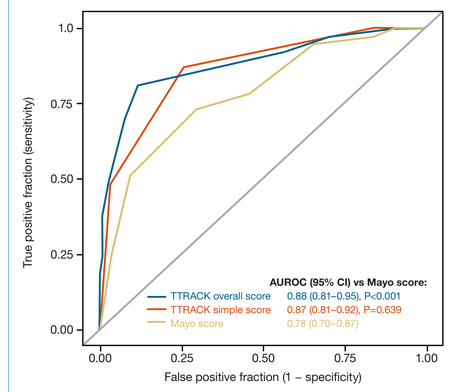
[a] Only the 6 variables included in the multivariate analysis are shown.
ATTR-CM=transthyretin amyloid cardiomyopathy; CTS=carpal tunnel syndrome; LVEF=left ventricular ejection fraction

Figure 3: (A) Diagnostic scores and (B) prevalence of high risk scores by scoring system in the validation cohort



ATTR-CM=transthyretin amyloid cardiomyopathy

Figure 4: ROC curves for the diagnostic scores by scoring system in the validation cohort



[a] Determined using Delong's test for ROC curves.
AUROC=area under the ROC curve; ROC=receiver operating characteristic

CONCLUSIONS

- The 2 newly developed TTRACK diagnostic scores, including an overall score with 6 clinical variables and a simple score with only 3 variables, were able to identify ATTR-CM risk in older patients with unexplained HCM, warranting further clinical evaluation.
  - The TTRACK overall score seemed to outperform the Mayo score. Both scores had 6 different variables.
- Additional investigation is needed to evaluate the generalizability and applicability of the TTRACK diagnostic scores in other relevant patient populations.

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DISCLOSURES

FC: Honoraria for advisory board participation: Akcea, Alnylam, AstraZeneca, Bayer, Novo Nordisk, Pfizer; unconditional research grants: Pfizer. **BMR:** Consulting and speaker fees: Pfizer. **GP:** Honoraria for advisory board participation: Alnylam, Bayer, Pfizer; unconditional research grants: Pfizer. **RJ:** Speaker fees and travel support: Pfizer. **A-MV:** Speaker and consultancy fees, member of advisory boards, or appeared on expert panels: Amgen, AstraZeneca, Bayer, Berlin Chemie Menarini, Boehringer Ingelheim, Egis, Krka, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier, Terapia, Viatris, Vifor Pharma, Zentiva. **GZ:** Honoraria for advisory board participation: Alnylam, Bayer, Pfizer. **TD:** Consulting fees: Alnylam, GlaxoSmithKline, Pfizer, Prothena; honoraria: Alnylam, Pfizer, Prothena; research grants: GlaxoSmithKline, Pfizer; clinical trial support: Alnylam, Ionis, Pfizer. **AC-P:** Employee of eXYSTAT and a paid consultant to Pfizer in connection with this study. **PM, CM:** Employees of and own stock/options in Pfizer. **PE:** Consultancy fees: Alnylam, AstraZeneca, Pfizer; educational grants: Pfizer. **PG-P:** Speaking fees: Alnylam Pharmaceuticals, AstraZeneca, Bridgebio, Intellia, Ionis Pharmaceuticals, Novo Nordisk, Intellia, Pfizer; consulting fees: Akcea, Alexion, Alnylam Pharmaceuticals, AstraZeneca, ATTRalus, Bayer, Bridgebio, General Electric, Intellia, Neurimmune, Novo Nordisk, Pfizer; research/educational support to his institution: Alnylam Pharmaceuticals, AstraZeneca, Bridgebio, Intellia, Novo Nordisk, Pfizer.

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Electronic Poster

Please access the poster via the internet at: https://www.pfi.sr/TTRACK-Diagnostic-Score-Poster

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