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RESEARCH ARTICLE

The Mayo ATTR-CM score versus other diagnostic scores and cardiac biomarkers in patients with suspected cardiac amyloidosis

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Aims Several scores were developed to help the diagnosis of cardiac amyloidosis (CA). The most recent one, being the Mayo transthyretin amyloidosis cardiomyopathy (ATTR-CM) score, was not externally validated. We compared the diagnostic performance of the ATTR-CM score with previous tools (increased wall thickness [IWT] score, AMYLoidosis Index [AMYLI] score, and cardiac biomarkers) in a cohort of patients evaluated for a suspicion of CA.

Methods and results We analysed 362 consecutive patients referred to a third-level centre for suspected CA. Overall, 132 (36%) had transthyretin CA (ATTR-CA), and 91 (25%) immunoglobulin light chain CA (AL-CA); CA was excluded in 139 (38%). ATTR-CM score had a good diagnostic performance to distinguish ATTR-CA from AL-CA or no CA, with an area under the curve (AUC) of 0.795 (95% confidence interval [CI] 0.747–0.842, $p < 0.001$), and ATTR-CA from no CA (AUC 0.822, 95% CI 0.774–0.871, $p < 0.001$). Results were consistent in both patients with preserved (AUC 0.787, 95% CI 0.726–0.848, $p < 0.001$), and reduced or mildly reduced ejection fraction (AUC 0.790, 95% CI 0.709–0.871, $p < 0.001$). The ATTR-CM score showed a better discrimination compared to IWT and AMYLI score to distinguish ATTR-CA from AL-CA or no CA ($p = 0.002$), but not to distinguish ATTR-CA from no CA ($p = 0.270$). Diagnostic accuracy was significantly higher for the ATTR-CM score as compared to the rule-in cut-off of high-sensitivity troponin T.

Conclusion The Mayo ATTR-CM score has a good performance in identifying patients with ATTR-CA, with also better discrimination power when compared to other scores and biomarkers.

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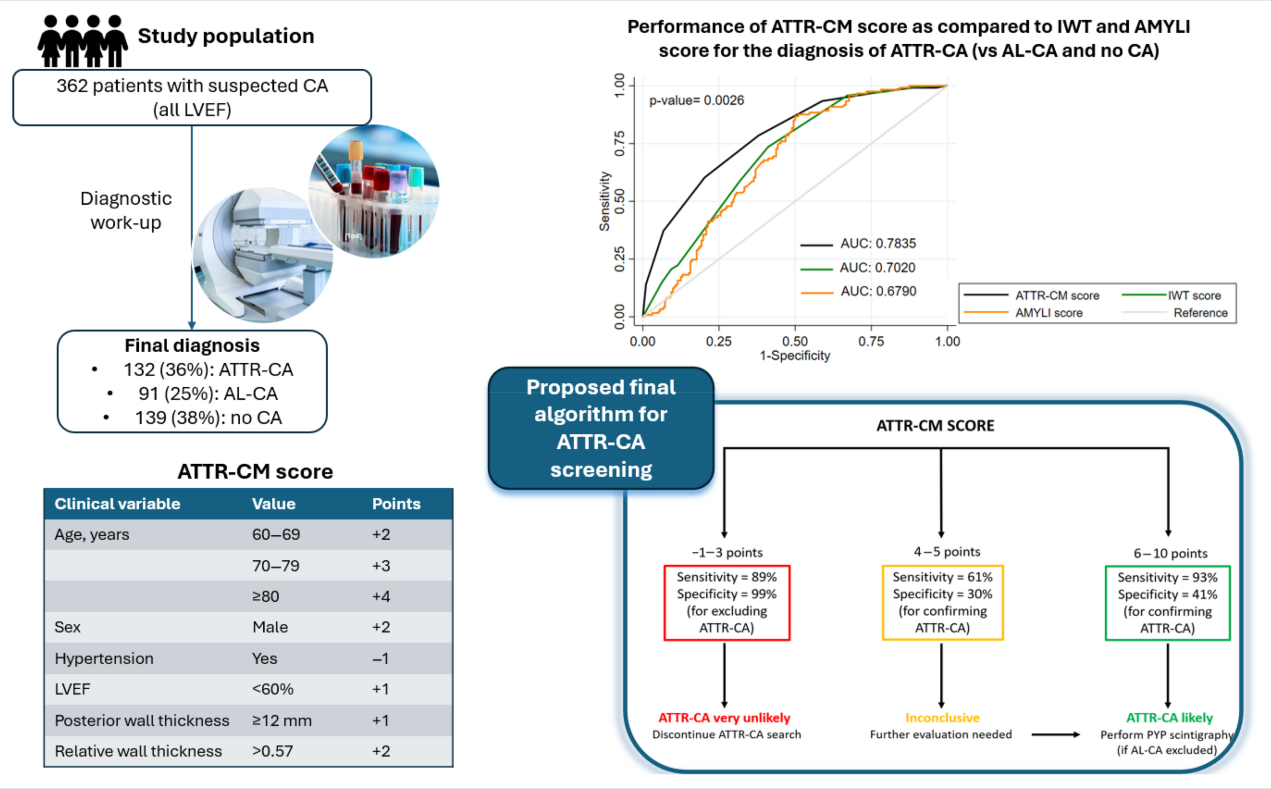
Graphical Abstract



Clinical variable	Value	Points
Age, years	60–69	+2
	70–79	+3
	≥80	+4
Sex	Male	+2
Hypertension	Yes	–1
LVEF	<60%	+1
Posterior wall thickness	≥12 mm	+1
Relative wall thickness	>0.57	+2

Proposed algorithm to screen for transthyretin cardiac amyloidosis (ATTR-CA). AL-CA, immunoglobulin light-chain cardiac amyloidosis; AMYLI, AMYLoidosis Index; AUC, area under the curve; IWT, increased wall thickness; LVEF, left ventricular ejection fraction; PYP, pyrophosphate.

Keywords Cardiac amyloidosis • Transthyretin • ATTR • Diagnosis • Scores • Mayo score

Introduction

Cardiac amyloidosis (CA) is an infiltrative disease caused by the deposition of misfolded proteins. Most cases of CA are due to the deposition of misfolded transthyretin (ATTR-CA) or immunoglobulin light chains (AL-CA).[1,2] ATTR-CA was traditionally considered a rare disease. The introduction of a diagnostic algorithm not requiring tissue biopsy, greater disease awareness and the availability of new therapies have led to a substantial increase in ATTR-CA diagnoses.[3,4]

The first crucial step of the diagnostic algorithm is the diagnostic suspicion of CA. Several echocardiographic scores have been developed and applied to help clinicians identify patients who may have CA.[5–9] The increased wall thickness (IWT) score, proposed in 2020 and subsequently validated in an external population,[7,10] includes variables from standard and speckle-tracking echocardiography. The AMYLoidosis Index (AMYLI) score was developed selecting two of these echocardiographic features, namely relative wall thickness and E/e′ ratio, and can be applied when speckle-tracking imaging is not available.[8] More recently, a simple clinical and echocardiographic score, the Mayo transthyretin amyloidosis cardiomyopathy (ATTR-CM) score, was proposed as a new tool to aid the identification of patients with heart failure and preserved ejection fraction (HFpEF) requiring a screening for ATTR-CA.[9] Discrimination and calibration of the ATTR-CM score were strong. A score of 6 or more was proposed as a cut-off for the search of ATTR-CM.[9]

Other elements that could help diagnose CA are cardiac biomarkers. N-terminal pro-B-type natriuretic peptide (NT-proBNP) <180 ng/L and high-sensitivity troponin T (hs-TnT) <14 ng/L were proposed as cut-offs to reliably exclude CA and hs-TnT 86 ng/L as rule-in cut-off, with an added value to the IWT score.[11]

Our study aims were (i) to validate the ATTR-CM score in an external cohort of patients referred for suspected CA, regardless of left ventricular ejection fraction (LVEF), and (ii) to compare the

diagnostic performance of the ATTR-CM score with previously proposed scores and diagnostic biomarkers.

Methods

Study population

We evaluated consecutive patients referred from 2011 to 2021 to a third-level centre (Cardiology Department, Fondazione Toscana Gabriele Monasterio, Pisa) for suspected CA. Patients underwent clinical history and physical examination, electrocardiogram, transthoracic echocardiogram, laboratory exams, and further exams to confirm or exclude the diagnosis of CA. CA was diagnosed when AL or ATTR amyloid was demonstrated on tissue specimens from endomyocardial biopsy, or when there was imaging evidence of cardiac involvement plus amyloid in a peripheral tissue biopsy (as suggested by guidelines).[1,12] After 2016, ATTR-CA was diagnosed non-invasively in cases with an intense myocardial uptake of bone tracers (Perugini scores 2–3) and no monoclonal protein.[1,13]

The study protocol conformed to the 1975 Declaration of Helsinki, and was approved by the Institutional Human Research Committees of the Fondazione Toscana Gabriele Monasterio. All patients provided written informed consent.

Scores and biomarkers

The Mayo ATTR-CM, IWT and AMYLI scores were calculated as previously described.[7–9]

The ATTR-CM score included six variables: age (60–69 years, +2 points; 70–79 years, +3 points; ≥80 years, +4 points), history of hypertension (−1 point), male sex (+2 points), relative wall thickness (RWT) (>0.57, +2 points), posterior wall thickness (≥12 mm, +1 point) and LVEF (<60%, +1 point) (*Graphical Abstract*).[9]

Parameters for the IWT score calculation were RWT (>0.6, +3 points), E/e′ (>11, +1 point), tricuspid annular plane systolic excursion (TAPSE) (≤19 mm, +2 points), global longitudinal strain (≥ −13%, +1 point), systolic apex-to-base ratio (>2.9, +3 points). The AMYLI score was defined as the product of RWT and E/e′ (RWT*E/e′).[7] RWT was calculated as two-times posterior wall thickness divided by the left ventricular diastolic diameter; the systolic apex-to-base ratio was calculated as apical septal longitudinal strain divided by basal septal longitudinal strain.

NT-proBNP 180 ng/L and hs-TnT 14 ng/L were selected as rule-out cut-offs, and hs-TnT 86 ng/L as rule-in cut-off for CA, as previously suggested.[11] We finally performed an additional analysis using a modified ATTR-CM score that included biomarkers as an additional variable. Scores for biomarkers were assigned as follows: if NT-proBNP <180 ng/L or hs-TnT <14 ng/L, −1 point; if NT-proBNP ≥180 ng/L and hs-TnT between 14 and 86 ng/L, 0 point; if NT-proBNP ≥180 ng/L and hs-TnT >86 ng/L, +1 point.

Patients with missing data for the calculation of each score or biomarkers were excluded from the analysis.

Statistical analysis

The normal distribution of continuous variables was explored through the Shapiro–Wilk tests. Continuous variables are presented as mean ± standard deviation when normally distributed, and as median and interquartile range when non-normally distributed. Categorical variables are presented as counts and percentages. To compare groups, ANOVA test or Kruskal–Wallis test were used, as appropriate. The performance of the ATTR-CM score was evaluated in terms of discrimination and calibration. Discrimination was measured using the area under the curve (AUC) of the receiver operating characteristic. Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test with a *p*-value of >0.05 indicating good calibration.

A two-sided *p*-value of <0.05 was considered as statistically significant for all the analyses. Statistical analyses were performed using Stata 16.1 (StataCorp LLC, College Station, TX, USA).

Results

Out of 398 patients, 36 (9%) patients were excluded due to missing data for calculation of the ATTR-CM score. Of the 362 included patients, 132 (36%) were diagnosed with ATTR-CA, and 91 (25%) with AL-CA. CA was excluded in 139 (38%) (*Figure 1*).

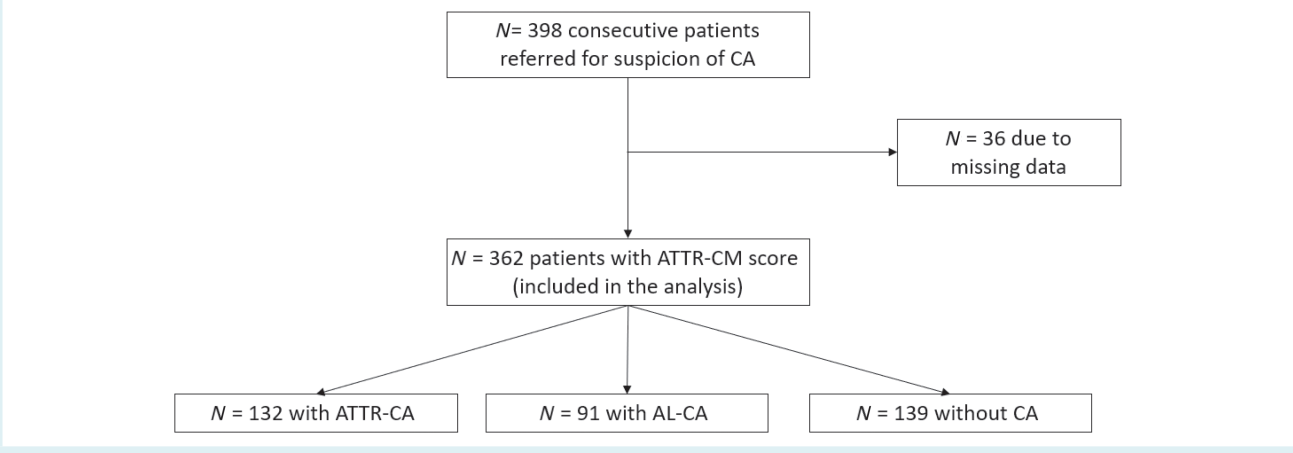


Figure 1 Flowchart of the study population. AL, immunoglobulin light chain; ATTR, transthyretin; CA, cardiac amyloidosis; CM, cardiomyopathy.

Table 1 Baseline characteristics of the study population

Variable	All ($n = 362$)	ATTR-CA ($n = 132$)	AL-CA ($n = 91$)	No CA ($n = 139$)	p-value
Clinical characteristics					
Age (years)	79 (72–83)	82 (76–85)	73 (65–78)	79 (74–84)	**<0.001**
Male sex, *n* (%)	247 (68)	110 (83)	54 (59)	83 (60)	**<0.001**
BMI (kg/m^2)	26.3 (24.0–29.1)	26.0 (23.8–28.1)	25.3 (22.8–28.8)	27.1 (25.3–29.8)	**0.002**
SBP (mmHg)	124 (115–140)	130 (115–140)	120 (105–130)	125 (120–140)	**<0.001**
DBP (mmHg)	70 (65–80)	73 (65–80)	70 (60–75)	70 (70–80)	**<0.001**
Hypertension, *n* (%)	111 (31)	47 (36)	17 (19)	47 (34)	**0.015**
Atrial fibrillation, *n* (%)	120 (33)	55 (42)	19 (21)	46 (33)	**0.005**
NYHA class, *n* (%)					0.518
I	59 (16)	20 (15)	11 (12)	28 (20)	
II	179 (50)	64 (49)	50 (55)	65 (47)	
III	117 (33)	46 (35)	27 (30)	44 (32)	
IV	7 (1)	2 (1)	3 (3)	2 (1)	
Laboratory findings					
NT-proBNP (ng/L)	5674 ± 7013	4970 ± 4128	7891 ± 9901	4785 ± 6638	**0.015**
hs-TnT (ng/L)	72.9 ± 75.6	74.1 ± 79.6	101.3 ± 93.7	54.8 ± 51.5	**<0.001**
eGFR (ml/min/1.73 m^2)	55 (31–69)	55 (32–68)	58 (39–72)	55 (26–69)	0.508
Echocardiographic findings					
LVEF (%)	55 (45–60)	52 (43–56)	55 (48–60)	58 (50–65)	**<0.001**
LVEF ≥50%, *n* (%)	245 (68)	76 (58)	61 (67)	108 (78)	**0.002**
LVEF <60%, *n* (%)	255 (70)	107 (81)	68 (75)	80 (58)	**<0.001**
LVEDV (ml)	102 (83–130)	95 (83–118)	90 (66–109)	113 (96–147)	**<0.001**
LVEDVi (ml/m^2)	54 (44–69)	50 (45–64)	46 (36–60)	60 (51–74)	**<0.001**
LVESV (ml)	46 (35–65)	47 (38–62)	40 (30–51)	51 (35–69)	**0.029**
LVESVi (ml/m^2)	24 (17–33)	24 (18–30)	21 (14–28)	26 (18–35)	**0.018**
IVS (mm)	15 (13–17)	17 (14–19)	14 (12–16)	14 (12–15)	**<0.001**
IVS ≥12 mm, *n* (%)	314 (87)	126 (95)	76 (84)	112 (81)	**<0.001**
LVPW (mm)	13 (12–15)	15 (13–17)	13 (11–15)	12 (11–13)	**<0.001**
LVPW ≥12 mm, *n* (%)	275 (76)	121 (92)	66 (73)	88 (63)	**<0.001**
RWT	0.55 (0.45–0.67)	0.64 (0.55–0.77)	0.58 (0.44–0.75)	0.49 (0.41–0.55)	**<0.001**
RWT >0.57, *n* (%)	155 (43)	84 (64)	46 (51)	25 (18)	**<0.001**
LVMI (g)	148 (121–171)	160 (145–200)	131 (107–157)	140 (114–161)	**<0.001**
LAVI (ml/m^2)	44 (37–50)	45 (39–51.9)	42 (33.5–46.8)	43 (36.6–49.2)	**<0.001**
LAVI >34 ml/m^2, *n* (%)	286 (79)	118 (90)	62 (68)	106 (80)	**0.006**
TAPSE (mm)	18 (14–21)	17 (13–19)	18 (14–21)	19 (16–22)	**<0.001**
PASP (mmHg)	43 (35–48)	44 (38–48)	41 (33–48)	40 (34–49)	0.270
TAPSE/PASP (mm/mmHg)	0.40 (0.32–0.54)	0.39 (0.29–0.46)	0.40 (0.32–0.54)	0.45 (0.35–0.59)	**<0.001**

Significant p values are reported in bold.
AL-CA, immunoglobulin light chain cardiac amyloidosis; ATTR-CA, transthyretin cardiac amyloidosis; BMI, body mass index; CA, cardiac amyloidosis; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hs-TnT, high-sensitivity troponin T; IVS, interventricular septum; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; RWT, relative wall thickness; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.

Baseline characteristics

Patients with ATTR-CA were older and more often male compared to those with AL-CA or without CA. They also showed greater impairment of LVEF, with more thickened interventricular septum and left ventricular posterior wall, and higher RWT. Furthermore, patients with ATTR-CA displayed more pronounced left atrial dilatation and worse right ventricular systolic function (*Table 1*).

ATTR-CM score

The proportion of patients with a final diagnosis of ATTR-CA progressively increased in parallel with ATTR-CM scores (*Figure 2*).

The score had a good performance in predicting the diagnosis of ATTR-CA versus AL-CA or no CA with an AUC of 0.795 (95% confidence interval [CI] 0.747–0.842, $p < 0.001$) (*Figure 3A*) and a good calibration ($p = 0.809$). The AUC for the diagnosis of ATTR-CA versus no CA was 0.822 (95% CI 0.774–0.871, $p < 0.001$) (*Figure 3B*). Results were consistent in both patients with HFpEF (AUC 0.787, 95% CI 0.726–0.848, $p < 0.001$; online supplementary *Figure S1*) and patients with an LVEF <50% (AUC 0.790, 95% CI 0.709–0.871, $p < 0.001$; online supplementary *Figure S2*), as well as in those with heart failure with reduced ejection fraction (LVEF ≤40%) (AUC 0.752, 95% CI 0.633–0.870, $p = 0.001$; online supplementary *Figure S3*).

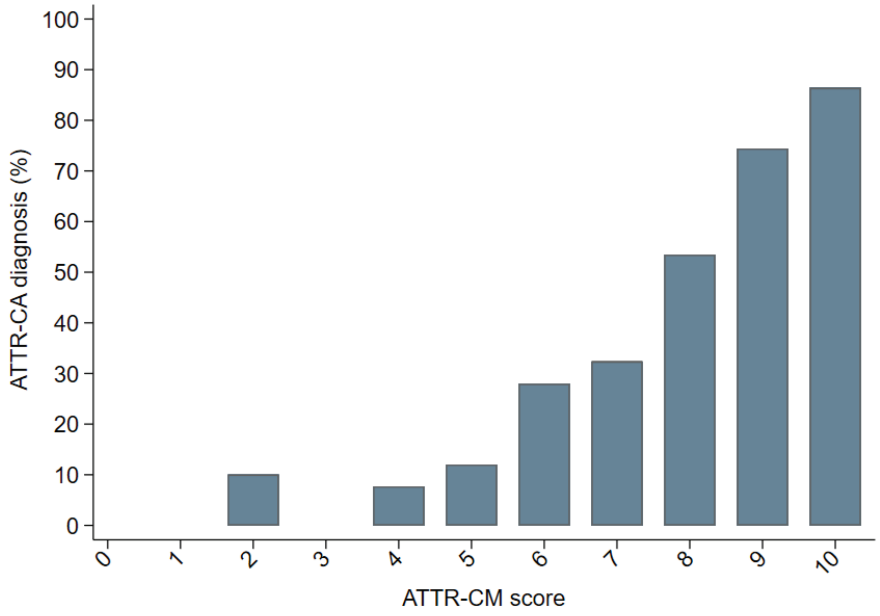


Figure 2 Proportion of patients with confirmed diagnosis of transthyretin cardiac amyloidosis (ATTR-CA) stratified by the transthyretin amyloidosis cardiomyopathy (ATTR-CM) score.

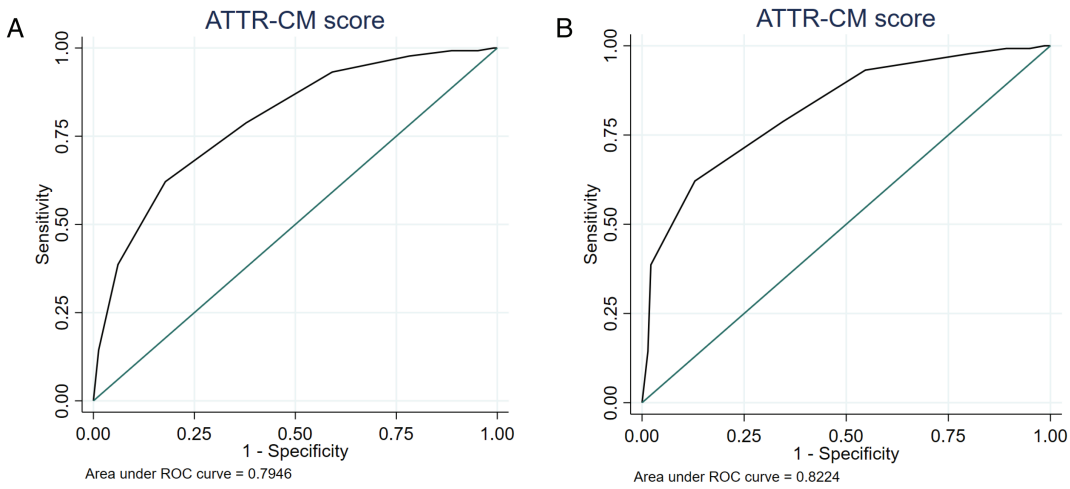


Figure 3 Performance of the transthyretin amyloidosis cardiomyopathy (ATTR-CM) score for the diagnosis of (*A*) transthyretin versus immunoglobulin light chain cardiac amyloidosis and no cardiac amyloidosis; (*B*) transthyretin cardiac amyloidosis versus no cardiac amyloidosis. ROC, receiver operating characteristic.

A total of 259 (71.5%) patients had an ATTR-CM score ≥6. The proportion of patients with an ATTR-CM score ≥6 ranged from 55% of patients with no CA and 66% of patients with AL-CA to 93% of patients with ATTR-CA (*Table 2*). A score value of 6 had a sensitivity of 93% and a specificity of 41%, a positive predictive value of 47% and a negative predictive value of 91% for the final diagnosis of ATTR-CA. Only one patient with a score ≤3 had ATTR-CA and using 3 as a low-risk cut-off, the score had a sensitivity of 89% and a specificity of 99% in excluding ATTR-CA (*Graphical Abstract*). Sensitivity and specificity for different ATTR-CM score cut-off in the whole cohort are reported in *Table 3*.

ATTR-CM score versus other diagnostic scores

Among the 311 patients with data available for all the three scores, the ATTR-CM score showed a better discrimination compared to the AMYLI and IWT scores to distinguish ATTR-CA from AL-CA

Table 2 Distribution of the study population according to the ATTR-CM score

Variable	All ($n = 362$)	ATTR-CA ($n = 132$)	AL-CA ($n = 91$)	No CA ($n = 139$)
ATTR-CM score ≤3, *n* (%)	27 (7.5)	1 (0.8)	11 (12)	15 (11)
ATTR-CM score 4–5, *n* (%)	76 (21)	8 (6)	20 (22)	48 (35)
ATTR-CM score ≥6, *n* (%)	259 (71.5)	123 (93)	60 (66)	76 (55)

AL-CA, immunoglobulin light chain cardiac amyloidosis; ATTR-CA, transthyretin cardiac amyloidosis; CA, cardiac amyloidosis.

Table 3 Sensitivity and specificity of the ATTR-CM score in identifying transthyretin cardiac amyloidosis (ATTR-CA) patients at different cut-offs (vs. non-ATTR-CA)

ATTR-CM score	Sensitivity	Specificity	Likelihood ratio +	Likelihood ratio −	FP, *n* (%)	FN, *n* (%)	TP, *n* (%)	TN, *n* (%)
≥0	100%	0%	1	—	230 (64)	0	132 (36)	0
≥1	100%	0%	1	—	230 (64)	0	132 (36)	0
≥2	100%	1%	1.01	—	228 (63)	0	132 (36)	2 (1)
≥3	99%	5%	1.04	0.17	219 (61)	1 (0)	131 (36)	11 (3)
≥4	99%	11%	1.12	0.07	204 (56)	1 (0)	131 (36)	26 (8)
≥5	98%	22%	1.25	0.06	180 (50)	3 (1)	129 (35)	50 (14)
≥6	93%	41%	1.58	0.17	136 (38)	9 (3)	123 (34)	94 (25)
≥7	79%	62%	2.09	0.34	87 (24)	28 (8)	104 (29)	143 (39)
≥8	62%	82%	3.49	0.46	41 (11)	50 (14)	82 (23)	189 (52)
≥9	39%	94%	6.33	0.65	14 (4)	81 (22)	51 (14)	216 (60)
≥10	14%	99%	11.08	0.87	3 (1)	113 (31)	19 (5)	227 (63)

FN, false negative; FP, false positive; Nd, ; TN, true negative; TP, true positive.

or no CA ($p = 0.002$) (*Figure 4A*). AUC for ATTR-CM, IWT and AMYLI were 0.784 (0.733–0.834), 0.702 (0.646–0.758) and 0.679 (0.621–0.737), respectively.

After the exclusion of patients with AL-CA, the ATTR-CM score did not show a better discrimination compared to the AMYLI and IWT scores to distinguish ATTR-CA from no CA ($p = 0.270$) (*Figure 4B*).

ATTR-CM score versus cardiac biomarkers

Both NT-proBNP and hs-TnT had higher values in patients with CA compared to patients with no CA. The highest values were reported among patients with AL-CA (*Table 1*).

Using hs-TnT 86 ng/L as rule-in cut-off, AUC was 0.493 (95% CI 0.448–0.538) and 0.532 (95% CI 0.486–0.578) for the diagnosis of ATTR-CA versus AL-CA and no CA and of ATTR-CA versus no CA, respectively. Diagnostic accuracy was significantly higher for the ATTR-CM score (both $p < 0.001$). Only three patients had both NT-proBNP <180 ng/L and hs-TnT <14 ng/L, and none of them was diagnosed with CA.

ATTR-CM score enriched with cardiac biomarkers

The AUC for the modified ATTR-CM score, including biomarkers as an additional variable, was 0.784 (95% CI 0.733–0.835, $p < 0.001$) for ATTR-CA versus AL-CA and no CA and 0.837 (95% CI 0.788–0.886, $p < 0.001$) for ATTR-CA versus no CA. A score ≥6 had a sensitivity of 94% and a specificity of 40% with no significant improvement in diagnostic performance of the score enriched with biomarkers compared to the original ATTR-CM score.

Discussion

The main findings of our study can be summarized as follows: (i) the ATTR-CM score seems effective in discriminating ATTR-CA from AL-CA or absence of CA among patients referred to a specialized centre for suspected CA; (ii) the ATTR-CM score had a better discrimination power as compared with previous scores (AMYLI and IWT scores) and biomarkers to distinguish ATTR-CA from non ATTR-CA (including both AL-CA and no CA); and (iii) novel cut-offs of the ATTR-CM score might be proposed in order to select patients worthy of diagnostic work-up for ATTR-CA.

Cardiac amyloidosis is a well-known cause of HFpEF and it may be strictly related to other cardiologic (e.g. aortic stenosis) and non-cardiologic comorbidities.[14,15] The prevalence of ATTR-CA has been reported to be about 13% among patients with HFpEF and about 8–16% in patients undergoing transcatheter aortic valve replacement for severe aortic stenosis.[16,17] The consensus statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases proposed the screening of patients for CA when left ventricular wall hypertrophy

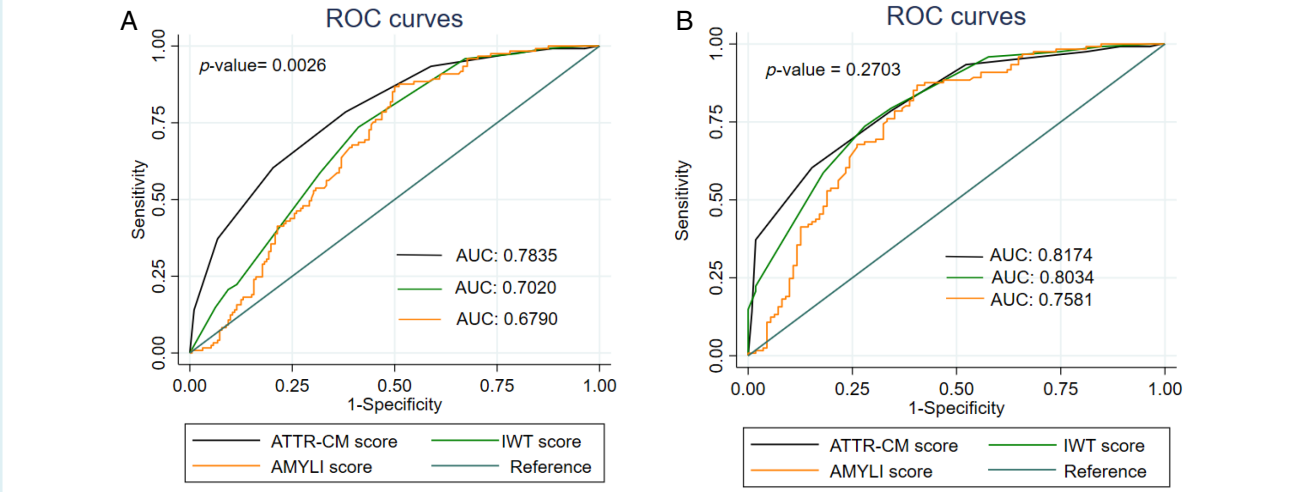


Figure 4 Performance of the transthyretin amyloidosis cardiomyopathy (ATTR-CM) score as compared to increased wall thickness (IWT) and AMYLoidosis Index (AMYLI) score for the diagnosis of (*A*) transthyretin cardiac amyloidosis (vs. immunoglobulin light chain cardiac amyloidosis and no cardiac amyloidosis); (*B*) transthyretin cardiac amyloidosis versus no cardiac amyloidosis. ROC, receiver operating characteristic.

(≥12 mm) is associated with at least one of the 'red flags', such as hospitalization for heart failure, aortic stenosis, bilateral carpal tunnel syndrome, lumbar canal stenosis, etc.[1] However, it might be difficult, as well as not always worth it, considering the limited resources, to test all these patients for CA. The recently proposed ATTR-CM score may facilitate the identification of patients who should undergo further testing, particularly for non-cardiologists.

In our cohort of patients with suspected CA, ATTR-CM score ≥6 revealed a 93% sensitivity and 41% specificity for the diagnosis of ATTR-CA, which is almost in line with previous values reported by Davies *et al.*[9] (sensitivity of 93% and a specificity 62%). The high sensitivity suggests to directly address patients with ATTR-CM score ≥6 to specific diagnostic testing (*Graphical Abstract*). The lower specificity in our study, as compared to Davies *et al.*, might be related to the population pre-selection, at high-risk for CA, with a consequent low number of patients not having CA. In contrast, a score ≤3 showed a great sensitivity and specificity to exclude CA, allowing doctors to identify the patients who can easily discontinue the pathway for amyloidosis diagnosis, avoiding futile testing. Compared with the study by Davies *et al.*, which included patients with HFpEF, we enrolled patients referred for a suspicion of CA regardless of LVEF. In this context, patients with intermediate scores (from 4 to 5) require a more in-depth diagnostic assessment to enlighten other evocative features or, in general, to continue the specific diagnostic work-up of CA. Discontinuing the search for ATTR-CA in these patients might lead to misdiagnosis. Furthermore, in the context of our research, a high negative predictive value is the most important aspect of a diagnostic test. False negative results are, indeed, to be avoided as they would lead stopping of the diagnostic assessment in patients with CA. The results of our study show the value of our method with a high negative predictive value which allows to rule out CA with a low risk of false negative results. Thus, we provided further evidence supporting the utility of the ATTR-CM score in a high-risk population.

The *Graphical Abstract* shows the suggested novel algorithm and possible pathways in the screening of patients according to the ATTR-CM score. This might be particularly useful for non-specialized cardiologist or for general practitioners, who are asked to select patients that require referral to specialized centre. Importantly, the score performed well also in patients with LVEF <50%, broadening the population to which it can be applied.

Additionally, we compared the novel ATTR-CM score with previous tools developed to anticipate the diagnosis of CA. The ATTR-CM score showed a better diagnostic performance for ATTR-CA (vs. non-ATTR-CA) compared to other scores, such as IWT and AMYLI.[7,8,10] Diagnostic performance was similar distinguishing between ATTR-CA and no CA. However, the IWT score is a complex echocardiographic score that includes parameters like RWT, E/e′, TAPSE, global longitudinal strain and systolic apex-to-base ratio. Those parameters may not be accessible in the outpatient or non-cardiological settings. On the other hand, the ATTR-CM score, including easily accessible clinical and echocardiographic values, can be helpful in an early screening for ATTR-CA.

Cardiac biomarkers such as NT-proBNP and hs-TnT were previously reported to have a good diagnostic value,[11] but in our population their diagnostic performance was lower as compared with the ATTR-CM score. Furthermore, a modified ATTR-CM score enriched with cardiac biomarkers did not have a better diagnostic accuracy in our population. Similarly, neither NT-proBNP nor hs-TnT were additive to the final multivariable model in the study by Davies *et al.*[9] Nevertheless, we confirmed that low cut-off values of biomarkers (NT-proBNP <180 ng/L or hs-TnT <14 ng/L) reliably exclude the diagnosis of ATTR-CA as previously reported.[11]

Early diagnosis of ATTR-CA is nowadays crucial to allow patients to receive as earliest as possible disease-modifying treatments. Of

note, the ATTR-CM score showed a lower diagnostic performance for AL-CA. In our cohort, 12% of patients with AL-CA had an ATTR-CM score ≤3. Thus, AL-CA cannot be ruled out even in the presence of low ATTR-CM scores. In addition, since AL-CA is a medical emergency, it must be always ruled out before proceeding with ATTR-CA diagnostic pathway.

Limitations

This is a retrospective observational study, and confounding factors may have affected the results. The score was tested on patients already selected for suspected CA, therefore it may not perform as well in a broader population with a much lower prevalence of CA.

About 9% of patients evaluated for the suspicion of CA were excluded due to missing data for calculation of the ATTR-CM score, which, in addition to the small sample size, also limits the interpretability of the results. However, no systematic differences were found between the population with missing values (excluded from the analysis) and the population included in the present analysis. Thus, we can assume that data were missing at completely random. Additionally, in a sensitivity analysis using multiple imputation (10 iterations, 10 completed datasets generated) for missing data,[18] results were consistent with the main analysis. Finally, due to incomplete information for the calculation of the score, it was not possible to provide a comparison with the T-Amylo score.[6]

Conclusion

This study represents the first external validation of the ATTR-CM score in a large population of patients with a suspicion of CA and broadens its application regardless of LVEF. Due to its high negative predictive value, the score seems to be a useful tool allowing a further selection of patients worthy of diagnostic testing.

Supplementary Information

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

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