ORIGINAL ARTICLE

Transthyretin Cardiac Amyloidosis. Development of a Prediction Model and Scoring Scale for Diagnosis: the *deteCTTAR* Score

Amiloidosis cardíaca por transtiretina. Desarrollo de un modelo de predicción y escala de puntuación para el diagnóstico: score deteCTTAR

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ABSTRACT

Background: To verify the diagnosis of transthyretin cardiac amyloidosis (ATTR-CA) in its early stages, certain warning signs or "red flags" have been lately identified to guide suspicion. However, to date, there is little evidence regarding the diagnostic sensitivity and specificity of each red flag or whether there is any combination of variables that can reliably predict the presence of ATTR-CA.
Objective: The aim of this study was to develop a prediction model based on clinical, electrocardiographic and/or echocardiographic variables to establish a scoring scale to guide the diagnosis of ATTR-CA.
Methods: The medical records of 342 patients with cardiac scintigraphy (CS) for suspected ATTR-CA were analyzed: 171 patients with a positive diagnosis were compared with the same number of patients with a negative diagnosis. Clinical, electrocardiographic and echocardiographic data were analyzed and included in univariate and multivariate logistic regression models. A 0-8 scoring scale was built and a receiver operating characteristic (ROC) curve was generated. The area under the curve (AUC) with its 95% CI was then calculated.
Results: The following variables were identified as predictors of ATTR-CA in univariate and multivariate logistic regression models: interventricular septum (IVS) ≥16 mm (OR 3.6, 95% CI 1.8-7.1), male gender (OR 7.9, 95% CI 3.6-17.1), grade II or III diastolic dysfunction with pseudonormal or restrictive relaxation pattern (OR 12.7, 95% CI 6.1-26.3), and history of bilateral carpal tunnel syndrome (CTS) (OR 24.4, 95% CI 6.0-97.8).
Based on the OR obtained, a scoring scale was created showing an AUC of 0.88 (95% CI 0.84-0.91, p<0.001), and a value ≥3, with high sensitivity and specificity, was identified to predict ATTR-CA (AUC 0.82 95% CI 0.77-0.87).
Conclusions: The prediction model allowed the development of a scoring scale that demonstrated high sensitivity and specificity to strongly guide the diagnosis of ATTR-CA.

Key words: Amyloidosis - Prealbumin- Restrictive Cardiomyopathy - Diastolic Heart Failure - Systolic Heart Failure

RESUMEN

Introducción: Con el objetivo de establecer el diagnóstico de amiloidosis cardíaca por transtiretina (AC-TTR) en etapas precoces, en los últimos años, se lograron identificar ciertas señales de alerta o ¨banderas rojas¨ para orientar la sospecha. Sin embargo, hasta el momento, contamos con escasa evidencia acerca de la sensibilidad y especificidad diagnóstica de cada bandera roja o de si existe alguna combinación de variables que pueda predecir en forma confiable la presencia de AC-TTR.
Objetivo: Desarrollar un modelo de predicción basado en variables clínicas, electrocardiográficas y/o ecocardiográficas que permita establecer una escala de puntuación para guiar el diagnóstico de la AC-TTR.
Material y métodos: Se analizaron las historias clínicas de 342 pacientes con centellograma cardíaco (CC) por sospecha de AC-TTR: 171 pacientes con diagnóstico positivo fueron comparados con igual número de pacientes con diagnóstico negativo. Se analizaron datosclínicos, electrocardiográficos y ecocardiográficos, los cuales fueron incluidos enmodelos de regresión logística uni y multivariados. Se construyó una escala depuntuación de 0-8 y se generó una curva de característica operativa del receptor (ROC). Posteriormente, se calculó el área bajo la curva (AUC) con su IC del 95%.
Resultados: En modelos de regresión logística uni y multivariados, se identificaron como predictores de AC-TTR: el septum interventricular (SIV) ≥16mm (OR 3,6, IC 95% 1,8-7,1), sexo masculino (OR 7,9, IC 3,6-17,1), disfunción diastólica grado II y III con patrón de relajación seudonormal o restrictivo (OR 12,7, IC 95% 6,1-26,3) y el antecedente de túnel carpiano bilateral, TCB (OR 24,4, IC 95% 6,0-97,8).

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En función de los OR obtenidos se creó la escala de puntuación que mostró un AUC 0,88 (IC 95% 0,84-0,91; p< 0.001) y se identificó el valor ≥3, con alta sensibilidad y especificidad para predecir AC-TTR (AUC 0,82, IC 95% 0,77-0,87).
Conclusión: El modelo de predicción obtenido permitió desarrollar una escala de puntuación que demostró una alta sensibilidad y especificidad para orientar fuertemente el diagnóstico de AC-TTR.

Palabras clave: Amiloidosis - Prealbúmina - Cardiomiopatía Restrictiva - Insuficiencia Cardíaca Diastólica - Insuficiencia Cardíaca Sistólica

INTRODUCTION

Transthyretin cardiac amyloidosis (ATTR-CA) is an infiltrative cardiomyopathy caused by the extracellular deposition of amyloid as a consequence of transthyretin disaggregation and/or misfolding. (1)

Although its prevalence remains uncertain, in certain clinical scenarios such as hypertrophic cardiomyopathy (HCM), severe aortic stenosis (SAS) or heart failure with preserved left ventricular ejection fraction (HFpEF) it is usually more frequent, ranging between 13% and 17% of cases. (2-5)

In recent years, the emergence of cardiac scintigraphy (CS) with phosphonates as a non-invasive diagnostic method, together with the advent of new drugs for specific therapy, have led to a growing interest in this pathology, generating a notable increase in the diagnosis. (6)

A great advance in this regard was the identification of certain clinical, electrocardiographic and imaging variables as warning signs or "red flags" to guide suspicion and attempt to detect patients in earlier stages of the disease. However, so far, we have little evidence about the diagnostic sensitivity and specificity of each red flag, or whether there is any combination of variables that can reliably predict the presence of ATTR-CA. (7)

It is known that ATTR-CA is a slow and progressive disease, with a long asymptomatic or subclinical period. It is precisely in these stages where early diagnosis can be crucial to improve the clinical evolution and prognosis of those who suffer from this disease. Phosphonate CS imaging is highly sensitive and specific for diagnosis, when performed in the appropriate clinical context. However, to delineate when it is appropriate to perform it or not is still a challenge.

We conducted this study with the aim of developing a predictive model and subsequently a scoring scale, based on clinical, electrocardiographic and echocardiographic variables, to guide the early diagnosis of ATTR-CA.

METHODS

A single-center and retrospective study was designed. The electronic medical records of 342 patients referred to our service between January 2016 and April 2024 for CS with Tc99m-hydroxymethylene diphosphonate (HMDP) for suspected ATTR-CA were analyzed. Cardiac scintigraphy with HMDP was performed according to current guidelines. The images obtained were analyzed qualitatively according to the Perugini scale. A positive diagnosis of ATTR-CA was considered in the presence of cardiac uptake with grade 2 or 3 HMDP (in the absence of light chains in serum and urine). A negative diagnosis for ATTR-CA was considered for cardiac uptake grade 0. (8,9) Patients without previous consultations and/or studies in our institution were excluded from the analysis.

A total of 171 patients with a positive diagnosis of ATTR-CA were compared with an equal number of patients with a negative diagnosis, randomly selected from our database from a total of 564 CS with HMDP presenting with grade 0 uptake. The populations were not matched for gender or age, as both variables were shown to be predictors in other previously published scoring scales.

Clinical, electrocardiographic and echocardiographic data were analyzed in both groups. All red flags were included, except for proteinuria, global longitudinal strain and late gadolinium enhancement, which were excluded from the analysis due to high data loss.

Definition of variables

Left ventricular relaxation pattern was defined according to the following echocardiographic parameters: (10,11)

- grade I diastolic dysfunction: E/A ratio ≤0.8 + E wave ≤ 50 cm/s, and the absence of 2 or 3 of the following parameters: (a) E/e' ratio >14, (b) tricuspid regurgitation (TR) jet velocity >2.8 m/s, and (c) indexed left atrial (LA) volume >34 ml/m^2;
- grade II diastolic dysfunction: E/A ratio ≤0.8 + E wave >50 cm/s, or E/A ratio > 0.8 and <2, and the presence of 2 or 3 of the (a), (b) and (c) parameters mentioned in the previous section;
- grade III diastolic dysfunction: E/A ratio ≥2
- indeterminate diastolic dysfunction when it does not meet the above criteria.

Interventricular septum (IVS) hypertrophy was defined as diastolic interventricular septum thickness ≥12 mm (12), and bilateral carpal tunnel syndrome (CTS) as the surgical history or presence of current symptoms compatible with this syndrome. (13)

Pseudo infarction pattern was defined as the presence of QS complexes in leads V1-V2, in the absence of a history of myocardial infarction, and microvoltage as the presence of QRS complexes <5 mV in frontal leads or <10 mV in precordial leads.

Statistical analysis

Quantitative variables were expressed as median with their corresponding interquartile range (IQR) and were compared with the Mann-Whitney test. Qualitative variables were expressed as percentages and were compared using the multiple chi-square test.

All the data collected were included in univariate logistic regression models. Those with statistical significance were subsequently included in multivariate logistic regression models to evaluate their predictive value in TTR-CA diagnosis.

Variables identified as predictors in the multivariate models were used to build a prediction scale with a 0-8 score.

According to the ORs obtained, 1 point was assigned for ORs between 1 and <7; 2 points for ORs between 7 and 21, and 3 points for ORs >21.

Sample calibration was evaluated by the Hosmer-Lemeshow statistical test. To determine the predictive capacity of the scoring scale, a receiver operating characteristic (ROC) curve was generated and the area under the curve (AUC) with its 95% CI was calculated as a measure of discrimination.

The level of statistical significance was established as $p < 0.05$.

SPSS Statistics version 26 was used to perform the analyses.

Ethical considerations

The study was approved by the Research Committee of our institution and by an independent Ethics Committee.

RESULTS

Table 1 summarizes baseline characteristics of both groups with the variables included in the univariate analysis.

In the ATTR-CA group, male gender, incidence of bilateral CTS, peripheral neuropathy, atrioventricular block, and grade II or III diastolic dysfunction pattern were significantly more prevalent. In the group without ATTR-CA, diabetes, smoking, history of coronary artery disease, HF with left ventricular ejection fraction (LVEF) ≥50%, marked LA dilatation, and severe AS were significantly more prevalent.

Statistically significant differences in IVS thickening were also observed: most patients without ATTR-CA had thickness <12 mm or between 12 and 16 mm, with a median (IQR) of 13.3 mm (12.6-14.1), while in the ATTR-CA group the majority showed an IVS thickness ≥16mm, with a median (IQR) of 16.6 mm (16.1-17.2) .

In our analysis, microvoltage and pseudoinfarction pattern (predictor variables of ATTR-CA in other models) showed no significant differences between the two groups.

There were no patients with grade 1 cardiac uptake, nor patients with grade 0 uptake and positive serum and urine light chains.

Within the group with positive ATTR-CA, 13 patients (8%) had IVS thickness ≥12 mm without any red flag. Another 3 patients (2%) although they had red flags, did not have increased IVS thickness and, in addition, one patient had neither condition.

Four patients presented positive genetic test (hereditary ATTR-CA), the most frequent mutation being Val50Met and only one of them presented the Val142Ile variant.

Table 2 shows the multivariate analysis of the significant variables in the univariate analysis. Table 3 shows the variables identified as predictors of AC-TTR in the multivariate analysis and the score assigned to each of them, for the preparation of our prediction scale (*deteCTTAR* score).

In the ROC curve analysis, the scale showed an AUC of 0.88 (95% CI 0.84-0.91, $p < 0.001$) (Fig. 1A). A value ≥3 was identified as having the best combination of sensitivity and specificity for predicting ATTR-CA, with an AUC of 0.82 (95% CI 0.77-0.87) (Fig. 1B and C), and OR 22.9 (95% CI 12.3- 42.5, $p<0.001$) for having the disease.

There was no evidence of significant differences in the number of red flags present between the groups, nor that a greater number of red flags implies a higher risk of ATTR-CA.

DISCUSSION

In our work, male gender, IVS thickness ≥ 16 mm, grade II or III diastolic dysfunction (also known as pseudonormal or restrictive relaxation pattern) and bilateral CTS were predictors of ATTR-CA.

Lack of differences in the number of red flags between patients with and without the disease confirms the low specificity of these conditions to arrive at a diagnosis.

In recent years, two scoring scales for the early diagnosis of ATTR-CA were published. One of them, the transthyretin amyloid cardiomyopathy score (ATTR-CM score) searched for ATTR-CA among patients with IVS hypertrophy and HF with LVEF ≥40%. (14)

However, according to our results, of the total number of patients with a positive diagnosis of ATTR-CA, only 44 patients (26%) had HFpEF, 73 patients (42%) showed no signs/symptoms of HF, while 54 (32%) had decreased LVEF.

Although it is known that ATTR-CA is a pathology historically related to HFpEF, it should be remembered that the natural evolution of the disease without specific treatment leads to progressive deterioration of myocardial histoarchitecture and function. Initially, the isolated deposition of amyloid fibrils affects diastolic function, but later, with excessive accumulation, sarcomere coupling is affected, damaging systolic function. (15)

Therefore, in our study, patients with decreased LVEF could be a consequence of the natural evolution of the disease (and hence, of a late diagnosis) or could be due, in some cases, to the coexistence of other diseases. It is important to emphasize that 21% of this subgroup of patients had a history of coronary artery disease. This highlights the fact that the search for ATTR-CA should not only focus on cardiomyopathies of unexplained etiology, since coexistence with ischemic-necrotic cardiomyopathy can be frequent.

In the other scale (the T-Amylo score), patients had to present as a necessary condition an IVS thickness ≥12 mm associated with one or more red flags to establish the risk of presenting ATTR-CA. (16) However, in our study, 17 patients (10%) with a diagnosis of ATTR-CA did not have increased IVS thickness or red flags.

Although the presence of ATTR-CA in patients without IVS thickening is not widely reported, one study found 5% prevalence of the disease in patients with HFpEF and IVS <12 mm. (17) This could be ex-

Table 1. Baseline characteristics of both groups and variables analyzed in the univariate model.

	ATTR-CA (n=171)	No ATTR-CA (n=171)	p
Clinical Variables			
Age (years)	82 (76-86)	82 (75-87)	0.820
Male gender	155 (90%)	95 (55%)	< 0.001
Hypertension	133 (78%)	138 (80%)	0.505
Diabetes	29 (17%)	47 (27%)	0.019
Dyslipidemia	104 (60%)	110 (64%)	0.502
Smoking	72 (42%)	92 (53%)	0.031
History of coronary artery disease	36 (21%)	71 (42%)	< 0.001
Narrow medullary canal	8 (5%)	2 (1%)	0.054
Atrial fibrillation	89 (52%)	101 (59%)	0.191
Biceps rupture*.	0	0	-
Bilateral carpal tunnel syndrome*.	43 (25%)	3 (2%)	< 0.001
HF, LVEF ≥ 50%*.	44 (26%)	102 (59%)	< 0.001
HF, LVEF <50%*.	54 (32%)	39 (23%)	0.068
Hypotension - normotension* +	4 (2%)	2 (1%)	0.410
Autonomic dysfunction*.	4 (2%)	0	-
Peripheral neuropathy*.	9 (5%)	0	-
PPM Implantation*	44 (26%)	53 (31%)	0.283
Family history *	0	0	-
Skin bruising*.	0	0	-
Electrocardiographic variables			
Microvoltage *	26 (15%)	28 (16%)	0.766
Pseudoinfarction pattern*.	54 (32%)	48 (28%)	0.478
AVB*	42 (25%)	22 (13%)	0.005
LBBB	47 (27%)	48 (28%)	0.903
RBBB	22 (13%)	20 (12%)	0.741
Echocardiographic variables			
IVS <12 mm	4 (2%)	57 (33%)	< 0.001
IVS ≥12 and <16 mm	67 (39%)	86 (50%)	0.038
IVS ≥16 mm	100 (58%)	28 (16%)	< 0.001
IVS (mm)	16.6 (16.1-17.2)	13.3 (12.6-14.1)	< 0.001
LA mild dilation (35 to 41 mL/m^2)	61 (36%)	45 (26%)	0.061
LA moderate dilation (42 to 48 mL/m^2)	55 (32%)	44 (26%)	0.189
LA severe dilation (>48 mL/m^2)	27 (16%)	69 (40%)	< 0.001
E/e' ratio ≥15	77 (45%)	61 (36%)	0.077
LVEF >50%.	90 (53%)	107 (63%)	0.062
Severe AS*	8 (5%)	44 (26%)	< 0.001
Normal relaxation pattern	16 (9%)	38 (22%)	0.002
Grade I diastolic dysfunction pattern (impaired relaxation)	41 (24%)	68 (39%)	0.003
Grade II diastolic dysfunction pattern (pseudonormal)	38 (22%)	15 (9%)	0.001
Grade III diastolic dysfunction pattern (restrictive)	58 (34%)	1 (<1%)	< 0.001
Indeterminate relaxation pattern	18 (11%)	49 (28%)	< 0.001
0 red flags	14 (8%)	8 (5%)	0.260
1 red flag	63 (37%)	75 (44%)	0.185
2 red flags	69 (40%)	54 (32%)	0.909
3 red flags	22 (13%)	26 (15%)	0.533
4 red flags	2 (1%)	8 (5%)	0.054
5 red flags	1 (<1%)	0	-

ATTR-CA: Transthyretin cardiac amyloidosis; AS: aortic stenosis; AVB: atrioventricular blockade; HF: heart failure; IVS: interventricular septum; LA: left atrial; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; PPM: permanent pacemaker; RBBB: right bundle branch block.

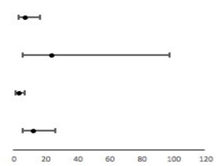
Tabla 2. Multivariate analysis

Variable	OR	95% CI	p
Male gender	7.9	(3.6-17.1)	<0.001
BCT	24.4	(6.0-97.8)	<0.001
LVEF >50%	1.2	(0.4-4.2)	0.682
AVB	0.6	(0.1-3.1)	0.632
IVS≥16mm	3.6	(1.8-7.1)	<0.001
Severe LA dilation	0.1	(0.1-0.2)	0.042
Severe AS	0.1	(0.1-0.4)	<0.001
Normal relaxation pattern	0.3	(0.1-0.8)	0.014
Impaired relaxation pattern	2.6	(0.9-7.3)	0.076
Pseudonormal relaxation pattern	4.1	(1.2-12.9)	0.017
Restrictive relaxation pattern	10.3	(7.2-23.4)	0.034
Indeterminate relaxation pattern	0.2	(0.1-1.22)	0.083

AS: Aortic stenosis; AVB: Atrioventricular block; BCT: Bilateral carpal trunnel; IVS: Interventricular septum, LA: left atrial; LVEF: Left ventricular ejection fraction; OR: Odds ratio

Table 3. Variables identified as predictors in the *deteCTTAR* score

Variable	Points	Prediction	OR (95% CI)	p
MasCuline	2 points		7.9 (3.6-17.1)	<0.001
BCT	3 points		24.4 (6.0-97.8)	<0.001
Increased Thickness IVS ≥ 16mm	1 points		3.6 (1.8- 7.1)	<0.001
Pseudonormal or restrictive Relaxation pAttern	2 points		12.7 (6.1-26.3)	<0.001

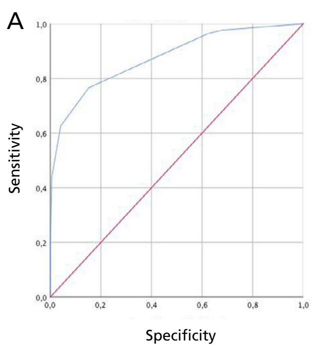


BCT: Bilateral carpal tunnel; IVS: Interventricular septum.

B

POINTS	SENSITIVITY	SPECIFICITY	AUC	95% CI
≥0	100%	0%%	0.5	(0.43- 0.56)
≥1	97%	33%	0.65	(0.59-0.70)
≥2	96%	38%	0.67	(0.61-0.73)
≥3	76%	85%	0.82	(0.77-0.87)
≥4	62%	95%	0.79	(0.74-0.84)
≥5	44%	96%	0.71	(0.66-0.77)
≥6	17%	100%	0.58	(0.52-0.64)
≥7	13%	100%	0.56	(0.50-0.62)
8	6%	100%	0.52	(0.46-0.59)

A



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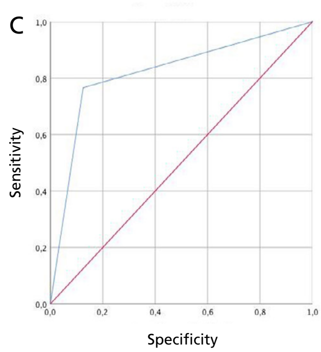


Fig. 1. (A) ROC curve of the prediction model; (B) Sensitivity, specificity and area under curve (AUC) according to each score; (C) ROC curve of the ≥3 value in the scoring scale.

plained in a manner analogous to what occurs with the ischemic cascade, in which molecular methods can detect it even before changes in the electrocardiogram, motility alterations or symptoms become evident.

Both phenomena (myocardial ischemia and ATTR-CA) have a long subclinical period, in which early diagnosis is fundamental to change the prognosis of the disease. (18)

Possibly, in the case of ATTR-CA, if we wait to meet more suspicious conditions (greater IVS thickness or greater number of red flags), the diagnosis is achieved with more advanced disease and with myocardial damage already established. In addition, the new drugs approved in our country do not remove myocardial amyloid deposits, but rather stabilize the TTR molecule to prevent its disintegration, thus avoiding further accumulation. All this leads to the need of trying to establish an early diagnosis, even before the increase in IVS thickness becomes evident. (19)

Thus, the *deteCTTAR* score could be more comprehensive than the T-Amylo score and the ATTR-CM score, since it could discriminate the risk of ATTR-CA among patients, regardless of whether or not they meet the classic warning signs for suspicion and the LVEF value (Fig. 2 and 3)

It is known that CS with phosphonates has a high sensitivity and specificity for the noninvasive diagnosis of ATTR-CA. However, there is currently no agreement in the literature on the appropriate moment to perform it.

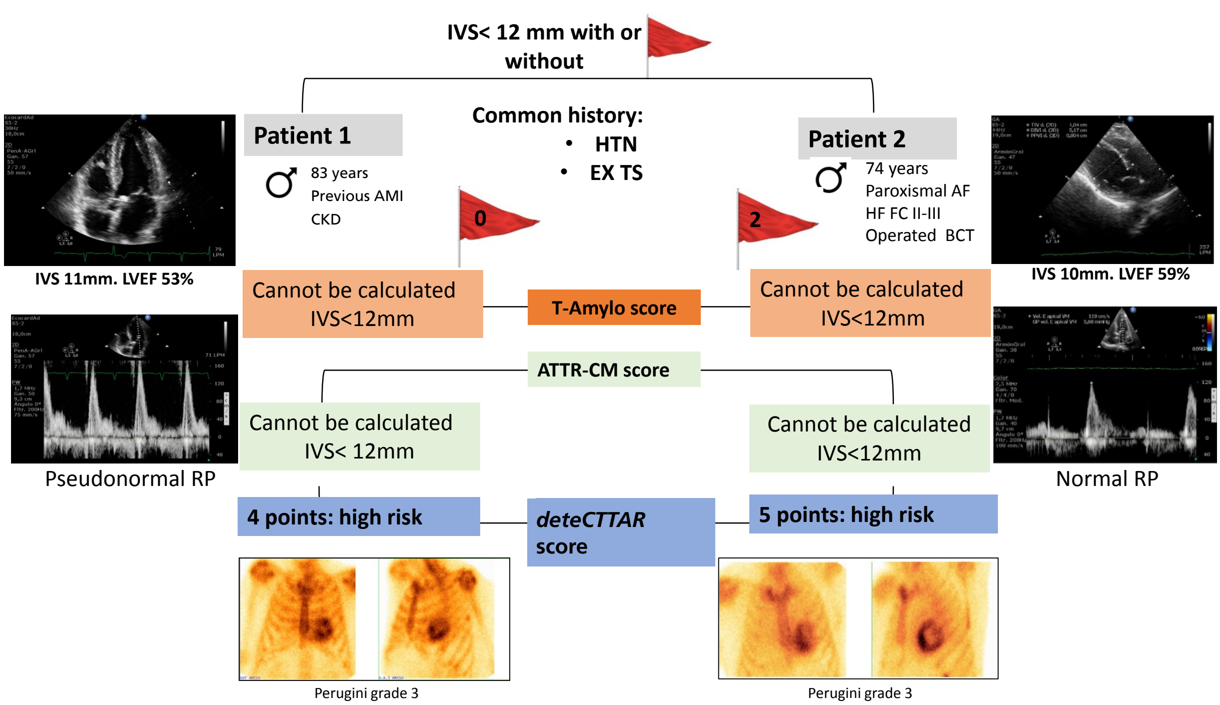
Some guidelines propose that it should be performed directly in certain clinical scenarios, without the need to apply scoring scales to determine the risk of each patient. For others, CS should be requested only in the presence of increased IVS thickness associated with one or more red flags, HFpEF or severe AS. (20-23)

Although it is more common to find ATTR-CA among patients over 65 years of age with HFpEF and severe AS than in the general population, these variables alone were not shown to be predictors of the disease. (2-5, 24-26)

As for IVS thickness, there is no doubt that if it is severely increased, the difference that could exist in the measurement between different operators or machines would not have too much repercussion. However, in values close to 12 mm, an error in the measurement (due to poor technique, poor acoustic window or lack of operator experience) according to the scoring scales in force to date, would mean ruling out the diagnostic suspicion of ATTR-CA.

Previously to the ATTR-CM and T-Amylo scores,

Fig. 2. Patients without IVS hypertrophy with ATTR-CA diagnosis. Patient 1, additionally, had no red flags and patient 2 had two red flags. The three scoring scales for ATTR-CA risk assessment were compared. In both the T-Amylo score and the ATTR-CM score it is not possible to establish risk due to IVS <12mm, whereas the *deteCTTAR* score identified both patients as being at high risk for the disease.



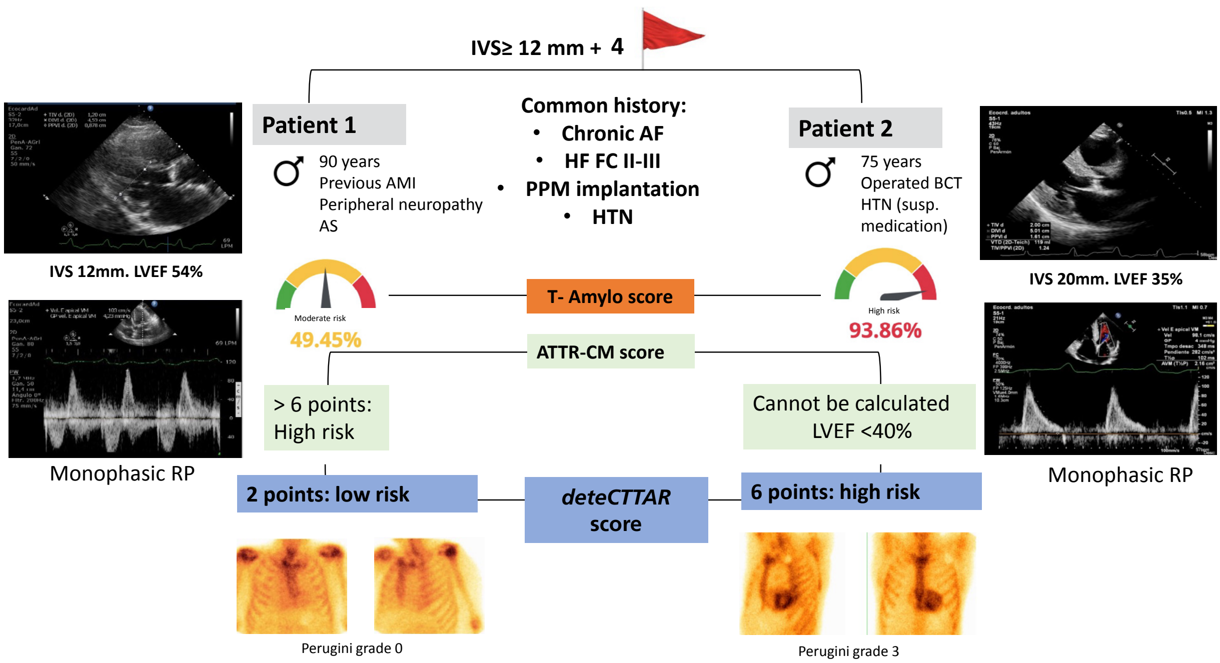
AF: Atrial fibrillation; AMI: Acute myocardial infarction; BCT: Bilateral carpal tunnel; CKD: chronic kidney disease; EX TS: Ex-tobacco smoker; HF FC. Heart failure functional class; HTN: Hypertension; IVS: Interventricular septum; LVEF: Left ventricular ejection fraction; RP: Relaxation pattern.

other prediction models were published but, unlike these, they only included echocardiographic and/or electrocardiographic parameters. (27,28) However, in our study, most of the variables included in these models were not predictors of ATTR-CA, with the exception of the relaxation pattern and IVS thickness.

Regarding clinical history, including red flags such as dysautonomia, peripheral neuropathy, hypotension-normotension, etc., the only one that showed a relationship with the diagnosis was having bilateral CTS.

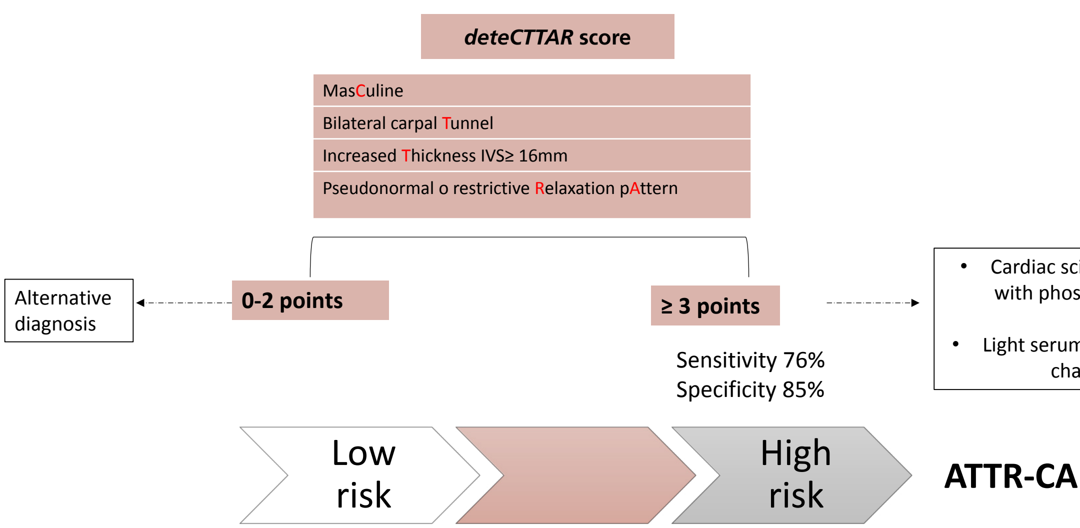
In our scale, a score ≥3 considerably increases the risk of ATTR-CA, so that only in these cases it would be indicated to perform a CS with phosphonates. In

Fig. 3. Patients with IVS increased thickness and 4 red flags. The three scoring scales for risk assessment of ATTR-CA were compared. For patient 1 (negative ATTR-CA), the T-Amylo score predicted an intermediate risk of ATTR-CA, the ATTR-CM score a high risk, while the *deteCTTAR* score, a low risk. In the case of patient 2, the T-Amylo score and the *deteCTTAR* score predicted a high risk of developing the disease, whereas the ATTR-CM score could not be applied due to the degree of LVEF impairment.



AF: Atrial fibrillation; AMI: Acute myocardial infarction; AS: Aortic stenosis; BCT: Bilateral carpal tunnel; HF FC: Heart failure functional class; HTN: Hypertension; IVS: Interventricular septum; LEFV: Left ventricular ejection fraction; PPM: Permanent pacemaker; RP: Relaxation pattern; susp: suspended

Fig. 4. Diagnostic algorithm proposed according to the *deteCTTAR* score



ATTR-CA: Transthyretin cardiac amyloidosis ; IVS: interventricular septum those patients with a score between 0-2, it would not be necessary to perform it, and an alternative diagnosis should be considered (Fig. 4). If clinical suspicion persists, a cardiac magnetic resonance imaging could be performed, since its high negative predictive value would finally rule out the disease.

According to our scale, the mere presence of bilateral CTS (3 points) would be a sufficient condition to request a CS with phosphonates. In these cases, in particular, the time since diagnosis and/or surgery should be considered, since amyloid infiltration of the median nerve usually precedes cardiac involvement by 5 to 9 years. Thus, a negative CS may not exclude the disease if it was performed early, so a strict cardiological follow-up would be appropriate. (29)

It should be noted that the greatest challenge encountered by all scoring scales for ATTR-CA is in patients with HCM. In the differential diagnosis with this entity, the physician's experience at the time of suspicion is fundamental, since epidemiology, family history and most of the time the electrocardiogram, can contribute to differentiate them, without the need to apply scoring scales.

The *deteCTTAR* score is the first score for the prediction of ATTR-CA developed with patients in our country. It can be applied in the office to any patient without the need to wait for conditions (red flags) that may delay diagnosis, using data obtained from the interrogation and a baseline echocardiogram.

Limitations

The study design was single-center, retrospective, with a relatively small database, so there could be an overfitting of the model.

The low number of patients causes the 95% CI of some predictors to be very wide, which implies lower prediction accuracy.

Although our data are encouraging, they require external validation in the future with a larger sample of patients.

CONCLUSIONS

The presence of increased IVS thickness associated with one or more red flags was not a necessary condition for the diagnosis of ATTR-CA.

The prediction model obtained allowed the development of a scoring scale that demonstrated high sensitivity and specificity to strongly guide the diagnosis of ATTR-CA.

A score ≥3 in the *deteCTTAR* score significantly increases the risk of ATTR-CA.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the web)

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