ESC European Society of Cardiology

European Heart Journal - Imaging Methods and Practice (2024) **2**, qyae105
https://doi.org/10.1093/ehjimp/qyae105

ORIGINAL ARTICLE

Echocardiographic red flags of ATTR cardiomyopathy a single centre validation

Michael Y. Henein[1], Björn Pilebro[1], and Per Lindqvist [2,*]

[1]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[2]Departments of Diagnostics and Intervention, Clinical Physiology, Umeå University, 907 37 Umeå, Sweden

Received 10 April 2024; accepted after revision 7 October 2024; online publish-ahead-of-print 8 October 2024

Abstract

Aims

Echocardiography plays an important role in suspecting the presence of transthyretin cardiomyopathy (ATTR-CM) in patients with heart failure, based on parameters proposed as 'red flags' for the diagnosis of ATTR-CM. We aimed to validate those measurements in a group of patients with ATTR-CM including ATTRv and ATTRwt.

Methods and results

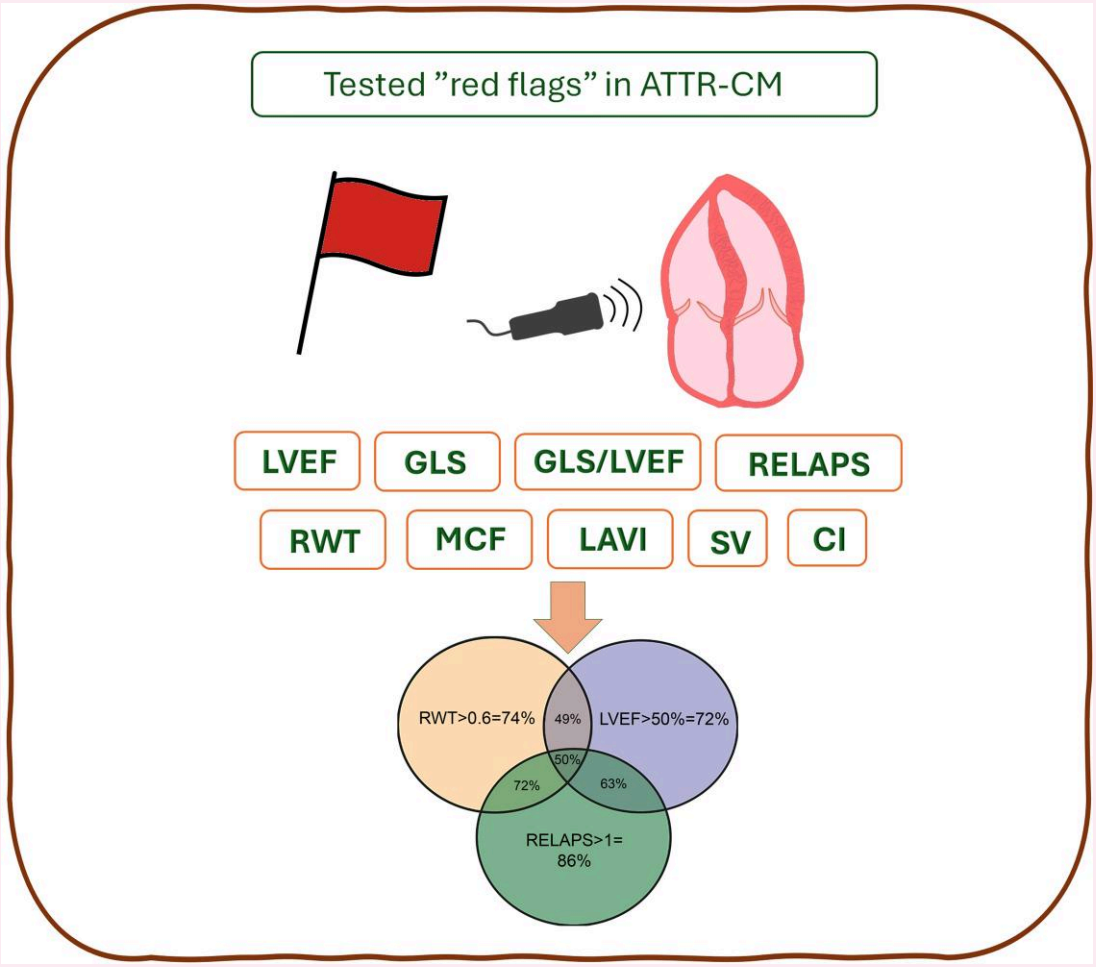
We tested a number of echocardiographic red flags in 118 patients with confirmed diagnosis of ATTR-CM. These variables were validated against healthy controls and patients with heart failure with left ventricular hypertrophy (LVH) but not ATTR-CM. The red flag measures outside the proposed cut-off values were also revalidated. In ATTR-CM, all conventional echocardiographic parameters were significantly abnormal compared with controls. Comparing ATTR-CM and LVH, LV wall thickness, LV diameter, E velocity, and relative apical sparing (RELAPS) were all different. Eighty-three per cent of ATTR-CM patients had RELAPS > 1.0, 73% had relative wall thickness (RWT) > 0.6, 72% had LVEF > 50%, 24% had global longitudinal strain (GLS) > −13%, 33% had LVEF/GLS > 4, and 54% had increased left atrial volume index (>34 mL/m^2). Forty per cent of ATTR-CM patients had stroke volume index < 30 mL/m^2 and 52% had cardiac index < 2.5 L/min/m^2. RELAPS, LVEF, and RWT, in order of accuracy, were the three best measures for the presence ATTR-CM in the patient cohort, who all had thick myocardium. The concomitant presence of the three disturbances was found in only 50% but the combination of RELAPS > 1.0 and RWT > 0.6 was found in 72% of the patient cohort.

Conclusion

Increased relative apical sparing proved the most accurate independent marker of the presence of ATTR-CM followed by normal LV ejection fraction and then increased relative wall thickness. The other proposed red flags for diagnosing ATTR-CM did not feature as reliable disease predictors.

* Corresponding author. E-mail: per.lindqvist@umu.se

Graphical Abstract



Keywords heart failure • transthyretin cardiomyopathy • left ventricular ejection fraction

Introduction

Transthyretin cardiomyopathy (ATTR-CM) is a disease caused by accumulation of misfolded transthyretin-protein (TTR) in the heart causing increased myocardial thickness, left ventricular (LV) cavity stiffness, and filling disturbances. If left untreated, the pathology may result in advanced heart failure (HF). ATTR amyloidosis exists in either the hereditary form (ATTRv) or the wild type (ATTRwt), with the latter form strongly associated with advanced age. ATTRwt amyloidosis has, over the last few years, been recognized as underdiagnosed and is probably the most common systemic amyloid disease.[1] Cardiac involvement is similar in both types of amyloidosis, but often with earlier onset in ATTRv patients.[2] Amyloid cardiomyopathy (CM) can also be caused by AL amyloidosis, where the immunoglobulin light chains misfold and form amyloid protein.[3] The AL CM share similar phenotypes and red flags for diagnosis with ATTR-CM but there are differences in myocardial involvement and prognosis.[3,4] However, irrespective of the aetiology, amyloid CM is often clinically misinterpreted as unspecified LV hypertrophy, hence is missed, particularly in patients with HF and preserved LVEF.[5,6] Studies have clearly shown fundamental differences between the pathophysiological mechanisms of ATTR-CM and hypertrophy-related HF, irrespective of LVEF.[6] Few previous studies have tested and reported the prevalence of abnormal cut-off values using the proposed red flags and compared them with findings in healthy controls and left ventricular hypertrophy (LVH).

The aim of this study is to validate the accuracy of the recommended 'red flags' cardiac structure and function markers of ATTR-CM in patients with both ATTRwt and ATTRv.

Methods

Population

We retrospectively investigated 118 patients, of whom 36 women, retrieved from our local database with ATTR-CM defined as a confirmed diagnosis and ventricular septal thickness > 12 mm. The diagnosis of ATTR-CM was confirmed based on a positive DPD (grades 2 and 3) scintigraphy and absence of monoclonal gammopathy or detecting amyloid protein in abdominal fat. All ATTR-CM patients had also undergone TTR gene sequencing.[7]

For comparison, we studied additional 58 healthy controls, 21 of whom were women, who previously served as controls in another study.[8] We

Table 1 Echocardiographic characteristic data in ATTR-CA, LVH, and healthy controls

	ATTR-CA (118)	LVH ($n = 31$)	Controls (58)	*P*-values ATTR-CA vs. controls	*P*-values ATTR-CM vs. LVH
Age, years	76 ± 9	76 ± 8	62 ± 10	<0.001	0.901
Females, %	24	37	56	<0.001	0.138
AF, %	30	15	0		
HF, %	100	100	0		
SBP, mmHg	130 ± 18	144 ± 22	133 ± 17	0.272	<0.001
DBP, mmHg	77 ± 10	85 ± 11	78 ± 9	0.268	<0.001
Height, cm	174 ± 9	144 ± 22	171 ± 9	0.05	0.705
Weight, kg	75 ± 15	87 ± 20	74 ± 13	0.741	0.001
NT-proBNP	2546 ± 3695	2514 ± 4886	—	—	0.520
Troponin	42 ± 39	32 ± 29	—	—	0.208
LVEF, %[a]	54 ± 11	53 ± 10	62 ± 6	<0.001	0.644
IVSD, mm	18 ± 4	16 ± 2	10 ± 1	<0.001	<0.01
PWT, mm	13 ± 3	10.5 ± 1.8	8 ± 1	<0.001	<0.001
LVDD, mm	44 ± 6	49 ± 7	49 ± 4	<0.001	<0.001
Mitral E-wave, cm/s	74 ± 23	64 ± 25	63 ± 13	<0.001	<0.05
Mitral E-wave DT, ms	184 ± 79	174 ± 73	206 ± 52	0.033	0.610
e′ lateral, cm/s	5.8 ± 1.9	5.1 ± 2.5	8.6 ± 2.1	<0.001	0.263
LAVI, mL/m^2 [a]	38 ± 13	43 ± 17	27 ± 8	<0.001	0.162
RWT[a]	0.73 ± 0.19	0.44 ± 0.12	0.34 ± 0.06	<0.001	<0.001
GLS, %[a]	−15 ± 4	−13 ± 5	−19 ± 3	<0.001	0.041
RELAPS[a]	1.9 ± 1.0	1.2 ± 1.2	0.5 ± 0.1	<0.001	<0.01
LV mass index, g/m^2 (ASE)	152 ± 41	133 ± 26	81 ± 19	<0.001	0.001
E/e′ lateral	13.3 ± 6.1	13.3 ± 4.1	7.8 ± 2.9	<0.001	0.965
LVEF/GLS[a]	4.1 ± 1.9	4.4 ± 1.2	3.4 ± 0.6	0.051	0.362
MCF[a]	0.26 ± 0.12	0.28 ± 0.11	0.5 ± 0.1	<0.001	0.475
SVI, mL/m^2 [a]	36 ± 12	35 ± 10	41 ± 6	0.029	0.611
CI, L/min/m^2 [a]	2.5 ± 0.9	2.3 ± 0.4	2.9 ± 0.5	0.027	0.252

IVSD, septal thickness in diastole; PWT, posterior wall thickness; AF, atrial fibrillation; HF, heart failure; LVDD, diastolic left ventricular diameter; E DT, early diastolic deceleration time; RWT, relative wall thickness; GLS, global longitudinal strain; RELAPS, relative apical sparing; EF, ejection fraction; SVI, stroke volume index; CI, cardiac index; MCF, myocardial contraction fraction.
[a]Red flag parameters tested.

also compared the ATTR patient cohort with 31 patients with LVH (septal thickness > 12 mm) but no cardiac amyloidosis based on normal DPD scintigraphy.

Echocardiography

From the previously performed echocardiographic examinations of the included patients and controls, at the time of diagnosis, we evaluated LV ejection fraction (EF) using Simpson bi plane method, left atrial volume index (LAVI), relative apical sparing (RELAPS), global longitudinal strain (GLS), LVEF/GLS, stroke volume index (SVI), cardiac index (CI), myocardial contraction fraction (MCF),[9] and relative wall thickness (RWT).[10] All measures were done blinded due to diagnosis. All these parameters were previously proposed as red flags for diagnosing ATTR-CA.[4,6,11] To qualify for red flag parameters, the following definitions were applied: normal LVEF > 50%,[6] increased LAVI > 34 mL/m^2, increased RELAPS > 1.0,[12] reduced GLS > −13%,[4] EF/GLS < −4,[13] SVI and CI < 30 mL/m^2, and <2.5 L/min/m^2.[3] Also, reduced MCF was defined as <0.234[13] and increased RWT as >0.6[4]

Statistics

All data are presented as mean and standard deviation. Comparison between ATTR-CM patients and controls was tested using parametric *t*-test. Distribution of tested variables in ATTR-CM and controls was shown as histogram and presented as 95% CI. Receiver operator curve (ROC) was used to identify the most accurate variable's area under the curve for diagnosing ATTR-CM from controls and LVH. To test the accuracy of proposed cut-off thresholds for each variable, we calculated sensitivity, specificity, positive predictive value, negative predictive values, accuracy, and Youden's index in ATTR-CM. Venn diagram was used to present the prevalence of the most accurate red flags and the accuracy of combined parameters.

Results

ATTR-CM vs. controls and LVH

Data from ATTR-CM, LVH, and controls are shown in *Table 1*. Of the 118 ATTR-CM patients, 79 had V 30M, 11 had other mutations, and 28 had ATTRwt. Of the patients with LVH, all had HF including systemic hypertension in 100%, additional coronary disease in 50%, three had additional moderate aortic valve disease, and five had diagnosis of hypertrophic cardiomyopathy. NYHA class was 1 in two patients, 2 in three patients, 3A in 18 patients, and 3B in seven patients. NYHA classification was missing in three patients.

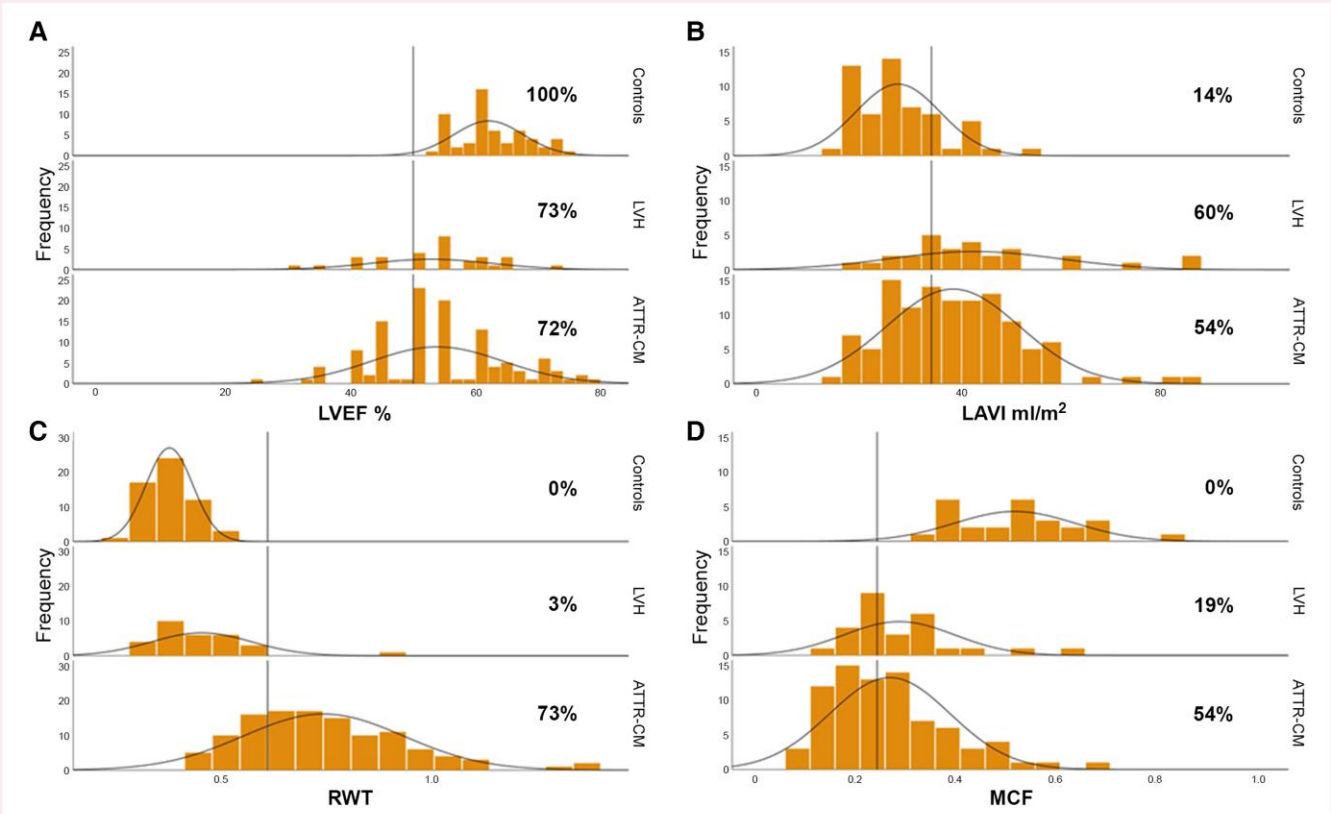


Figure 1 (*A*) LVEF in ATTR-CM, LVH, and in controls. (*B*) LAVI in ATTR-CM, LVH, and in controls. (*C*) RWT in ATTR-CM, LVH, and in controls. (*D*) MCF in ATTR-CM, LVH, and controls.

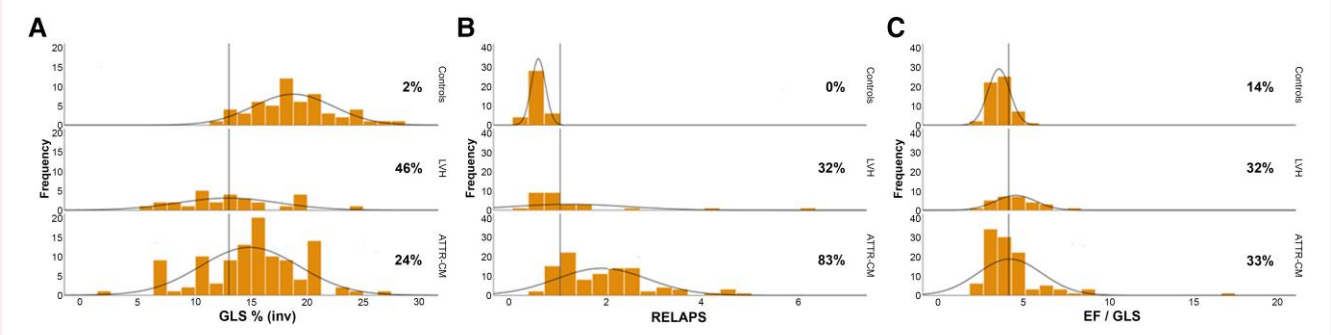


Figure 2 (*A*) GLS in ATTR-CM, LVH, and in controls. (*B*) RELAPS in ATTR-CM, LVH, and in controls. (*C*) EF/GLS in ATTR-CM, LVH, and controls.

All LV structural and functional parameters in ATTR-CM were significantly abnormal compared with controls ($P < 0.001$ in all). Also, mitral E-wave deceleration time was shorter $P = 0.033$ and stroke volume and cardiac index were both reduced ($P = 0.029$, $P = 0.027$) in ATTR-CM with respect to controls. When ATTR-CM was compared with LVH, ATTR-CM wall thickness proved thicker (septal thickness in diastole and posterior wall thickness $P < 0.01$), LV diameter smaller ($P < 0.001$), and mitral E velocity and apical sparing (RELAPS) both higher ($P < 0.001$).

All controls had LVEF > 50% as did most of ATTR-CM patients (*Figure 1A*) except 28% who had LVEF < 50%, most of whom had clinical diagnosis of heart failure with mildly reduced left ventricular ejection fraction. A total of 73% of the LVH patients had LVEF > 50%. A total of 55% of ATTR-CM patients had LAVI > 34 mL/m^2, the respective percentage in the LVH was 60% and in controls was 14% (*Figure 1B*). A total of 73% of the ATTR-CM patients had RWT > 0.6 compared with only 3% in LVH and none in controls (*Figure 1C*). A total of 54% of the ATTR-CM patients had MCF < 0.234 g/mL compared with 19% in LVH and none in controls (*Figure 1D*). A total of 83% patients with ATTR-CM had RELAPS > 1.0 but only 32% in LVH and none of the controls (*Figure 2B*). A total of 24% of ATTR-CM patients

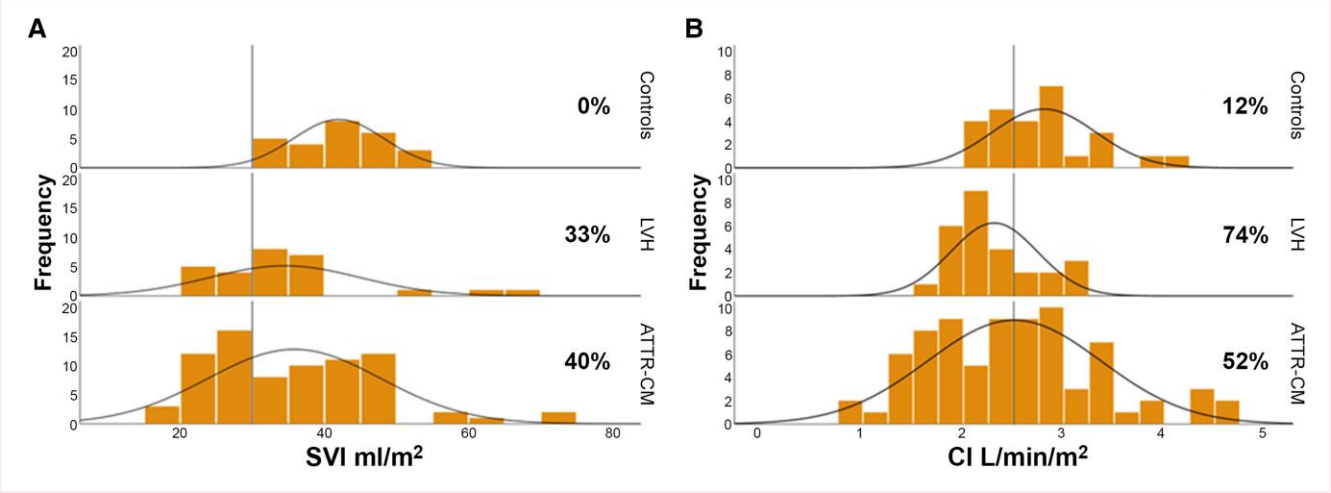


Figure 3 (*A*) SVI in ATTR-CM, LVH, and controls. (*B*) CI in ATTR-CM, LVH, and controls.

Table 2 **Red flag parameters due to sensitivity, specificity, PPV, NPV, and accuracy in diagnosing ATTR-CM**

Method	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden's index
LVEF	>50%	100	65	75	100	83	0.65
LAVI	>34 mL/m^2	86	46	54	82	63	0.32
RELAPS	>1.0	100	69	82	100	88	0.69
GLS	≥ −13%	90	56	64	86	52	0.31
LVEF/GLS	>4	90	56	64	86	76	0.46
MCF	<0.234 g/mL	100	37	48	100	60	0.37
RWT	>0.6	100	62	72	100	81	0.62
SVI	<30 mL/m^2	97	39	46	96	59	0.36
CI	<2.5 L/min/m^2	80	21	52	50	52	0.1

RWT, relative wall thickness; GLS, global longitudinal strain; RELAPS, relative apical sparing; LVEF, left ventricular ejection fraction; SVI, stroke volume index; CI, cardiac index; MCF, myocardial contraction fraction.

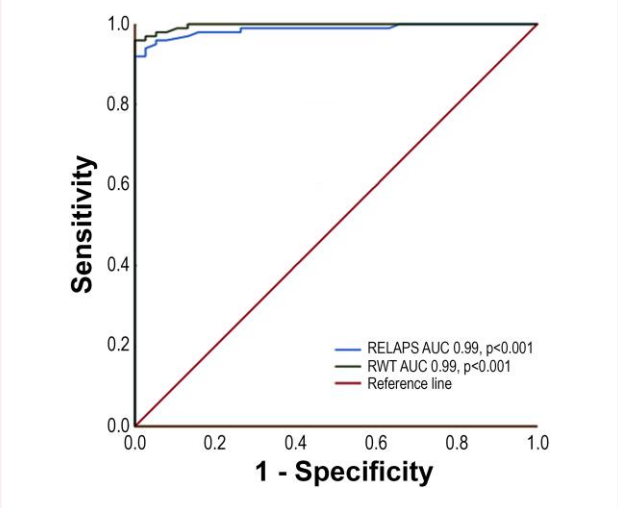


Figure 4 ROC analysis comparing RELAPS and RWT.

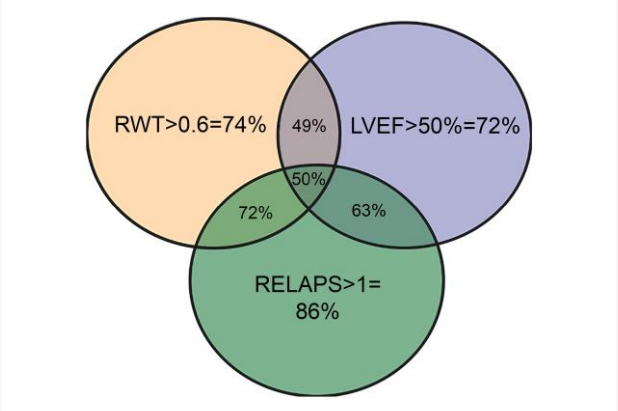


Figure 5 Venn diagram showing the prevalence of the cut-off values for RWT, RELAPS, and LVEF individually and in combination.

had GLS < −13%, compared with 46% in LVH and only 2% of controls (*Figure 2A*). EF/GLS > 4 was more common in the two patient groups, 33% in ATTR-CM and 54% in LVH compared with only 14% in controls (*Figure 2C*).

SVI was < 30 mL/m^2 in 40% of ATTR-CM patients compared with 33% in LVH but none in controls. Cardiac index < 2.5 L/min/m^2 was present in 52% of the ATTR-CM patients compared with 74% in the LVH group and only 12% in controls (*Figure 3A and B*). RWT proved to be the best variable that identified ATTR-CM from controls and LVH, followed by MCF and RELAPS.

Accuracy of red flag measures for ATTR-CM

Analysis of the sensitivity, specificity, predictive values, accuracy, and Youden's index in ATTR-CM is shown in *Table 2*. RELAPS > 1.0, RWT > 0.6, and LVEF > 50% proved the most accurate parameters supporting the diagnosis of ATTR-CM. On ROC analysis, RWT (AUC = 0.99) and RELAPS (AUC = 0.99) proved the most accurate parameters for diagnosing ATTR-CM (*Figure 4*). Venn diagram showed RELAPS > 1 as the most common abnormal red flag in diagnosing ATTR-CM, followed by RWT > 0.6 and LVEF > 50%, according to their individual power of accuracy. Combined abnormal three variables was found in only 50% of patients. Combined RELAPS > 1 and RWT > 0.6 was found in 72% of patients (*Figure 5*).

Discussion

Findings

In this study, we succeeded in identifying three LV structural and function parameters that accurately predicted the presence of ATTR-CM in a group of patients with previously confirmed diagnosis, therefore can be considered as strong red flags for ATTR-CM. This conclusion is derived from a detailed comparison with healthy controls and a group of LVH patients but without ATTR-CM. The three parameters achieved the top accuracy, out of the 10 parameters previously recommended for diagnosing ATTR-CM, which were sold as 'red flags' for suspicion of ATTR-CM.[4,6,11] RELAPS > 1.0 proved the most accurate (88%) cardiac function parameter for diagnosing ATTR-CM. This was followed by ejection fraction > 50% (83% accurate) and RWT > 0.6 (81% accurate). The first two most accurate parameters represent two different aspects of LV function, whereas RWT represents structural LV changes in the form of concentrically increased wall thickness. RWT proved to be the most discriminative variable for ATTR-CM compared with both LVH and controls. The presence of the three parameters combined accurately diagnosed only 50% of patients whereas the combination of abnormal RWT and RELAPS together was present in 72% of patients with ATTR-CM. Of note, all proposed red flag parameters were abnormal in the patients' group as a whole compared with healthy controls.

ATTR-CM is known to affect both the subendocardial and mural layers of the myocardium, hence compromising LV long axis function, mainly at the basal and mid-cavity level, thus showing a typical apical sparing strain pattern.[12] Another common finding is the commonly seen biventricular involvement with ATTR-CM[8] and sometimes restrictive filling pattern with reduced stroke volume and cardiac output.[4] These abnormalities are seen in the absence of classical electric markers of LVH on 12-lead surface ECG. However, combining ECG and echocardiographic increased LV wall thickness (>12 mm) has recently shown excellent accuracy in differentiating ATTR-CM from LVH, particularly when using a ratio of RWT and S wave amplitude in aVR.[10,14] The abovementioned red flags have been used for identifying ATTR-CA in patients with HF and a significant suspicion of amyloid disease.[4,11,13,15,16]

Data interpretation

Our findings highlight the importance of assessing LV systolic function in patients suspected to have ATTR-CM. The commonly used marker of global LV systolic function, i.e. ejection fraction, proved the second accurate predictor of ATTR-CM following RELAPS. This supports the previous reports that suggested that ATTR-CM is commonly found in patients with heart failure with preserved left ventricular ejection fraction (HFpEF) and highlights the importance of separating the two conditions from each other, when necessary.[6] RELAPS can be normal (using cut-off < 1) in ATTR-CM and can also be increased in other causes for HF,[17] which we found in our study. Previous studies have shown that RELAPS is not always reliable to be used as red flag for cardiac amyloidosis[18] and also not reflecting amyloid burden.[19] However, these studies included AL amyloidosis that might influence the optimal cut-off value and the accuracy using RELAPS. However, the pattern of 'cherry on the top' or apical strain can be supported by myocardial biopsy and MRI studies that have shown the amyloid distribution in ATTR-CM, at the subendocardial layer of the basal and mid-cavity regions of the LV with the apex spared.[20,21,22,23] The third predictor of ATTR-CM was RWT. Although myocardial thickness is a well-recognized feature of amyloid heart disease, the concentric form is accurate in predicting the ATTR-CM pathology. All our ATTR-CM patients had RWT > 0.42 and increased LV mass index (>95 g/m^2 for females and 115 g/m^2 for males), hence flagged as having concentrically increased wall thickness. Recent studies using score system for identifying ATTR-CM showed that RWT > 0.6 was highly accurate in identifying ATTR-CM supporting the results from our study.[4,24]

The rest of the 10 proposed red flags did not feature as independently accurate parameters for diagnosing ATTR-CM. Myocardial early diastolic velocities proved to be poor discriminator for ATTR-CM because they reflect the basal longitudinal LV function, with the apical part spared from the pathology. Markers of raised LA pressure did not show a consistent pattern in diagnosing our patients, suggesting significant variability of ATTR-CM severity in our patients, with some having mild myocardial disease with relatively compliant LV cavity while others having more aggressive disease and stiff LV cavity, hence causing raised LA pressure.

LV GLS disappointedly proved to be a very poor predictor of ATTR-CM. This could be explained on basis of GLS software design of assessing global LV deformation, with all segments included and not recognizing the pathology-spared apex in ATTR. Finally, only 40% of our cohort had SVI < 35 mL/m^2 and 52% had CI < 2.5 L/min/m^2, making it difficult to suggest a uniform phenomenon of low flow in ATTR-CM patients.[15]

Study limitations

One explanation of the difference in the accuracy of the parameters we identified, compared with other studies, is that ours were based on only ATTR-CM and none of our patients had AL amyloid disease as was the case with other studies. In addition, most of our patients had ATTR-CM mainly due to ATTRv caused by V30 M mutation. The second limitation was the unknown duration of the ATTR-CM pathology that, if known, may have helped in classifying the patients into early and late pathology. We mainly tested identifying patients with ATTR-CM hence did not report the accuracy of the parameters that could exclude the disease. The comparison between ATTR-CM and healthy controls might seem unnecessary but we consider it justified in order to validate the confidence interval in the two groups.

Clinical applications

In patients suspected to have ATTR-CM, relative apical sparing pattern is the most accurate independent predictor of the correct diagnosis of

myocardial infiltration, followed by normal LV ejection fraction and thirdly increased LV relative wall thickness, all having accuracy > 80%. Reduced myocardial global longitudinal strain > −13% is also unlikely to accurately confirm the presence of ATTR-CM and myocardial infiltration.

Conclusion

Increased relative apical sparing proved the most accurate independent predictor of the presence of ATTR-CM followed, in order of accuracy, by normal LV ejection fraction then increased relative wall thickness. The seven other proposed red flags for diagnosing ATTR-CM did not feature as reliable disease predictors.

Conflict of interest: P.L. is a consulting lecturer and a member of advisory board of Pfizer.

Consent

The study was approved by the Swedish ethical review authority. All patients and controls provided written informed consent.

Funding

P.L. was supported by grants from The Swedish Heart and Lung foundation (20160787, 20200160,20230174) and The Swedish Research Council (2019-01338 2022-01254).

Data availability

The majority of the data underlying this article can be shared upon reasonable request to the corresponding author.

Lead author biography

My name is Per Lindqvist, and I am Professor in Clinical Physiology at Umeå University, Sweden. I have researched in cardiac imaging, especially using Doppler echocardiography, since 2000. I have previously mainly focused on cardiac haemodynamics at rest and exercise and especially assessing right heart function. More recently, I have moved my research interest to improve diagnosis for cardiac amyloidosis. I have more than 140 peer-reviewed articles published and 35 in H-index (Google Scholar).

References

1. Lindmark K, Pilebro B, Sundstrom T, Lindqvist P. Prevalence of wild type transtyrethin cardiac amyloidosis in a heart failure clinic. *ESC Heart Fail* 2021;**8**:745–9.
2. Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, Velazquez EJ *et al.* Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: further analyses from ATTR-ACT. *JACC Heart Fail* 2021;**9**:115–23.
3. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M *et al.* Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation* 2014;**129**:1840–9.
4. Boldrini M, Cappelli F, Chacko L, Restrepo-Cordoba MA, Lopez-Sainz A, Giannoni A *et al.* Multiparametric echocardiography scores for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2020;**13**:909–20.
5. Lund LH, Eldhagen P. Diagnosing heart failure with preserved ejection fraction in cardiac amyloidosis or diagnosing cardiac amyloidosis in heart failure with preserved ejection fraction? *Europ J Heart Fail* 2022;**24**:2387–9.
6. Oghina S, Bougouin W, Bezard M, Kharoubi M, Komajda M, Cohen-Solal A *et al.* The impact of patients with cardiac amyloidosis in HFpEF trials. *JACC Heart Fail* 2021;**9**:169–78.
7. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A *et al.* Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail* 2021;**23**:512–26.
8. Arvidsson S, Henein MY, Wikstrom G, Suhr OB, Lindqvist P. Right ventricular involvement in transthyretin amyloidosis. *Amyloid* 2018;**25**:160–6.
9. Rubin J, Steidley DE, Carlsson M, Ong M-L, Maurer MS. Myocardial contraction fraction by M-mode echocardiography is superior to ejection fraction in predicting mortality in transthyretin amyloidosis. *J Card Fail* 2018;**24**:504–11.
10. Arnberg E, Eldhagen P, Lofbacka V, Venkateshvaran A, Pilebro B, Lindqvist P. RWT/SaVR-A simple and highly accurate measure screening for transthyretin cardiac amyloidosis. *J Clin Med* 2022;**11**:4120.
11. Aimo A, Chubuchny V, Vergaro G, Barison A, Nicol M, Cohen-Solal A *et al.* A simple echocardiographic score to rule out cardiac amyloidosis. *Eur J Clin Invest* 2021;**51**:e13449.
12. Phelan D, Collier P, Thavendiranathan P, Popovic ZB, Hanna M, Plana JC *et al.* Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012;**98**:1442–8.
13. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J *et al.* Echo parameters for differential diagnosis in cardiac amyloidosis: a head-to-head comparison of deformation and nondeformation parameters. *Circ Cardiovasc Imaging* 2017;**10**:e005588.
14. Lofbacka V, Suhr OB, Pilebro B, Wixner J, Sundstrom T, Lindmark K *et al.* Combining ECG and echocardiography to identify transthyretin cardiac amyloidosis in heart failure. *Clin Physiol Funct Imaging* 2021;**41**:408–16.
15. Dorbala S, Cuddy S, Falk RH. How to image cardiac amyloidosis: a practical approach. *JACC Cardiovasc Imaging* 2020;**13**:1368–83.
16. Arana-Achaga X, Goena-Vives C, Villanueva-Benito I, Solla-Ruiz I, Rengel Jimenez A, Gaspar TI *et al.* Development and validation of a prediction model and score for transthyretin cardiac amyloidosis diagnosis: T-amylo. *JACC Cardiovasc Imaging* 2023;**16**:1567–80.
17. Abecasis J, Lopes P, Santos RR, Maltes S, Guerreiro S, Ferreira A *et al.* Prevalence and significance of relative apical sparing in aortic stenosis: insights from an echo and cardiovascular magnetic resonance study of patients referred for surgical aortic valve replacement. *Eur Heart J Cardiovasc Imaging* 2023;**24**:1033–42.
18. Cotella J, Randazzo M, Maurer MS, Helmke S, Scherrer-Crosbie M, Soltani M *et al.* Limitations of apical sparing pattern in cardiac amyloidosis: a multicenter echocardiographic study. *Eur Heart J Cardiovasc Imaging* 2024;**25**:754–61.
19. De Gaspari M, Sinigiani G, De Michieli L, Della Barbera M, Rizzo S, Thiene G *et al.* Relative apical sparing in cardiac amyloidosis is not always explained by an amyloid gradient. *Eur Heart J Cardiovasc Imaging* 2023;**24**:1258–68.
20. Mehta P, Chapel DB, Goyal N, Yu DB, Mor-Avi V, Narang A *et al.* A histopathologic schema to quantify the burden of cardiac amyloidosis: relationship with survival and echocardiographic parameters. *Echocardiography* 2019;**36**:285–91.
21. Hahn VS, Yanek LR, Vaishnav J, Ying W, Vaidya D, Lee YZJ *et al.* Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail* 2020;**8**:712–24.
22. Syed IS, Glockner JF, Feng D, Araoz PA, Martinez MW, Edwards WD *et al.* Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2010;**3**:155–64.
23. Kim JY, Hong YJ, Han K, Lee HJ, Hur J, Kim YJ *et al.* Regional amyloid burden differences evaluated using quantitative cardiac MRI in patients with cardiac amyloidosis. *Korean J Radiol* 2021;**22**:880–9.
24. Davies DR, Redfield MM, Scott CG, Minamisawa M, Grogan M, Dispenzieri A *et al.* A simple score to identify increased risk of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. *JAMA Cardiol* 2022;**7**:1036–44.