Combining ECG and echocardiography to identify transthyretin cardiac amyloidosis in heart failure

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Abstract
Aims/background: Transthyretin amyloid (ATTR) amyloidosis cardiomyopathy is an underdiagnosed, causatively treatable cause of heart failure (HF). The aim of this study was to evaluate the efficacy of electrocardiogram (ECG) and echocardiography on patients with increased interventricular septum diameter (IVSd) to identify ATTR cardiac amyloidosis (ATTR-CA) patients.

Methods: We investigated 58 patients with HF and an IVSd > 14 mm. Included were 33 ATTR-CA patients and 25 controls that consisted of non-amyloidosis HF patients with negative 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy. We used echocardiography including 2D speckle-tracking strain and a 12-lead ECG to test the accuracy to differentiate the groups.

Results: We found high diagnostic accuracy (98%) for differentiating ATTR-CA from HF controls using a combination of R amplitude in -aVR from ECG and relative wall thickness acquired from echocardiography. With this combined model (RWT/R in -aVR), the sensitivity was 100% and specificity was 95% using a cut-off value of 0.90. Furthermore, the area under the curve was 99% and the negative predictive value was 100%.

Conclusion: We found that a simple combination of ECG and echocardiographic parameters used in clinical settings was able to differentiate ATTR-CA from other aetiologies of HF with increased interventricular septum thickness. The high sensitivity and negative predictive value render the algorithm useful for selection of patients for further diagnostic procedures for ATTR-CA.

KEYWORDS
cardiac amyloidosis, ECG, echocardiography, heart failure, transthyretin amyloidosis

INTRODUCTION
Transthyretin (TTR) amyloid (ATTR) amyloidosis is the most common type of systemic amyloidosis, and can be subdivided into a hereditary type transthyretin amyloidosis (ATTRv) and a wild type transthyretin amyloidosis (ATTRwt; Falk, 2005; Maleszewski, 2015). Cardiac involvement is often present in ATTR, and is also a common cause for cardiac amyloidosis (CA; Falk and Dubrey, 2010). The prevalence of ATTR cardiac amyloidosis (ATTR-CA) was previously considered low, but recent studies indicate that ATTR-CA amyloidosis is more common than presumed. (Gonzalez-Lopez, et al., 2017; Mohammed, et al., 2014; Tanskanen, et al., 2008).
Findings giving suspicion of ATTR-CA can be obtained with echocardiography and electrocardiogram (ECG), although the final diagnosis is set either by tissue biopsy or non-invasively with nuclear scintigraphy (Gillmore, et al., 2016; Haeeez & Bavry, 2020). Typical echocardiographic findings linked to ATTR-CA include increased wall thicknesses followed by restrictive ventricular filling patterns. Relative apical sparing (RELAPS) pattern from cardiac deformation is associated with ATTR-CA (Aljaroudi, et al., 2014; Jurcuţ, et al., 2020).

ECG findings in ATTR-CA commonly include the absence of signs of LV hypertrophy despite increased LV wall thickness on echocardiography. To our knowledge, there are no studies comparing ECG and echocardiographic findings in ATTR-CA to other aetiologies of heart failure (HF) and increased wall thickness.

The aim of this study was to investigate the use of echocardiography and ECG to identify ATTR-CA patients among patients with an increased septal thickness (IVSd). Our hypothesis was that an optimal combination of echocardiography and ECG can accurately identify ATTR-CA patients from other causes of HF and increased wall thickness.

### 2 | MATERIALS AND METHODS

#### 2.1 | Patient selection

All patients within the primary catchment area of Umeå University Hospital, who had been treated at the departments of internal medicine or cardiology between January 2010 and May 2018, were cross-sectionally investigated. Patients with an ICD-10 diagnosis of HF (I50), cardiomyopathy (I42, I43) or hypertensive heart disease (I11) were investigated. Inclusion criteria for further investigation in the patients were (1) IVSd > 14 mm, (2) absence of other types of CA than ATTRwt and ATTRv, and (3) completed evaluation for transthyretin amyloidosis by either a 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy examination or by endomyocardial biopsy. A flowchart of patient selection is described in Figure 1. The prevalence of ATTRwt in a portion of this cohort was recently published (Lindmark, et al., 2020).

Forty-nine patients met the inclusion criteria for participation in the study. Of these, 24 patients constituted the ATTRwt amyloidosis group, and 25 non-amyloidosis HF patients constituted the control group. Three ATTRwt patients were included via referrals to the Umeå University Hospital amyloidosis centre although they did not belong to the care district of Umeå University Hospitals. All other patients belonged to the Umeå University Hospital care district. One of the ATTRwt patients was diagnosed by endomyocardial biopsy, whereas the rest of the ATTRwt patients were diagnosed by DPD scintigraphy with a Perugini score of ≥2 along with a normal urine electrophoresis and a normal lambda/kappa ratio in blood in accordance with Gillmore et al. (2016). In addition, we retrospectively included nine patients with ATTRv from our local database that we defined as having ATTR-CA based on having a type A fibril type (n = 6) or a positive DPD scintigraphy (n = 3). This inclusion was done to test the diagnostic algorithm in a wider patient category of ATTR-CA.

Excluding light chain amyloidosis (AL-amyloidosis) in all patients was performed from blood and urine samples that were analysed regarding serum free light chain (FLC) abnormalities (Freelite, Binding Site reagent, reference range 0.27–1.64) and the presence of monoclonal bands. Patients with abnormalities in these analyses were evaluated, and their clinical history and disease progression were reviewed to assess the probability of AL-amyloidosis. Sequencing of the TTR-gene was performed on all patients to diagnose ATTRv amyloidosis. Fat biopsy was performed and fibril type settled in six ATTRv patients. (Paulsson Rokke, et al., 2020).

The control group consisted of HF patients with negative DPD scintigraphy examinations. Patients with a Perugini score of 1 were excluded from the study due to an uncertain diagnosis.

#### 2.2 | Data collection

Clinical records including the presence of atrial fibrillation, hypertension, atherosclerotic diseases, ischemic heart disease, diabetes mellitus, presence of pacemaker, HF medication, antithrombotic- and anticoagulation medication, and NYHA-classification were recorded through clinical examinations and by reviewing clinical records. Information about valvulopathies was obtained by echocardiographic examinations. Valvulopathies were defined as a severity grade of at least moderate or previous valve surgery due to valvulopathies. Perugini scores were performed based on established methods (Perugini, et al., 2005), and were obtained from clinical records. Height, weight and blood pressure were obtained from clinical records.

#### 2.3 | Echocardiography

Echocardiographic examination was performed using a Vivid E9 system (GE Medical Systems) equipped with an adult 1.5–4.3 MHz phased array transducer. All echoes were performed by one investigator (co-author PL). Standard views were used from the parasternal long axis-, short axis- and the apical four-chamber views. Chamber quantification and flow velocities were obtained using pulsed and continuous-wave Doppler techniques as proposed by recent guidelines (Lang, et al., 2005, Quinones, et al., 2002).

Relative wall thickness (RWT) was calculated according to the American society of echocardiography (ASE) recommendations (2 x posterior wall thickness [PWT]/Left ventricular diastolic diameter [LVDd]). LV mass was calculated through the Devereux formula (0.8(1.04([LVDd + PWT + IVSd]/3 [LVDd]^3)) + 0.6) (Lang, et al., 2015). LV wall thickness was measured as septal thickness + posterior wall thickness.

Pulsed wave tissue Doppler analysis was also done to assess the mean of LV lateral and septal myocardial early diastolic velocities (e'),
FIGURE 1  Flow-chart describing study population. Abbreviations: N, number of patients; IVSD, interventricular septum diameter; AL-amyloidosis – light chain amyloidosis; DPD, 99mTc-3.3-diphosphono-1,2-propanodicarboxylic acid; ATTRwt, wild type transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis
and then E/e’ was calculated (Mitter, et al., 2017). All Doppler recordings were obtained at a sweep speed of 50–100 mm/s with a superimposed ECG (lead II). Off-line analyses were done using commercially available software (General Electric, EchoPac version BT 13, 113.0), and the means of three consecutive cardiac cycles were calculated.

2.4 | Assessment of LV deformation function

Anatomical landmarks were used, and care was taken for echocardiographic image acquisition to ensure adequate LV tracking, and to avoid foreshortening of the LV cavity when measuring global strain of the LV. Longitudinal myocardial deformation was assessed by two-dimensional echocardiography using speckle tracking and was analyzed offline. From the apical four-chamber, two-chamber and apical parasternal long-axis views, the endocardial border of the septal, apical and lateral wall of the LV were done manually in order to analyse global LV strain measurements. Strain recordings from three cardiac cycles were averaged to assess the global longitudinal strain (GLS). GLS was measured at end systole with the reference point set at the onset of two consecutive QRS-complexes of the superimposed ECG. We calculated RELAPS as the average apical strain/ (average basal strain + average mid strain). Strain analyses were measured using a dedicated workstation (General Electric, EchoPac version BT 13, 113.0). GLS impairment was defined as more than −20% in accordance with reference values from the European Society of Cardiology (Löffbacka et al., 2017).

2.5 | Electrocardiography

A standard 12-lead ECG examination (50 mm/s, 0.1 mV/mm) was recorded for all patients. ECGs were analysed for rhythm, presence of anterior pseudo-infarction, conduction abnormalities and QRS-amplitudes including left ventricular hypertrophy and low voltage. Left ventricular hypertrophy was defined according to the Sokolow-Lyon index (S in V1 + R in V5, V6 > 3.5 mV), while low voltage was defined both as a Sokolow-Lyon index <1.5 mV, and the traditional definition defined as a max amplitude in limb leads <0.5 mV, or max amplitude in precordial leads <1.0 mV. ECG amplitudes were excluded from analysis if a deviation from the normal electrical conduction occurred due to ventricular pacing or left bundle branch block. All ECG amplitudes were measured manually by one examiner (co-author VL) and presented in mV.

2.6 | DPD scintigraphy

All patients were investigated with an Infinia Hawkeye hybrid single-photon-emission computed-tomography gamma camera (SPECT-CT; General Electric Medical Systems) with a low-energy high-resolution collimator. An intravenous injection of ~750 MBq DPD was performed 3 h prior to the acquisition of whole-body planar image, followed by a non-contrast, low-dose CT scan and a SPECT acquisition, 60 projections, iteratively reconstructed to a 128 x 128 matrix (OSEM, 3 iterations, 10 subsets) with scatter and CT-based attenuation correction. Reconstruction of SPECT images was performed on the Xeleris workstation (GE Healthcare). DPD scores were reported by two experienced clinicians using the Perugini grading system (Perugini, et al., 2005) with grade 0 being negative and grades 1–3 increasingly positive.

2.7 | Statistics

Statistical analyses were performed using SPSS®, version 26 (IBM). Baseline characteristics are presented as mean, maximum and minimum values for continuous variables. Percentages were used to describe categorical variables. Categorical variables were compared using chi-square tests, and continuous variables were compared using Student’s T-tests for normally distributed data or Mann-Whitney U tests for non-normally distributed data. Normal distribution was examined through the Shapiro-Wilks tests. p-values were presented with a 0.05 level of statistical significance.

2.8 | Ethics

The study complies with the declaration of Helsinki and the study protocol was approved by the Regional Ethics Committee of Umeå (reference numbers: 2016–435–31 M, 2018–418–32 M, 2018–137–32 M) and all subjects gave written informed consent to participate in the study.

3 | RESULTS

The mean duration between the first HFdiagnosis and the positive DPD scintigraphy was 2 years (SD 2.8) with a range of 0–8 years. Demographic and echocardiographic data for both groups are presented in Table 1. ATTR-CA patients had significantly lower blood pressure.

Only a few differences in comorbidities were seen between groups (Table S1). Hypertension was more common in the control group (p = 0.001). One patient with ATTR-CA had been diagnosed with diabetes mellitus, whereas the prevalence of diabetes mellitus in the control group was 36%. Heart failure medications differed in the usage of angiotensin II receptor blocker (ARB)/angiotensin-converting enzyme (ACE) inhibitors and betablockers, which were less common in the ATTR-CA group (p < 0.01). The usage of loop diuretics was more common in the ATTR-CA group (p = 0.033).

3.1 | ECG

The most common abnormal heart rhythm in the ATTR-CA group was atrial fibrillation (AF) seen in 33%, atrioventricular block type I in 24%, left atrial hemiblock (LAH) 52% and anterior infarction pattern in 29%.
Several differences were found in ECG characteristics between ATTR-CA patients and controls. Left atrial hemiblock (LAH) and anterior infarction patterns were more commonly found in the ATTR-CA group \((p < 0.05)\). None of the ATTR-CA patients, but six of the controls (32%) met the criteria for LVH according to the Sokolow-Lyon criteria \((p = 0.001; \text{Table } S1)\).

Low voltage according to the Sokolow-Lyon criteria was in the ATTR-CA group found in 43% compared to none in the control group \((p = 0.001)\). Traditional low voltage criteria were met in 11% in the ATTR-CA group and none in the control group \((p = 0.147)\).

### 3.2 | Echocardiography

The mean left ventricular ejection fraction (LVEF) in the ATTR-CA group was 50% compared to 53% in the control group \((p = 0.201)\). In the ATTR-CA group, 67% had a HF with preserved ejection fraction (HFrEF) defined as a LVEF ≥50%, compared to 76% in the control group \((p = 0.187)\).

Significantly increased PWT \((p < 0.001)\), RWT \((p < 0.001)\) and wall thickness \((p < 0.01)\) were observed in the ATTR-CA group. RELAPS was significantly higher in the ATTR-CA group \((p < 0.001)\). When investigating RELAPS with a cut-off value ≥1, a RELAPS pattern was present in 78% in the ATTR-CA group compared to only 17% in the control group \((p < 0.001; \text{Table } 1)\).

### 3.3 | ROC-analysis

Parameters that showed a statistically significant difference between ATTR-CA patients and controls were further investigated with ROC-analysis. These results are presented in Table 2. The univariate echocardiographic parameters with the highest AUC from ROC analysis were RWT (AUC 88%), RELAPS (AUC 86%) and PWT (AUC 85%). ROC curves for echocardiography parameters are presented in Figure 2a. The best univariate ECG predictors for differentiating groups included R in -aVR (AUC 94%), R in II (AUC 91%), and R in I (AUC 89%; Figure 2b).

The Sokolow-Lyon index displayed a sensitivity of 74% and a specificity of 58% with a cut off value of 18.5 mm; AUC was 72%.

### 3.4 | Multivariable analysis

When analysing echocardiographic and ECG parameters with multivariable analysis, the best diagnostic performances were obtained by pairing R in -aVR from ECG with echocardiographic parameters with the highest AUC. The best diagnostic accuracy was found with the following combinations: RWT/R in -aVR (AUC 99%), RELAPS/R in -aVR (AUC 96%) and PWT/R in -aVR (AUC 96%). Multivariate ROC analyses are presented in Figure 2c. When comparing the two groups according to the algorithm proposed by Gustavsson, et al. (2015), sensitivity of 74% and specificity of 74% were found.

### TABLE 1 | Echocardiographic and demographic characteristics in study populations

|                  | ATTR-CA | Controls |
|------------------|---------|----------|
|                  | N       | Mean     | Min  | Max  | SD   | N     | Mean     | Min  | Max  | SD   | p-Value |
| Age (years)      | 33/33   | 77       | 53   | 91   | 10   | 25/25 | 76       | 63   | 97   | 7    | 0.786   |
| HR (bpm)         | 33/33   | 76       | 54   | 107  | 12.9 | 25/25 | 68       | 49   | 104  | 14.3 | 0.051   |
| Height (cm)      | 31/33   | 174      | 153  | 187  | 7    | 25/25 | 173      | 158  | 194  | 9    | 0.668   |
| Weight (kg)      | 31/33   | 79       | 60   | 117  | 13   | 25/25 | 87       | 57   | 131  | 21   | 0.187   |
| BMI (kg/m²)      | 31/33   | 26       | 20   | 37   | 4    | 25/25 | 29       | 22   | 43   | 6    | 0.094   |
| Systolic blood pressure (mmHg) | 33/33   | 124      | 95   | 155  | 15   | 25/25 | 144      | 98   | 187  | 18   | <0.001  |
| Diastolic blood pressure (mmHg) | 31/33   | 77       | 60   | 95   | 11   | 25/25 | 85       | 61   | 110  | 11   | 0.005   |
| LVDD (mm)        | 33/33   | 44.7     | 35   | 55   | 4.7  | 25/25 | 49.0     | 40   | 60   | 5.7  | 0.003   |
| IVSD (mm)        | 33/33   | 17.5     | 15   | 25   | 2.2  | 25/25 | 17.4     | 15   | 30   | 4.0  | 0.078   |
| PWT (mm)         | 33/33   | 13.6     | 7    | 19   | 2.7  | 25/25 | 10.3     | 7    | 13   | 1.7  | <0.001  |
| E/e’             | 30/33   | 16.1     | 5.0  | 34.3 | 6.5  | 22/25 | 13.3     | 3.6  | 21.0 | 4.2  | 0.082   |
| RWT (mm)         | 33/33   | 0.3      | 0.3  | 1.0  | 0.4  | 25/25 | 0.4      | 0.3  | 0.6  | 0.1  | <0.001  |
| Wall thickness (mm) | 33/33   | 31       | 22   | 38   | 3.9  | 25/25 | 28       | 22   | 43   | 4.9  | 0.007   |
| LV-mass index (g/m²) | 33/33   | 149.7    | 99.8 | 207.4 | 29.0 | 25/25 | 138.3    | 87.4 | 215.7 | 32.7 | 0.2167  |
| GLS (%)          | 32/33   | 12.7     | 5.5  | 22.0 | 3.9  | 23/25 | 12.4     | 5.6  | 19.6 | 4.0  | 0.831   |
| RELAPS           | 32/33   | 1.7      | 0.6  | 9.4  | 1.6  | 23/25 | 1.0      | 0.3  | 6.0  | 1.1  | <0.001  |

Note: p-values indicate mean or median value comparisons between groups and bold text indicates a significant difference.

Abbreviations: E, early diastolic blood flow velocity; e’, early diastolic myocardial velocity; GLS, global longitudinal strain; IVSD, interventricular septum diameter; LVDD, left ventricular diastolic diameter; LV-mass, left ventricular-mass; Max, max value; Mean, mean value; Min, min value; N, number of patients; PWT, posterior wall thickness; RELAPS, relative apical sparing; RWT, relative wall thickness; SD, standard deviation; Wall thickness, IVSD + PWT.
et al., 2020; Phelan, et al., 2012). However, strain echocardiography has a diagnostic accuracy similar to that previously described (Boldrini, et al., 2020). RWT and RELAPS showed previously suggested to be a “red flag” in the diagnosis of CA, was also present in ATTR-CA (Phelan, et al., 2012). RWT/R- aVR ≥ 0.90.

RWT/R- aVR was tested in 10 healthy controls, 11 biopsy verified type A fibril with ATTRv and 6 patients with hypertrophic cardiomyopathy (HCM) that were previously evaluated by our group (Gustavsson, et al., 2015). All controls had a RWT/R- aVR < 0.56, all HCM had a RWT/R- aVR < 0.50, but all ATTRv had a RWT/R- aVR ≥ 0.90.

3.5 Validation of the combination of RWT/R-aVR

The RWT/R in -aVR was tested in 10 healthy controls, 11 biopsy verified type A fibril with ATTRv and 6 patients with hypertrophic cardiomyopathy (HCM) that were previously evaluated by our group (Gustavsson, et al., 2015). All controls had a RWT/R- aVR < 0.56, all HCM had a RWT/R- aVR < 0.50, but all ATTRv had a RWT/R- aVR ≥ 0.90.

4 DISCUSSION

We found that by using the R amplitude in -aVR from ECG ATTR-CA patients with increased septal thickness >14mm could be accurately separated from non-ATTR-CA HF patients despite similar septal thicknesses. In addition, when using a combined model of R- aVR from ECG and RWT from echocardiography, the prediction was even more accurate and provided a simple and clinically useful tool to identify patients with ATTR-CA among HF patients with thickened hearts. A non-invasive and simple method for identifying ATTR-CA patients with high probability is important and can optimize clinical strategy for final diagnosis (i.e. bone tracer scintigraphy).

The majority of the ATTR-CA patients could be categorized at a first assessment as patients with HF of the HfPEF-type, which was earlier shown to be a common type of HF in ATTR-CA patients (Gonzalez-Lopez, et al., 2015). However, approximately 33% of our investigated patients had LVEF < 50%. Therefore, it is important to also suspect ATTR-CA in HF patients with reduced LVEF, which is commonly found late in the ATTR-CA disease. Other findings in echocardiography included a restrictive filling pattern and a high relative wall thickness, which is commonly found in ATTR-CA.

Impaired left ventricular deformation with a RELAPS-pattern, previously suggested to be a "red flag" in the diagnosis of CA, was also present in ATTR-CA (Phelan, et al., 2012). RWT and RELAPS showed a diagnostic accuracy similar to that previously described (Boldrini, et al., 2020; Phelan, et al., 2012). However, strain echocardiography has several limitations in clinical practice, of which operator and vendor dependency are two. RWT seems to be a clinically useful variable for identification of CA, and especially ATTR-CA. The measure is not technically advanced and has been part of clinical echocardiography since many years. The RWT measure has a high sensitivity for identifying both AL and ATTR amyloidosis. Boldrini and co-workers found RWT of more than 0.6 mm was highly suggestive for ATTR amyloidosis (Boldrini, et al., 2020). They also found that a diagnostic sensitivity of 46% and a specificity of 98% were achieved by using a multi-parametric model that includes RWT together with E/e', TAPSE, GLS and a systolic apex to base strain ratio. We found that a RWT > 0.5 could distinguish ATTR-CA with high accuracy from HF with hypertrophy from other causes.

Our ECG findings included a high prevalence of arrhythmias with a high occurrence of both atrial fibrillation and atrioventricular blocks in ATTR-CA patients; this is in accordance with previous findings (Gonzalez-Lopez, et al., 2017). We found a relatively low prevalence of low voltage measured both as traditional low voltage and low voltage according to the Sokolow-Lyon index. This supports previous assumptions suggesting that low voltage has a lower prevalence in ATTR-CA compared to other types of CA, that is AL-amyloidosis (Rapezzi, et al., 2009). This finding also indicates that low voltage and Sokolow-Lyon index might be an overrated indicator for ATTR-CA. However, since ATTR-CA is probably the most common type of CA, and possibly the most underdiagnosed type of CA, improved indicators for identifying ATTR-CA are needed. One potential indicator for this in ATTR-CA could be the R-wave amplitude in -aVR. In our study, we found similar diagnostic accuracy in R-wave amplitude for diagnosing ATTR-CA as previously shown by Huang, et al. (2015).

4.1 Clinical use and impact of a combined diagnostic model

When combining the R-wave in -aVR with the echocardiographic parameters, substantially high diagnostic accuracy, sensitivity and
FIGURE 2 (a) Receiver operating characteristics (ROC) curve of univariate electrocardiogram parameters. Abbreviations: R, R-wave amplitude; AUC, area under the curve. (b) Receiver operating characteristics (ROC) curve of univariate echocardiography parameters. Abbreviations: RWT, relative wall thickness; RELAPS, relative apical sparing; PWT, posterior wall thickness; AUC, area under the curve. (c) Receiver operating characteristics (ROC) curve of multivariate parameters consisting of R-wave amplitude in -aVR and echocardiography parameters. Abbreviations: RWT, relative wall thickness; RELAPS, relative apical sparing; PWT, posterior wall thickness; R, R-wave amplitude; AUC, area under the curve.
negative predictive values were obtained. These findings and particularly the high diagnostic accuracy of using combined RWT/R in -aVR suggest that ATTR-CA can be identified accurately with routine ECG, and conventional and well-established echocardiographic examination, without the need for a more advanced speckle-tracking echocardiography technique. This formula could potentially be used as a screening method for accurate selection of HF patients with increased wall thickness that ought to be further investigated with bone scintigraphy or other modalities useful for CA diagnosis. This simple echo and ECG based formula may also reduce the number of unnecessary radiations by using bone scintigraphy investigation.

4.2 | Limitations

Because we did not have access to a sufficient number of patients with AL cardiomyopathy, a relatively small patient material is the largest limitation of this study. Endomyocardial biopsies were not performed, and in the patients with positive DPD and abnormal FLC analysis and monoclonal gammapathy, AL-amyloidosis cannot be ruled out. However, the slow rate of disease progression and the absence of renal involvement observed in these patients strongly suggests ATTR amyloidosis. Furthermore, the high rate of monoclonal gammapathy (MGUS) in ATTRwt has recently been presented. (Sidiqi, et al., 2019).

A relatively large proportion of the patients in both the ATTR-CA group and the control group had underlying coronary artery disease, which is another possible factor that can affect the results even though it mirrors the clinical reality in the patient groups. Although ATTR-CA is more common in men, a skewed presentation of study populations may be present since one of the inclusion criteria was an IVSd > 14 mm. These high IVSd criteria can potentially exclude some women due to thinner cardiac walls. Therefore, it is not certain if our findings can be translated to female ATTR-CA patients. Further, a number of patients had either left bundle branch block or pacemaker, which limited ECG analysis in the algorithm. However, in that situation, a RWT > 0.5 still has an accuracy of 86% in identifying ATTR-CA.

5 | CONCLUSION

We found a simple diagnostic formula useful in differentiating ATTR-CA from other etiologies of HF with increased interventricular septum thickness. By combining only two variables, R in -aVR from ECG and RWT from echocardiography, we found a very highly accurate model identifying ATTR-CA in HF clinics. We suggest this model as important for screening patients before bone scintigraphy or tissue biopsy is performed for a final diagnosis.

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CONFLICT OF INTEREST

Pilebro, Lindqvist and Sundström had a consultancy agreement with Pfizer.

DATA AVAILABILITY STATEMENT

The data of this study are not submitted due privacy for the patients. However, central data supporting findings are available upon request from the corresponding author.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the Supporting Information section.

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