ECG/echo indexes in the diagnostic approach to amyloid cardiomyopathy: A head-to-head comparison from the AC-TIVE study

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ABSTRACT

Background and aims: The discordance between QRS voltages on electrocardiogram (ECG) and left ventricle (LV) wall thickness (LVWT) on echocardiogram (echo) is a recognized red flag (RF) of amyloid cardiomyopathy (AC) and can be measured by specific indexes. No head-to-head comparison of different ECG/echo indexes among subjects with echocardiographic suspicion of AC has yet been undertaken. The study aimed at evaluating the performance and the incremental diagnostic value of different ECG/echo indexes in this subset of patients.
Methods: Electrocardiograms of subjects with LV hypertrophy, preserved ejection fraction and $\geq$ 1 echocardiographic RF of AC participating in the AC-TIVE study, an Italian prospective multicenter study, were independently analyzed by two cardiologists. Low QRS voltages and 8 different ECG/echo indexes were evaluated. Cohort specific cut-offs were computed.
Results: Among 170 patients, 55 (32 %) were diagnosed with AC. Combination of low QRS voltages with interventricular septum $\geq$ 1,6 cm was the most specific (specificity 100 %, positive predictive value 100 %) ECG/echo index, while the ratio between the sum of all QRS voltages and LVWT <7,8 was the most sensitive and accurate (sensitivity 94 %, negative predictive value 97 %, accuracy 82 %). When the latter index was added to a model using easily-accessible clinical variables, the diagnostic accuracy for AC greatly increased (AUC from 0,84 to 0,95; $p = 0{,}007$).

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Conclusions: Among patients with non-dilated hypertrophic ventricles with normal ejection fraction and echocardiographic RF of AC, easily-measurable ECG/echo indexes, mainly when added to few clinical variables, can help the physician orient second level investigations. External validation of the results is warranted.

1. Introduction

Thickened left ventricle (LV) is the hallmark of amyloid cardiomyopathy (AC) and results from progressive amyloid deposition in the myocardial extracellular space rather than myocyte hypertrophy [1]. When combined with other echocardiographic typical structural and functional features, it may raise suspicion of AC [2,3]. We recently reported an AC prevalence of 28.6 % among subjects with hypertrophic, non-dilatated hearts with preserved LV ejection fraction (EF) and at least one echocardiographic red flag (RF) of AC, identified from an unselected general population, within the "National Survey of Prevalence and Accuracy of Echocardiographic Red Flags of Amyloid Cardiomyopathy in Consecutive Patients Undergoing Routine Echocardiography" (AC-TIVE) study [4]. An accuracy above 70 % for AC detection was obtained in presence of $\geq$ 2 echocardiographic RFs.

In full-blown AC, the thickened LV can be associated with low QRS complex voltages (LQVs) on the surface electrocardiogram (ECG) [5,6], which prevalence ranges from 35 % to 55 % and is higher in patients with light chain AC (AL-AC) or advanced AC [1]. Conversely, LQVs are uncommon in earlier stages of cardiac amyloid infiltration. In this setting, a discordance between QRS voltages on ECG and LV wall thickness (LVWT) or mass (LVM) measured with echocardiogram is more frequently found [3,7], which can be measured by specific ECG/echo indexes. However, different ECG/echo indexes have been developed over time and there is uncertainty about which is the index with the highest accuracy for increasing the suspicion of AC among patients with echocardiographic findings suggestive of AC.

The present study was designed to evaluate the performance and the possible incremental diagnostic value of different ECG/echo indexes combing QRS voltages and LVWT or LVM among patients included in the Phase 2 of the AC-TIVE study.

2. Methods

2.1. Study Design

AC-TIVE study is a national, multicenter, prospective cohort study involving 13 tertiary centers across Italy. The local Regional Institutional Review Board approved the study (identifier 199_2019), and the participating Centres obtained local institutional review board approvals for the collection of prospective anonymous data. The study was conducted according to the Declaration of Helsinki. The study design was previously described [4,8]. In summary, the AC-TIVE study included two phases: 1) Phase 1, recording phase, consisting in a screening for echocardiographic RF suggestive of AC among patients > 55 years old presenting "AC compatible" echocardiograms (i.e. interventricular septum (IVS) $\geq$ 12 mm in women and $\geq$ 13 mm in men, LV ejection fraction $\geq$ 50 % and indexed end-diastolic LV volume $\leq$ 85 mL/m2). "AC suggestive" echocardiograms were defined as "AC compatible" echocardiograms plus at least one of the following echocardiographic RF suggestive of infiltration: (a) restrictive filling pattern and/or increased LV diastolic filling pressures; (b) "granular sparkling" appearance of myocardium; (c) pericardial effusion; d) interatrial septum thickness >5 mm; (e) atrio-ventricular valves leaflets thickness > 5 mm; and, (f) LV "apical sparing" pattern (Table A1). Phase 2 consisted in a clinical evaluation of patients with "AC suggestive" echocardiograms with blood and urine tests and scintigraphy with bone tracer. Diagnosis of transthyretin related AC (ATTR-AC) was made in presence of Grade 2 or 3 myocardial uptake of radiotracer on cardiac scintigraphy and exclusion of clonal dyscrasia with blood and urine tests, according to Gillmore's algorithm [9] and the latest ESC Position Statement [2].

For the purposes of the present analysis, we collected the available ECGs of the 217 patients >55 years old with "AC suggestive" echocardiograms that completed Phase 2 of the AC- TIVE study (Fig. 1). All ECG were centrally collected and independently analyzed by 2 cardiologists (F.L., L.P.), blind to patients' characteristic and final diagnosis of AC. The average between the two measurements was taken for continuous variables. Patients with concomitant conditions known to cause LQVs (i.e., pericardial effusion (PE) > 20 mm, end-stage chronic obstructive pulmonary disease (COPD), massive bilateral pleural effusion) or interfering with QRS voltage analysis (i.e., ventricular paced rhythm and poor-quality ECG trace) were excluded from the study population.

2.2. Electrocardiographic analysis

ECG were analyzed for the following characteristics: (a) rhythm; (b) conduction abnormalities (i.e., first-degree atrioventricular block and bundle branch block); (c) pseudo infarction, defined as the presence of pathological Q wave in two or more contiguous leads (anterior and/or inferior) in the absence of a history of ischemic heart disease and/or evidence of akinetic/dyskinetic wall segments [10]; (d) LQVs defined as "Sokolow-Lyon index $\leq$ 15 mm", i.e. the sum of the S wave amplitude in lead V1 and of the R wave in V5 or V6 $\leq$ 15 mm (1,5 mV) [11], or "Low peripheral voltages", i.e. QRS amplitude in each peripheral lead $\leq$ 5 mm (0,5 mV) [12].

We measured and compared QRS voltages and LVWT or LVM according to the most commonly used ECG/echo indexes and relative cut offs proposed in previous studies:

1 Sokolow index divided by the cross-sectional area (CSA) of the LV wall indexed to body surface area, CSA = π*[(LV end-diastolic diameter/2 + mean LVWT)]^2 - π*(LV end-diastolic diameter/2)^2, (mm/cm2/m2). Cut off $\leq$ 1,175 [13];
2 Sokolow index divided by LVM index (LVMI) (mm/g/m2). Cut off $\leq$ 0,105 [14];
3 Sokolow index divided by maximum LVWT. Cut off $\leq$ 1,231 [14];
4 Low peripheral QRS voltage in combination with interventricular septal (IVS) thickness >1,98 cm, according to Rahman et al. [15];
5 Peripheral QRS score (sum of QRS voltages in the limb leads) divided by LVMI (mV/g/m2). Cut off $\leq$ 0,234 [14];
6 Peripheral QRS score divided by maximum LVWT (mV/cm). Cut off $\leq$ 2,56 [14];
7 Total QRS score (sum of QRS voltages in the limb and precordial leads) divided by LVMI (mV/g/m2). Cut off $\leq$ 0,695 [14];
8 Total QRS score divided by maximum LVWT (mV/cm). Cut off $\leq$ 7,769 [14];

Different measures of IVS thickness for the Rhaman index and cohort specific limit values of the other indexes were tested to identify the best performing cut-offs in our population.

2.3. Echocardiographic analysis

Echocardiographic quantitative parameters were measured by each participating centre based on current international recommendations

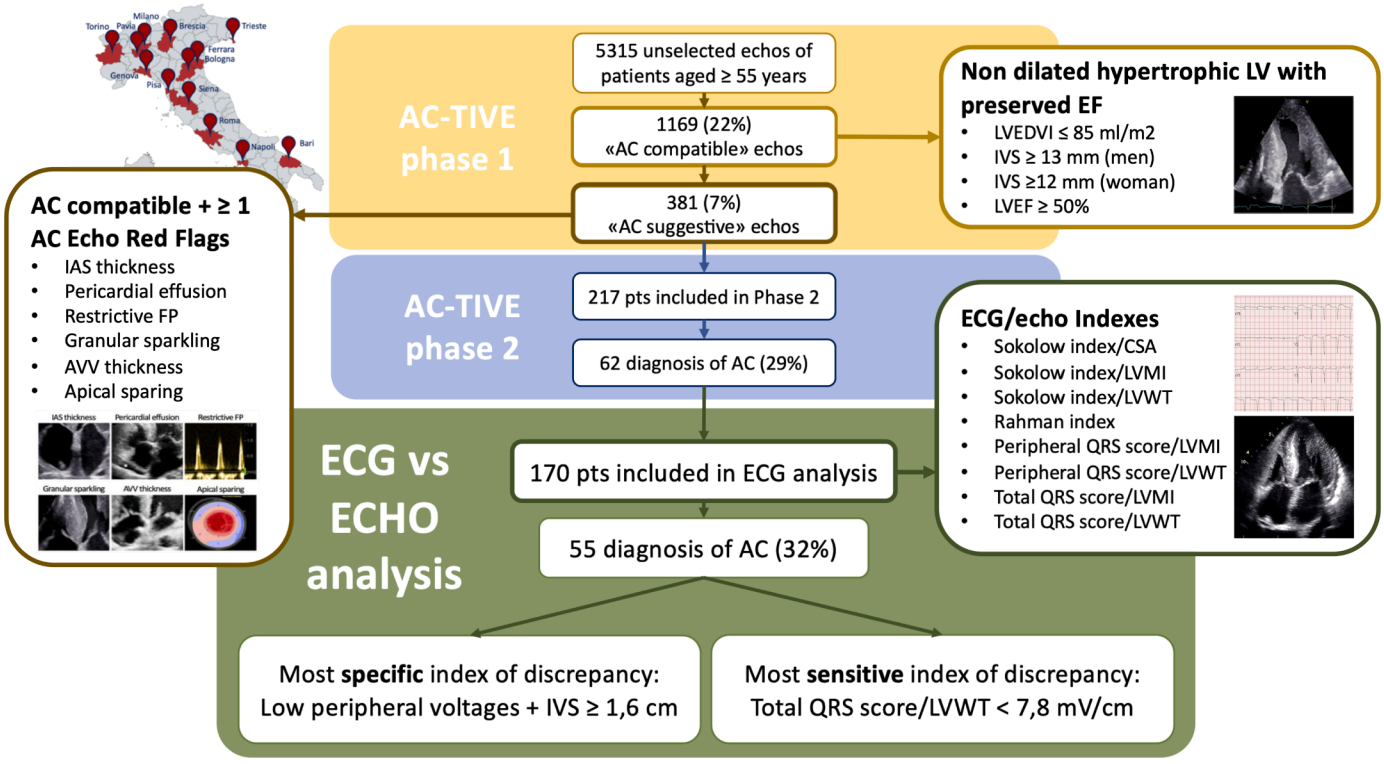


Fig. 1. Flow chart of the study. Legend: AC, amyloid cardiomyopathy; AVV, atrioventricular valve; CSA, cross-sectional area of the LV wall; ECG, electrocardiogram; echo, echocardiogram; FP, filling pattern; IAS, inter-atrial septum; IVS, interventricular septum; LV, Left Ventricle; LVEDVI, index LV end diastolic volume; LVEF, LV ejection fraction; LVMI, index LV mass; LVWT, LV wall thickness; Sokolow, Sokolow Index.

[16]. Specifically, maximum LVWT was measured for IVS and posterior wall in the parasternal long-axis view with M-mode approach or linear measurement from two-dimensional echocardiographic images, whichever was higher. LVMI was calculated by M-mode method and indexed to body surface area.

2.4. Statistical analysis

Descriptive statistics between the study groups were calculated. Continuous variables were expressed as median with interquartile range (IQR) [25°; 75°], according to the distribution shape. Differences between groups were evaluated using Mann– Whitney U test for continuous variables and the Chi square ($\chi 2$) or Fisher's exact test for dichotomous variables, as appropriate. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated using standard techniques. Receiver operator characteristic (ROC) curve analysis were performed to determine the accuracy of ECG/echo indexes in predicting the presence of AC. Youden test [17] was used to identify cohort specific cut-offs of the indexes. Binary logistic regression analyses were performed to assess a model including the clinical variables with the highest predictive value for the presence of AC and the best performing ECG/echo index. The best diagnostic performance in detecting AC was investigated according to the area under the curve (AUC).

A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 26.0 (IBM Corp, Armonk, New York) and R Statistical Software, Version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Among the 217 patients with an "AC suggestive" echocardiogram who completed Phase 2 of the AC-TIVE study, ECG was available for central evaluation in 195 cases (89 %). Of them, 170 patients were included in the study population (Fig. 1). Reasons for exclusion were poor quality ECG ($n = 4$, 2 %), severe COPD or PE > 20 mm ($n = 13$, 8 %) and ventricular paced rhythm ($n = 8$, 5 %). A final diagnosis of AC was achieved in 55 patients (32 %): 46 patients (84 %) were diagnosed with ATTR-AC and 9 patients (16 %) received a diagnosis of AL- AC. Most ATTR-AC patients were in NAC stage 1 (57 %) and had a Perugini grade 3 ($n = 30$, 65 %).

Baseline characteristics of patients with and without AC are summarized in Table 1. AC patients were more frequently male (71 % vs 52 %, $p = 0{,}016$). Compared to non-AC patients, they had lower frequency of arterial hypertension (40 % vs 75 %, $p < 0{,}001$) and higher rates of history of heart failure (HF) (40 % vs 17 %, $p = 0{,}001$), bilateral carpal tunnel syndrome (CTS) (49 % vs 8 %, $p < 0{,}001$) and atrial fibrillation (31 % vs 15 %, $p = 0{,}033$). According to rates of HF history, NTproBNP was higher among AC patients (1746 vs 448 pg/ml, p <0,001).

At echocardiographic evaluation, compared to non-AC, AC patients had higher LVWT (IVS 16 vs 14 mm, $p < 0{,}001$) and LVMI (168 vs 132 g/m^2, $p < 0001$), smaller LV dimensions (end-diastolic LV diameter 46 vs 48 mm, $p = 0{,}025$), and they reported more frequently pericardial effusion (38 % vs 21 %, $p = 0{,}017$). At ECG, there were similar rates of first-degree atrioventricular block and bundle branch blocks between AC and non-AC patients, while pseudonecrosis was more frequently observed in AC patients (36 % vs 15 %, $p = 0{,}001$). LQVs defined as "low peripheral voltages" (36 % vs 4 %, $p < 0{,}001$) and "Sokolow index ≤ 15 mm" (80 % vs 19 %, $p < 0{,}001$) were more frequently found among AC patients.

Table 1
Characteristics of patients with and without cardiac amyloidosis.

	Total ($n = 170$)	AC (=55)	No AC ($n = 115$)	P value	Available data
Age	75 (66-81)	78 (70-82)	74 (65-80)	0,098	170
Sex (male)	98 (58 %)	39 (71 %)	59 (51 %)	0,016	170
BMI (kg/m2)	26 (23-29)	25 (22-28)	27 (24-29)	0,034	124
Clinical data					
Arterial Hypertension	108 (64 %)	22 (40 %)	86 (75 %)	<0,001	170
PM	23 (19 %)	9 (26 %)	14 (16 %)	0,198	124
CKD	47 (38 %)	17 (49 %)	30 (34 %)	0,125	124
CTS	24 (19 %)	17 (49 %)	7 (8 %)	<0,001	124
Heart Failure	42 (25 %)	22 (40 %)	20 (17 %)	0,001	170
History of Atrial fibrillation	24 (19 %)	11 (31 %)	13 (15 %)	0,033	124
NTproBNP (pg/ml)	685 (288-1802)	1746 (978-3500)	448 (199-898)	<0,001	143
Electrocardiogram					
HR	75 (65-83)	79 (68-88)	75 (64-81)	0,055	170
SR	138 (82 %)	39 (71 %)	99 (86 %)	0,018	170
AF/AFl	32 (19 %)	16 (29 %)	16 (14 %)	0,018	170
1st degree AV Block	29 (17 %)	10 (18 %)	19 (17 %)	0,980	170
BBB	32 (19 %)	13 (24 %)	19 (17 %)	0,267	170
Pseudonecrosis	37 (22 %)	20 (36 %)	17 (15 %)	0,001	170
Sokolow (mm)	19 (13-23)	14 (12-15)	21 (19-24)	<0,001	124
Sokolow $\leq$ 15 mm	45 (36 %)	28 (80 %)	17 (19 %)	<0,001	124
Low Peripheral Voltages	25 (15 %)	20 (36 %)	5 (4 %)	<0,001	170
Total QRS score (mV)	10,4 (7,8-13,7)	8,2 (7,2-9,5)	12 (8,5-14,9)	<0,001	170
Echocardiogram					
IVS (mm)	15 (13-16)	16 (15-18)	14 (13-15)	<0,001	170
PW (mm)	13 (11-15)	15 (13-18)	12 (10-14)	<0,001	170
LVEDD (mm)	47 (43-51)	46 (42-50)	48 (44-51)	0,025	170
LVMI (gr/m2)	143 (116-172)	168 (141-194)	132 (111-158)	<0,001	170
LVEF (%)	60 (55-65)	55 (50-60)	60 (55-65)	<0,001	170
RV FAC (%)	39 (37-45)	38 (33-42)	39 (37-44)	0,271	132
RV wall (mm)	5 (4-7)	5 (4-8)	4 (4-6)	0,027	121
Pericardial effusion	29 (23 %)	21 (38 %)	24 (21 %)	0,017	170

Legend: AC, amyloid cardiomyopathy; AF, atrial fibrillation; AFl, atrial flutter; AV atrioventricular; BBB: Bundle Branch Block; BMI: body mass index; CSA: cross-sectional area of the LV wall; CKD, chronic kidney disease; CTS; carpal tunnel syndrome; HR: Heart Rate; IVS: interventricular septum; LV: Left Ventricle; LVEDD: LV end diastolic diameter; LVEF: LV ejection fraction; PM: pacemaker; PW: Posterior Wall; RV: right ventricle; Sokolow: Sokolow Index; SR: sinus rhythm.

3.2. ECG/echo indexes of discordance

Table 2 illustrates the median values of ECG/echo indexes according to the presence of AC. Table 3 summarizes the diagnostic performances of the ECG/echo indexes according to literature cut-offs. The most sensitive and accurate index was the total QRS score divided by maximum LVWT (sensitivity 91 %, accuracy 82 %), whereas the most specific was the Rahman index (specificity 100 %). Fig. 2 shows the accuracy of the ECG/echo indexes according to their AUC.

When cohort specific cut-offs were investigated, a specificity of 100 % was obtained with a "modified Rahman" using an IVS thickness $\geq$ 1,6 cm (i.e. 75° percentile), despite sensitivity was low (34 %). Conversely, the highest sensitivity (94 %) and negative predictive value (97 %) were obtained with the index "total QRS score divided by maximum LVWT" with a cut-off value of 7,8; when this index was satisfied (i.e. index < 7,8), a diagnostic accuracy of 82 % for AC was achieved (Fig. 3, Table 4). Fig. 4 shows a case of AC and the relative modified Rahman and QRS score/LVWT indexes' calculation.

3.3. Incremental diagnostic performance of voltages-to-wall thickness ratio

Table A.2 shows univariate and multivariable regression analyses based on clinical variables for the presence of AC. Among different clinical variables considered, the model including the 5 clinical variables with the highest predictive value (i.e., bilateral CTS, HF, arterial hypertension, age and male sex) achieved an AUC of 0,837. The addition of the total QRS score divided by maximum LVWT (i.e., the best performing ECG/echo index) to this clinical model resulted in a significant improvement of the diagnostic accuracy (AUC from 0,837 to 0,945; $p =$ 0,007) (Fig. 5).

3.4. Subgroup analysis: ATTR- AC

The findings from the overall cohort were further confirmed, after exclusion of patients with AL-AC, in dedicated sub-analyses for ATTR-AC diagnosis. In this cohort of 161 patients (46 of them with ATTR-

Table 2
Median values of ECG/echo indexes in the AC-TIVE population.

	Total population ($n = 170$)	AC patients ($n = 55$)	Non-AC patients ($n = 115$)	P value
1.Sokolow/CSA	1,41 (0,90-1,78)	0,83 (0,58-1,08)	1,57 (1,17-2,00)	<0,001
2.Sokolow/LVMI	0,14 (0,09-0,19)	0,09 (0,06-0,11)	0,17 (0,13-0,20)	<0,001
3.Sokolow/Max LVWT	1,32 (0,81-1,62)	0,78 (0,65-1,04)	1,46 (1,14-1,71)	<0,001
4.Rahman index	6 (5 %)	6 (17 %)	0 (0 %)	<0,001
5. Peripheral QRS/LVMI	0,33 (0,21-0,44)	0,19 (0,12-0,28)	0,38 (0,30-0,46)	<0,001
6. Peripheral QRS/Max LVWT	2,86 (1,89-3,64)	1,69 (1,27-2,28)	3,25 (2,65-3,90)	<0,001
7. Total QRS/LVMI	0,94 (0,69-1,16)	0,64 (0,44-0,75)	1,05 (0,88-1,25)	<0,001
8. Total QRS/Max LVWT	8,43 (5,98-1,01)	5,73 (4,73-6,67)	9,52 (8,12-10,59)	<0,001

Legend: CSA: cross-sectional area of the LV wall; LV: Left Ventricle; LVMI: LV mass index; Max LVWT: Maximum LV wall thickness; Sokolow: Sokolow Index.

Table 3
Diagnostic performance of the different ECG/echo indexes for the identification of AC in the overall population, according to literature cut-offs.

1. Sokolow/CSA			2. Sokolow/LVMI		
Statistic	Value	95 % CI	Statistic	Value	95 % CI
Sensitivity	88.6 %	73.3 % to 96.8 %	*Sensitivity*	69.4 %	51.9 % to 83.7 %
Specificity	74.2 %	63.8 % to 82.9 %	*Specificity*	77.2 %	67.3 % to 85.3 %
PLR	3.43	2.36 to 4.97	*PLR*	3.04	1.97 to 4.69
NLR	0.15	0.06 to 0.39	*NLR*	0.40	0.24 to 0.66
PPV	57.4 %	48.2 % to 66.2 %	*PPV*	55.4 %	44.6 % to 65.7 %
NPV	94.3 %	86.7 % to 97.7 %	*NPV*	86.1 %	78.9 % to 91.1 %
Accuracy	78.2 %	69.9 % to 85.1 %	*Accuracy*	74.9 %	66.5 % to 82.2 %
3.Sokolow/Max LVWT			4.Low Voltages+ MaxLVWT >1,98 cm		
Statistic	Value	95 % CI	Statistic	Value	95 % CI
Sensitivity	86.1 %	70.5 % to 95.3 %	*Sensitivity*	16.7 %	6.4 % to 32.8 %
Specificity	67.4 %	56.8 % to 76.8 %	*Specificity*	100.0 %	96.2 % to 100.0 %
PLR	2.64	1.91 to 3.64	*PLR*	na	na
NLR	0.21	0.09 to 0.47	*NLR*	0.83	0.72 to 0.96
PPV	51.9 %	43.9 % to 59.8 %	*PPV*	100.0 %	
NPV	92.2 %	83.9 % to 96.4 %	*NPV*	74.6 %	71.7 % to 77.3 %
Accuracy	72.8 %	64.3 % to 80.3 %	*Accuracy*	75.8 %	67.6 % to 82.9 %
5. Peripheral QRS/LVMI			6. Peripheral QRS/Max LVWT		
Statistic	Value	95 % CI	Statistic	Value	95 % CI
Sensitivity	65.7 %	47.8 % to 80.9 %	*Sensitivity*	80.0 %	63.1 % to 91.6 %
Specificity	85.4 %	76.3 % to 92.0 %	*Specificity*	77.5 %	67.5 % to 85.7 %
PLR	4.50	2.58 to 7.85	*PLR*	3.56	2.34 to 5.42
NLR	0.40	0.25 to 0.64	*NLR*	0.26	0.13 to 0.51
PPV	64.8 %	51.3 % to 76.2 %	*PPV*	59.3 %	48.9 % to 68.9 %
NPV	85.9 %	79.3 % to 90.7 %	*NPV*	90.5 %	82.9 % to 94.9 %
Accuracy	79.7 %	71.5 % to 86.4 %	*Accuracy*	78.2 %	69.9 % to 85.2 %
7. Total QRS/LVMI			8. Total QRS/Max LVWT		
Statistic	Value	95 % CI	Statistic	Value	95 % CI
Sensitivity	60.0 %	42.1 % to 76.1 %	*Sensitivity*	91.4 %	76.9 % to 98.2 %
Specificity	88.8 %	80.3 % to 94.5 %	*Specificity*	78.6 %	68.7 % to 86.6 %
PLR	5.34	2.81 to 10.16	*PLR*	4.28	2.84 to 6.46
NLR	0.45	0.30 to 0.68	*NLR*	0.11	0.04 to 0.32
PPV	68.6 %	53.4 % to 80.6 %	*PPV*	63.6 %	53.7 % to 72.5 %
NPV	84.5 %	78.3 % to 89.1 %	*NPV*	95.7 %	88.3 % to 98.5 %
Accuracy	80.4 %	72.3 % to 87.0 %	*Accuracy*	82.4 %	74.5 % to 88.6 %

Legend: AC: cardiac amyloidosis; CSA: cross-sectional area of the LV wall, LV: Left Ventricle; Max LVWT: LV wall thickness; Sokolow I: Sokolow Index; NLR, Negative Likelihood Ratio; NPV, Negative Predictive Value; PLR, Positive Likelihood Ratio; PPV, Positive Predictive Value.

AC), total QRS score divided by maximum LVWT had the highest NPV (96 %) and the modified Rahman index showed the highest PPV (100 %) (Table A.3). At ROC curve analysis, the addition of total QRS score divided by LVWT to the clinical model significantly increased the diagnostic accuracy (AUC from 0,860 to 0,943; $p = 0{,}034$) (Figure A.1).

4. Discussion

To the best of our knowledge, this is the first nationwide analysis assessing and comparing the diagnostic performance of various indexes measuring the discordance between QRS voltages on ECG and LVWT or LVMI assessed by echo for the diagnosis of AC among subjects from the general population presenting with hypertrophic, non-dilated heart with normal LVEF and at least one echocardiographic RF of the disease. The main findings can be summarized as it follows:

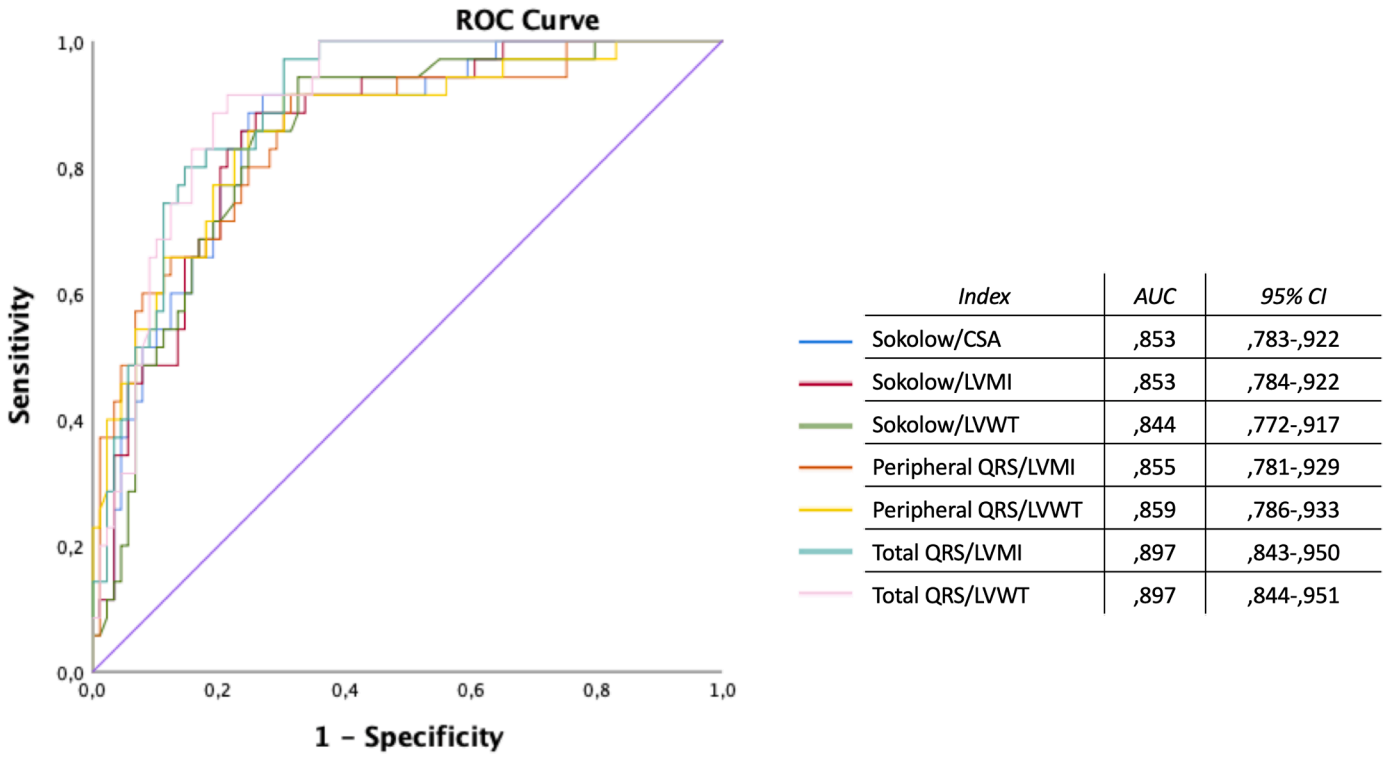
A The ratio between total QRS score and maximum LVWT was the most accurate ECG/echo index; when this index was not satisfied (i.e. index $\geq$ 7,8), AC was ruled out with a NPV of 97 %;
B The index combining LQVs with IVS thickness $\geq$1,6 cm was the most specific; when this criterion was satisfied, AC was diagnosed in all cases (specificity 100 %).
C Adding total QRS score divided by maximum LVWT to a clinical model using easily accessible variables (such as age, sex, arterial hypertension, HF and bilateral CTS) greatly increased diagnostic accuracy for AC, reaching an AUC of 0,95.

These results highlight the valuable contribution of ECG as first-line test for assessing patients with suspected AC, mainly used in combination with simple clinical and echocardiographic parameters. In everyday practice, patients accessing the echo-laboratory for any clinical reason and presenting with AC suggestive echocardiographic RFs may not receive the correct diagnosis due to low level of suspicion. The systematic combination of echo and ECG parameters can aid clinicians in raising the suspicion of AC and orienting second level diagnostic tests to confirm the presence of the disease (namely bone tracer scintigraphy, serum/urine immunofixation and cardiac magnetic resonance) [3].

The ECG, a widely available and cost-effective tool, can aid either the general practitioner or the primary care cardiologist orienting the suspicion of AC, prompting referral to the specialist, and the tertiary care cardiologist as a support in the differential diagnosis of cardiomyopathies. The echocardiographic laboratory is the most common crossroad between patients and cardiologists and the setting where the ECG can be careful evaluated with a cardiomyopathy-oriented approach [18]. In the present analysis, the discordance between LVWT and QRS voltages identified patients at higher risk of AC, with an accuracy above 90 % when integrated with few clinical information. This approach resulted in a higher diagnostic yield, promoting earlier diagnoses of ATTR-AC and hence, disease-modifying therapies' initiation, with positive impact on prognosis. Here we provide an integrated ECG, clinical and echocardiographic approach for the challenging scenario of patients with hypertrophic phenotype and $\geq$1 RF of AC (Fig. 3).

4.1. Prevalence of LQVs

LQVs are a well-known RF of infiltrative disease [5,11–15,19,20], but their prevalence varies greatly according to the definition adopted for "low voltages", AC etiology and the degree of amyloid infiltration.



Index	AUC	95% CI
Sokolow/CSA	,853	,783-,922
Sokolow/LVMI	,853	,784-,922
Sokolow/LVWT	,844	,772-,917
Peripheral QRS/LVMI	,855	,781-,929
Peripheral QRS/LVWT	,859	,786-,933
Total QRS/LVMI	,897	,843-,950
Total QRS/LVWT	,897	,844-,951

Fig. 2. ROC Curves: accuracy for AC diagnosis of the investigated ECG/echo indexes. Legend: AC, amyloid cardiomyopathy; CSA, cross-sectional area of the LV wall; IVS, interventricular septum; LV, Left Ventricle; LVMI, index LV mass; LVWT, LV wall thickness; Sokolow, Sokolow Index.

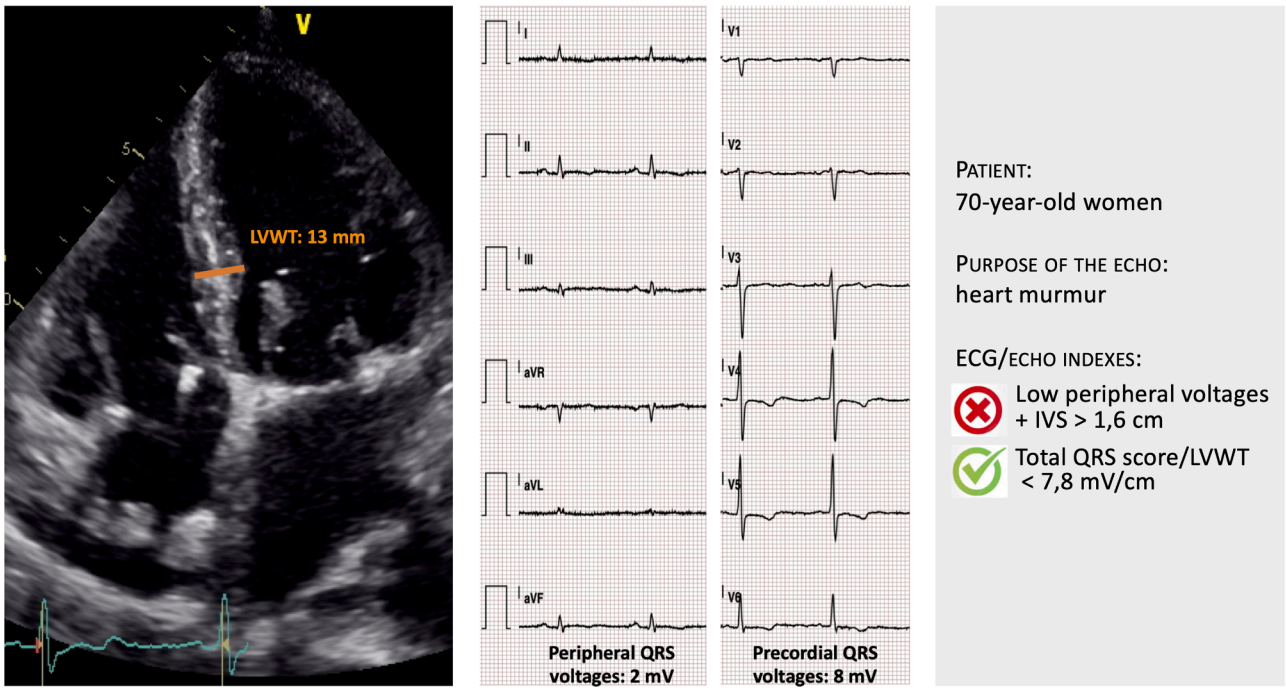


Fig. 3. Diagnostic value and clinical utility of the best performing ECG/echo indexes. Legend: AC, amyloid cardiomyopathy; AVV, atrioventricular valve; ECG, electrocardiogram; echo, echocardiogram; FP, filling pattern; IAS, interatrial septum; IVS, interventricular septum; LV, Left Ventricle; LVEDVI, index LV end diastolic volume; LVEF, LV ejection fraction.

Mussinelli et al. investigated the different definitions of LQVs, reporting the highest prevalence for "Sokolow-Lyon index $\leq$ 15 mm" (84 %), followed by "low peripheral voltages" (37 %) defined as a QRS amplitude $\leq$ 5 mm (0,5 mV) in each peripheral lead, and "low total voltages" (27 %) defined as a QRS amplitude $\leq$ 5 mm (0,5 mV) in each peripheral lead and QRS amplitude $\leq$ 10 mm (1 mV) in each precordial lead [5].

The frequency of LQVs ranged from 45 % to 70 % of cases in old series of patients with biopsy proven AL-AC [19,20]. Recent reports

Table 4
Diagnostic performance of the two most clinically relevant ECG/echo indexes for the identification of AC in the overall population reporting AC-TIVE cohort's specific cut-offs.

Low Voltages+ MaxLVWT ≥1,6 cm			Total QRS/Max LVWT < 7,8		
Statistic	Value	95 % CI	Statistic	Value	95 % CI
Sensitivity	34.29 %	19.13 % to 52.21 %	*Sensitivity*	94.29 %	80.84 % to 99.30 %
Specificity	100.00 %	95.94 % to 100.00 %	*Specificity*	77.53 %	67.45 % to 85.70 %
PLR	na	na	*PLR*	4.20	2.83 to 6.22
NLR	0.66	0.52 to 0.83	*NLR*	0.07	0.02 to 0.28
PPV	100.00 %		*PPV*	62.26 %	52.66 % to 71.00 %
NPV	79.46 %	75.28 % to 83.10 %	*NPV*	97.18 %	89.94 % to 99.25 %
Accuracy	81.45 %	73.48 % to 87.86 %	*Accuracy*	82.26 %	74.38 % to 88.53 %

Legend: AC: cardiac amyloidosis; LV: Left Ventricle; Max LVWT: LV wall thickness; NLR, Negative Likelihood Ratio; NPV, Negative Predictive Value; PLR, Positive Likelihood Ratio; PPV, Positive Predictive Value.

comparing the prevalence of electrophysiological abnormalities between AL and ATTR-AC showed higher rates of low voltages among AL-AC than in ATTR-AC (55–67 % vs 21–35 %, respectively) [1,21–23]. The higher frequency of LQVs reported in AL-CA may results from the presence of edema and inflammation secondary to direct cardiotoxicity from circulating free light chains depositing in the myocardium in combination with the expansion of the extra-cellular matrix produced by amyloid infiltration [1].

As a further element of heterogeneity, ECG can be performed in different stages of cardiac infiltration showing LQVs in longstanding ATTR-AC or increased or normal QRS voltages in early AL-AC. Moreover, QRS voltages change over time depending on disease evolution and dynamic changes have been demonstrated to be associated with outcome [1].

In this study cohort, results were consistent with literature, showing a prevalence of LQVs of 80 % according to the "Sokolow index ≤ 15 mm" definition and 36 % according to the "low peripheral voltages" definition among who received a definite diagnosis of AC. However, up to 19 % of patients with hypertrophic, non-dilated ventricles in whom the diagnosis of AC was excluded had LQVs, and up to 64 % of patients with AC did not present with LQVs. These findings strongly support the combined use of of ECG with echocardiographic evaluation to raise disease suspicion and achieve accurate AC diagnosis.

4.2. Paradigm shift from low QRS voltages to ECG/echo indexes

Combining QRS voltages with LV thickness or mass at echocardiography enhances the diagnostic accuracy of the traditional criterion "low QRS voltages". Caroll et al. was the first to observe that AC patients have excessive LVWT and LVMI, measured by the cross-sectional area of the LV wall in a transverse plane, in relation to LV systolic pressure and ECG voltages [13]. Subsequently, other indexes correlating QRS voltages at ECG and LVMI or LVWT at echocardiography were investigated in cohorts of patients with definite AC [14,15]. In our study, those ECG/echo indexes were tested in a subgroup of patients with echocardiographic features of AC (the Phase 2 AC-TIVE population), derived from an unselected cohort of subjects undergoing echocardiographic evaluation for reasons other than AC. Of note, results were widely consistent with literature, albeit some differences in diagnostic performance and specific cut offs values were identified, reflecting the inclusion of a more unselected population in our analysis compared to previous studies on highly selected cohorts of AL or ATTR-AC. In support of this statement, only 25 % of the study population and 40 % of AC population reported a history of HF while NTproBNP did not show to predict AC diagnosis, suggesting a population with pretty early diagnosis of AC. In this population, the best performing index was "total QRS score divided by maximum LVWT" (sensitivity 91 %, specificity 79 %), instead of "total QRS score divided by LVMI" (sensitivity 82 %, specificity 80 %) which was the best performing index detected by Quarta et al. among patients with a definite diagnosis of AC [14].

In recent years, clinical studies using non-invasive cardiac imaging, such as cardiac magnetic resonance with advanced tissue characterization, have provided further insights into myocardial tissue composition in AC. ATTR-AC has been associated with increased extent of amyloid deposition compared to AL-AC; moreover, ATTR-AC has also been associated with higher cardiomyocytes volume, which suggests myocytes hypertrophy [24]. Therefore, LQV is reasonably a "late phenomenon" that develops in full blown ATTR-AC, when significant cardiac involvement has already established.

In clinical practice, patients with early ATTR-AC commonly present with normal or increased QRS voltages, not raising *per se* the suspicion of an infiltrative cardiomyopathy [25,26], and represent the population where the ECG/echo indexes might potentially have the highest impact in raising suspicion of AC and orienting subsequent diagnostic work up.

Results from the present study support the use of two ECG/echo indexes for orienting the diagnostic work-up in suspected AC (Fig. 3):

- When "total QRS score divided by maximum LVWT" is ≥ 7,8 (i.e., index is not satisfied), AC can be ruled out with a NPV of 97 %. In this scenario, the likelihood of AC is extremely low and other diagnoses should be considered.
- When "total QRS score divided by maximum LVWT" is < 7,8 (i.e., index is satisfied), the accuracy for the presence of AC is as high as 82 %. In this scenario, AC should be suspected and patients should undergo dedicated diagnostic work, especially in presence of other suggestive feature AC.
- When low peripheral QRS voltages are found in combination with an IVS ≥ 1,6 cm (modified "Rahman index"), AC can be ruled in with a PPV of 100 %, supporting the decision to perform second-level diagnostic investigations to confirm AC diagnosis.

Although further studies are needed to confirm these findings, dedicated analyses performed after exclusion of AL-AC patients seemed to corroborate the diagnostic accuracy of these indexes for identification of ATTR-AC specifically. External validation of these ECG/echo indexes with the cut-off values identified in this study is required and prospective studies are advocated to assess their clinical impact in orienting diagnostic work up for AC in the real world.

5. Limitations

The size of the cohort included in this analysis was small because of a lower number of patients taking part into the phase 2 of AC-TIVE study (mostly due to the first and second waves of covid-19 pandemic) and the decision to exclude poor-quality ECG recordings to achieve accurate evaluation of ECG/echo indexes. Nevertheless, this is the first real-word study investigating the prevalence and accuracy of different ECG/echo indexes in a population of patients who underwent echocardiogram for unselected clinical reasons and had echocardiographic features suggestive of AC. Of note, the proportion and prevalence of AC, also regarding

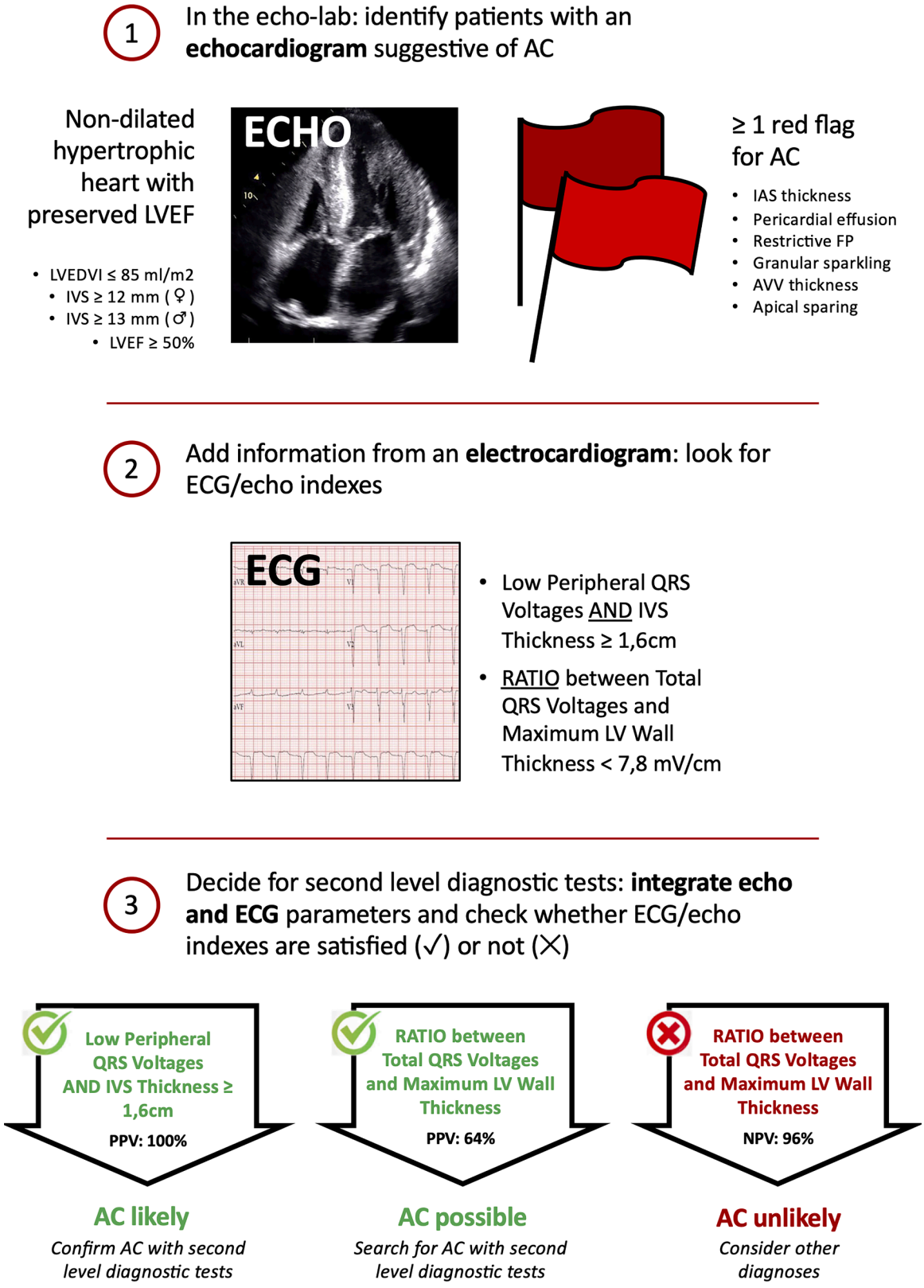


Fig. 4. Case of a female 70-year-old patient diagnosed with AC after enrollment in the ACTIVE study. IVS = 13 mm, presence of low peripheral QRS voltages, modified Rahman index not verified (highly specific index yet with low sensitivity), total QRS score/LVWT positive (= 7,7 mV/mm) (highly sensitive index with moderate specificity). Legend: AC, amyloid cardiomyopathy; ECG, electrocardiogram; echo, echocardiogram; IVS, interventricular septum; LV, Left Ventricle; LVWT, LV wall thickness.

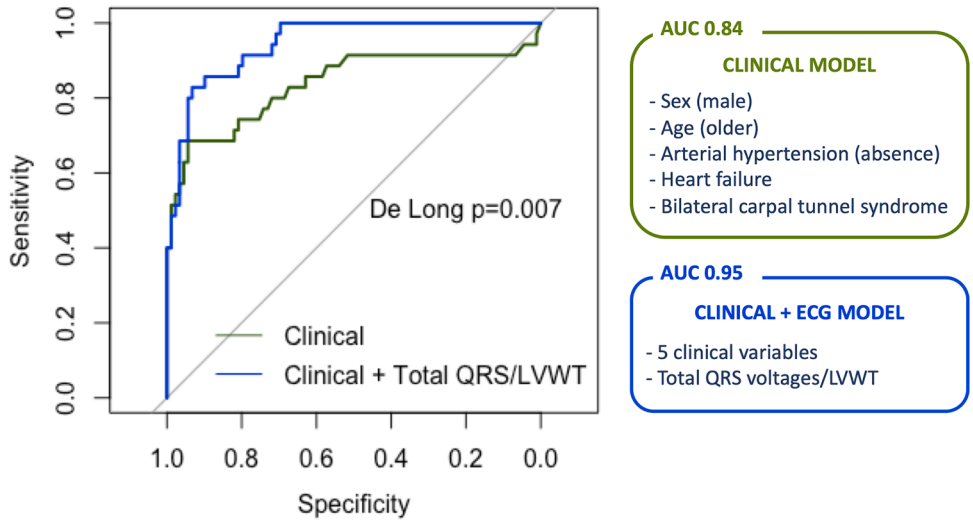


Fig. 5. ROC curves of the clinical model (dark green line, AUC 0,84) and clinical + total QRS score/maximum LVWT model (blue line, AUC 0,93) for AC diagnosis. Legend: AC, amyloid cardiomyopathy; AUC, area under the curve; LV, Left Ventricle; LVWT, LV wall thickness; ROC, receiver operating characteristic curve.

ATTR and AL amyloidosis, was similar to that of the AC-TIVE cohort. Dedicated analyses on AL-AC were not feasible in this study because of the limited number of patients diagnosed with AL-AC. Moreover, our findings are applicable among subjects with non-dilated, hypertrophic LV with normal EF and ≥1 RF of AC and might not be fully generalizable to unselected subjects from the general population. Finally, the evidences herein obtained should be tested in an external validation cohort to verify the robustness of the results.

6. Conclusion

Among subjects older than 55 years with non-dilated, hypertrophic ventricles with preserved LVEF and ≥1 echocardiographic RF of AC, easily-measurable ECG/echo indexes have the ability to enhance or significantly decrease the suspicion of AC. Total QRS score divided by maximum LVWT and low peripheral QRS voltage in combination with IVS ≥ 1,6 cm showed the highest discriminatory accuracy among all available ECG/echo indexes, and might potentially serve as novel tools for ruling out and ruling in AC diagnosis, respectively, especially when integrated to easily-obtainable clinical variables such as age, sex, arterial hypertension, HF and bilateral CTS.

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Data availability statement

No data were generated or analysed for or in support of this paper.

Declaration of Competing Interest

No conflicts of interest to declare for any Author in relation to the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.09.026.

Appendix

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