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RESEARCH LETTER
Cardiovascular Disease

A national survey on prevalence of possible echocardiographic red flags of amyloid cardiomyopathy in consecutive patients undergoing routine echocardiography: study design and patients characterization — the first insight from the AC-TIVE Study

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Raising the suspicion of amyloid cardiomyopathy (AC) is essential to orient additional tests and to achieve an early diagnosis before the development of clinically overt disease.[1,2] Notably, echocardiography is the technique with the greatest potential to raise the suspicion of AC by detecting specific signs ('red-flags') of cardiac infiltration.[3] However, the epidemiology of the echocardiographic red-flags of AC in the general population of patients referred to echocardiography without clinical suspicion of AC and their diagnostic accuracy remain unknown.[4,5]

This is a national, multicentre, prospective cohort study performed in 13 tertiary centres across Italy. The local Regional Institutional Review Board approved the study (identifier 199_2019), and the

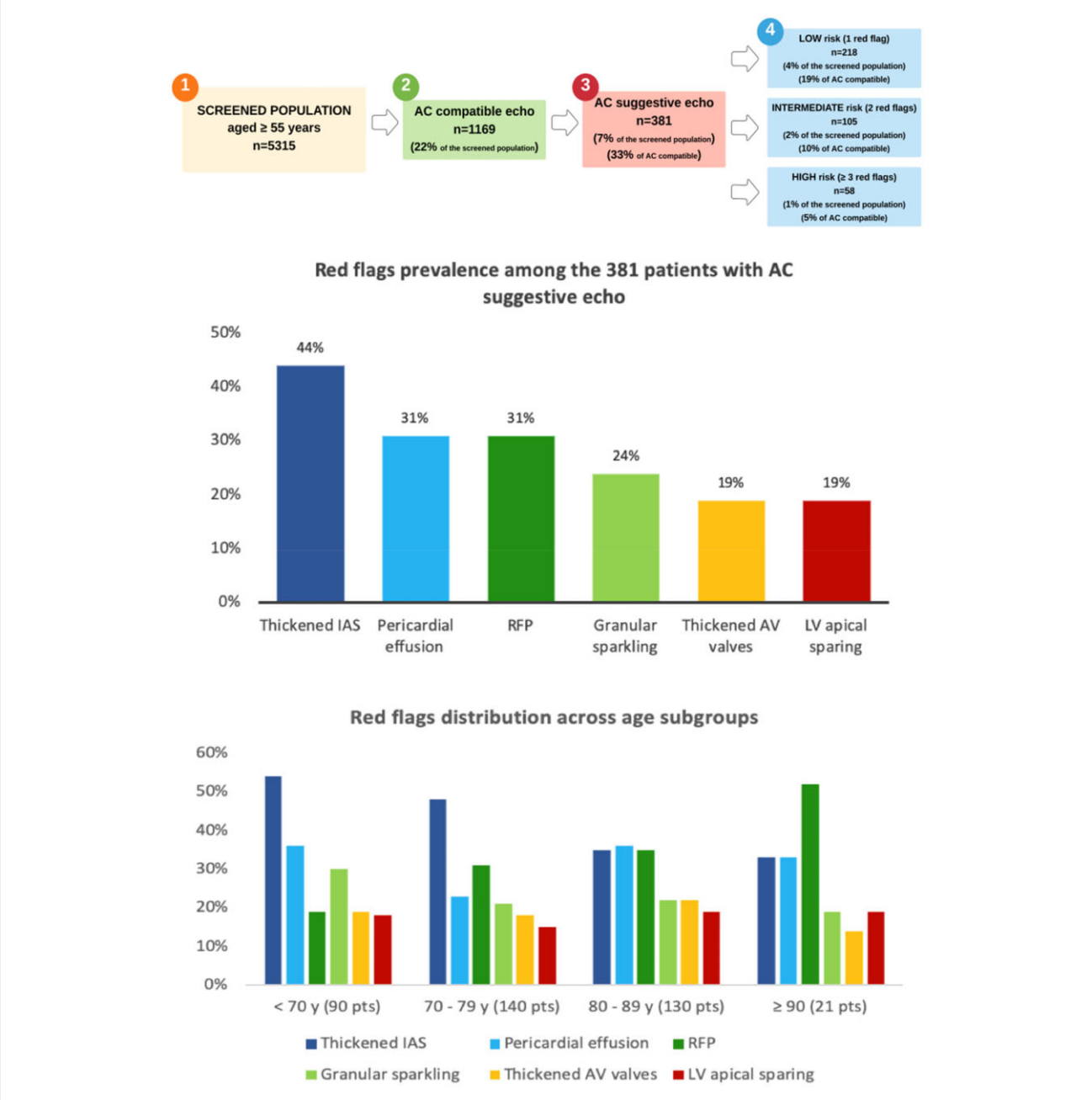

Figure 1 Prevalence of AC-suggestive echocardiograms among screened population (*upper panel*), prevalence of possible echocardiographic red-flags of AC (*middle panel*), and their distribution across age groups (*bottom panel*) in the subgroup of patients with high suspicion of AC. AC, amyloid cardiomyopathy; AV, atrioventricular; LV, left ventricular; IAS, interatrial septum; pts, patients; RFP, restrictive filling pattern; y, years.

participating centres obtained local institutional review board approvals for the collection of prospective anonymous data. The study was registered at ClinicalTrials.gov (#NCT04738266).

The study design consisted of two phases: (i) an observational phase (echocardiographic screening) and (ii) an interventional phase (specific diagnostic work-up for patients with ≥1 echocardiographic red-flags of AC). In this article, we present the study design and the results of phase 1. Phase 2 is ongoing.

All echocardiograms of consecutive inpatients and outpatients aged ≥55 years, performed within 15 consecutive working days, were collected. Patients referred for known or suspected AC, known hypertrophic cardiomyopathy or phenocopies were excluded. AC-compatible echocardiogram was defined as: (i) interventricular septum thickness ≥1.2 cm (women) or ≥1.3 cm (men); (ii) left ventricular (LV) ejection fraction (EF) ≥50%; and (iii) indexed end-diastolic LV volume ≤85 mL/m^2. AC-suggestive echocardiogram was defined as the presence of AC-compatible echocardiogram and at least one of the following red-flags: (i) restrictive filling pattern; (ii) granular sparkling; (iii) pericardial effusion; (iv) interatrial septum (IAS) thickness >0.5 cm; (v) atrio-ventricular (AV) valve thickness >0.5 cm; and (vi) LV apical sparing at speckle-tracking echocardiography.[6] IAS and AV valve thickness was measured from the four-chamber view. AC-suggestive echocardiograms were classified according to the number of echocardiographic red-flags: low (1 red-flag), intermediate (2 red-flags), and high (≥3 red-flags) suspicion of AC. Echocardiographic parameters were measured by the participating centres, according to international guidelines.[7,8]

Descriptive statistics between the study groups were calculated with appropriate statistical tests. A *P*-value <0.05 was considered statistically significant.

Of the 5315 screened echocardiograms, 1169 (22%) exams were AC-compatible. Among them, 381 exams (7.2% of the screened population; 33% of the AC-compatible echocardiograms) were classified as AC-suggestive, of which 218 (57%), 105 (28%), and 58 (15%; 1.1% of the whole population) patients had a low, intermediate, and high suspicion of AC, respectively (*Figure 1*, *upper panel*). The most common clinical indications to echocardiography in AC-suggestive patients were heart failure with preserve ejection fraction (HFpEF) (19.7%), ischaemic heart disease (15.2%), and severe valve disease (12.6%). Indications not included in the list were pooled and

Table 1 Characteristics of the population with suspected echocardiogram for AC, based on the number of suggestive echocardiographic red-flags

Parameters	*N* available	All (*n* ll (ab	1 red-flag (*n* = 218, 57%)	2 red-flags (*n* = 105, 28%)	≥3 red-flags (*n* = 58, 15%)	*P*-value	*P*-value[a]
Age, years	381	77 (70–83)	78 (70–83)	78 (71–83)	76 (68–84)	0.607	0.356
Men, %	381	191 (50%)	106 (49%)	49 (47%)	36 (62%)	0.135	**0.048**
HF, %	381	75 (19.7%)	37 (17%)	19 (18%)	19 (33%)	**0.024**	**0.007**
IVS, mm	381	13 (13–15)	14 (13–15)	13 (13–14)	14 (13–15)	0.192	0.537
IVS max, mm	381	14 (13–15)	14 (13–15)	13 (13–14)	15 (13–15)	0.063	0.427
EDVi, mL/m^2	358	51 (43–59)	49 (41–59)	52 (45–61)	52 (47–58)	**0.044**	0.124
E/*E*′	311	14 (10–18)	11 (8–17)	12 (10–18)	15 (12–19)	**0.002**	**0.017**
LVEF, %	381	59 (55–64)	61 (55–65)	55 (55–60)	55 (50–55)	**<0.001**	**<0.001**
RV dysfunction, %	370	35 (10%)	10% (20/209)	9% (9/104)	11% (6/57)	0.924	0.765
RV wall thickness, mm	227	7 (5–9)	5 (4–8)	6 (4–8)	8 (7–10)	**<0.001**	**<0.001**
LA diameter, mm	342	42 (37–47)	43 (38–50)	42 (38–46)	39 (36–43)	**<0.001**	**<0.001**
Moderate–severe valve disease, %	373	174 (47%)	47% (99/210)	47% (49/105)	45% (26/58)	0.952	0.762
Mitral regurgitation, %	172	82 (48%)	34% (33/97)	67% (33/49)	62% (16/26)	**<0.001**	0.124
Tricuspid regurgitation, %	173	56 (32%)	29% (28/98)	39% (19/49)	35% (9/26)	0.444	0.791
Aortic regurgitation, %	172	32 (19%)	14% (14/98)	25% (12/49)	23% (6/26)	0.262	0.514
Pulmonary regurgitation, %	173	4 (2%)	3% (3/98)	2% (1/49)	0% (0/26)	0.646	0.395
Mitral stenosis, %	173	4 (2%)	4% (4/98)	0% (0/49)	0% (0/26)	0.209	0.395
Aortic stenosis, %	174	80 (46%)	55% (54/99)	37% (18/49)	31% (8/26)	**0.030**	0.092
SPAP > 35 mmHg, %	337	139 (41%)	52% (93/180)	33% (33/100)	23% (13/57)	**<0.001**	**<0.001**
SPAP, mmHg	337	35 (28–44)	36 (30–46)	31 (27–42)	30 (25–35)	**0.003**	**0.030**
IVC > 21 mm, %	330	38 (12%)	13% (24/180)	10% (9/93)	9% (5/57)	0.519	0.476
IVC, mm	331	16 (13–18)	15 (12–18)	16 (13–18)	17 (15–20)	**0.026**	**0.009**

In detail, RV systolic dysfunction was defined as a tricuspid annular plane systolic excursion <0.7 cm, or, in absence of this information, a RV fractional area change <35%.
AF, atrial fibrillation; AV, atrioventricular; EDVi, end-diastolic volume indexed; HF, heart failure; IAS, interatrial septum; IVC, inferior vena cava; IVS, interventricular septum; LA, left atrium; LVEF, left ventricular ejection fraction; RFP, restrictive filling pattern; RV, right ventricle; SPAP, systolic pulmonary artery pressure. Boldface values identify statistically significant findings.
[a]*P*-value, comparison between patients with ≤2 red flags vs. ≥3 red flags.

accounted for 15.7% of cases. The baseline characteristics of the patients with AC-suggestive echocardiograms are summarized in *Table 1*.

Thickened IAS ($n = 169$, 44%) was the most frequent echocardiographic red-flag, followed by pericardial effusion ($n = 118$, 31%) and restrictive LV filling pattern ($n = 117$, 31%), granular sparkling appearance of the myocardium ($n = 90$, 24%), thickened AV valves ($n = 74$, 19%), and apical sparing pattern upon speckle-tracking analysis (66 out of 341 patients with available data, 19%). A similar prevalence of echocardiographic red-flags of AC was found in the subgroup with a high suspicion of AC (*Figure 1*, *middle panel*). Of note, the apical sparing pattern was found in 29%, 30%, and 41% of the patients with low, intermediate, and high AC suspicion, respectively. *Figure 1*, *bottom panel* shows the prevalence of echocardiographic red-flags according to age groups (<70 years, 70–79 years, 80–89 years, ≥90 years). The prevalence of thickened IAS decreased with ageing, and the prevalence of the restrictive LV filling pattern increased with ageing.

Compared to the other patients, the 58 patients with high echocardiographic AC suspicion were more frequently men (62% vs. 48%, in the high and non-high AC suspicion patients, respectively, $P = 0.048$); they presented more frequently with HFpEF (33% vs. 17%, $P = 0.007$), had a higher E/E' ratio [15 (11–18) vs. 10.5 (8–17), $P = 0.017$], a larger left atrial diameter and a thicker right ventricular wall [0.8 cm (0.7–1.0) vs. 0.6 cm (0.4–0.8), $P < 0.001$]. The distribution across age and the prevalence of valve diseases were similar among the patients with a high echocardiographic AC suspicion and the other patients (see *Table 1*).

To the best of our knowledge, this is the first report on the prevalence of possible echocardiographic red-flags of AC in a consecutive contemporary cohort of subjects undergoing clinically indicated echocardiography without any pre-test suspicion of AC. The present study is the largest mass screening campaign that measured the proportion of subjects with low, intermediate, and high echocardiographic suspicion of AC.

The main findings of the present study can be summarized as follows: (i) more than 7% of patients ≥55 years of age undergoing clinically-indicated echocardiography and 33% of patients with non-dilated, hypertrophic LV with preserved EF have echocardiographic red-flags of AC; (ii) patients with a high echocardiographic suspicion of AC (≥3 red-flags) represent 1% of patients ≥55 years of age undergoing clinically-indicated echocardiography and 5% of patients with AC-compatible echocardiograms; (iii) patients with highly AC-suggestive echocardiograms are more frequently referred to echocardiographic laboratories due to HFpEF; and (iv) thickened IAS is the most frequent possible echocardiographic red-flag of AC.

In light of the recent availability and effectiveness of specific therapies (such as tafamidis for transthyretin AC), and regardless of the final AC prevalence (which will be tested in phase 2 of this study), our results suggest the need to modify the current approach of echocardiographic laboratories in order to systematically focus on recognizing AC red-flags (in isolation or in combination).[9] Therefore, increasing awareness of amyloidosis and maintaining a cardiomyopathy-oriented interpretation of echocardiographic images are essential steps to achieve an early AC diagnosis as the benefits from specific therapy initiation are highest in the initial stages of this disease.[1,9] The echocardiographic laboratory should act as the crossroad between outpatient clinics of the territory and hospital wards, by playing a fundamental role in screening patients, raising the suspicion of AC and orienting diagnostic work-up.[9,10]

Data Availability Statement

The data underlying this article cannot be shared publicly as these results come from a currently ongoing study and for privacy laws on multicenter datasets. The data will be shared on reasonable request to the corresponding author.

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