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Clinical phenotypes of severe atrial cardiomyopathy and their outcome: A cluster analysis

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ABSTRACT

Background: Atrial cardiomyopathy (AtCM) encompasses patients with diverse demographics and comorbidities. This study aimed to identify phenotype groups with similar clinical characteristics, compare their mortality and atrial fibrillation (AF) event rates, and assess predictors of mortality.

Methods and Results: We performed a hierarchical cluster analysis using Ward's Method, based on 11 clinical variables. Among 724 consecutive patients with a dilated left atrium (LA), only 196 met the criterion for severe AtCM- defined as a dilated LA with a volume index $\geq$ 50 ml/m2. We identified 4 clusters: Cluster 1 –younger overweight patients with paroxysmal AF; Cluster 2 –older patients with heart failure (HF) and low BMI; Cluster 3 – diabetic patients with HF; and Cluster 4 – older patients with tachycardia-bradycardia syndrome and implanted pacemakers. Over a median follow-up of 20.6 months, Cluster 2 had the highest mortality rate (29.1 %), followed by Cluster 3 (20.6 %), compared to Clusters 1 and 4 (11.4 % and 10.8 %, respectively, $p = 0.045$). For AF events, Cluster 1 had the highest incidence (37 %), followed by Cluster 3 (35 %), Cluster 2 (24 %), and Cluster 4 (19 %, $p = 0.309$). Heart failure (HR 4.4, CI 1.5–12.7, $p = 0.006$), cancer (HR 3.3, CI 1.6–6.9, $p = 0.002$), and severe tricuspid regurgitation (HR 5.4, CI 2.6–11.3, $p < 0.001$) were predictors of poor outcomes.

Conclusion: In severe AtCM patients, four clusters were identified, each with unique comorbidities and mortality rates but similar AF event rates. Clinical and echocardiographic factors were linked to higher mortality risk.

1. Introduction

Atrial cardiomyopathy (AtCM) is a relatively new term encompassing structural and functional changes in the atria that can lead to arrhythmias and/or heart failure, in the absence of significant valvular or ventricular dysfunction. Several comorbidities are believed to play a significant role in atrial remodeling, including atrial fibrillation (AF), arterial hypertension, diabetes mellitus, obesity, obstructive sleep apnea, and aging. Additionally, structural and functional changes in the atria can result from conditions such as congestive heart failure, valvular diseases, cardiac amyloidosis, genetic disorders, and myocarditis [1,2]. There is also emerging evidence suggesting a possible relationship between ACM and cancer.

AtCM affects patients with diverse demographics, clinical characteristics, and comorbidities. Identifying phenotype groups with similar clinical characteristics is crucial for effective treatment, prognosis, and prevention of AtCM.

Cluster analysis, a data-driven approach commonly used in various research fields, measures differences between individual cases based on their characteristics and identifies clusters of similar patients. This method groups patients with similar properties and can uncover meaningful phenotypes within heterogeneous diseases [3]. Cluster phenotyping has been successfully applied in heart failure [4–6], chronic obstructive pulmonary disease [7], pulmonary arterial hypertension [8], and, more recently, atrial fibrillation [9–11].

Our study aims to determine whether cluster analysis can identify clinically relevant groups among severe AtCM patients and whether these clusters are associated with a different prognosis. This effort represents an initial step toward precision medicine in managing AtCM.

2. Methods

2.1. Study population

We included consecutive patients with severe atrial cardiomyopathy hospitalized in our Cardiology clinic from September 2020 to May 2023.

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Severe atrial cardiomyopathy was defined as a severely dilated left atrium (LA) with a volume index (LAVI) $\geq$ 50 ml/m^2, preserved left ventricular (LV) systolic function (ejection fraction $\geq$ 50 %), and no significant primary valvular or ventricular disease.

Our study was a prospective cohort study. Exclusion criteria were the presence of ventricular cardiomyopathy (dilated, hypertrophic, or infiltrative), moderate or severe left ventricular hypertrophy (interventricular septum and posterior wall thickness of LV $>$ 13 mm), primary valvular disease, acute coronary syndrome, pulmonary embolism, congenital heart disease, and constrictive pericarditis. Patients with pacemakers and cancer who did not meet these exclusion criteria were included in the study.

Demographic and clinical data were extracted from the hospital database and included age, sex, blood pressure, heart rate, smoking status, body mass index (BMI), and the presence of comorbidities (atrial fibrillation, heart failure, arterial hypertension, diabetes mellitus, obesity, obstructive sleep apnea, coronary artery disease, sinus node dysfunction (SND) or atrioventricular (AV) block, pacemaker, stroke, cancer) as well as current medications. Laboratory data collected included hemoglobin, creatinine levels, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and C-reactive protein (CRP). Estimated glomerular filtration rate (eGFR) was calculated using the 2021 CKD-EPI Creatinine formula. The CHA2DS2-VASc score was also calculated for each patient.

All patients underwent comprehensive two-dimensional echocardiography on a Philips Epiq 7C machine with a Matrix X5-1 transducer. The echocardiography included volumetric and speckle tracking analysis, performed by a single operator. A total of 32 echocardiographic parameters were analyzed, including strain measurements of the left and right atrium, and left and right ventricle. Measurements followed the European Association of Cardiovascular Imaging's recommendations for cardiac chamber quantification [12]. Strain analysis was conducted offline using TomTec software (Minnesota, USA 2021).

2.2. Outcome and follow up

The primary outcome of the study was all-cause mortality. Cardiovascular death was defined as death directly related to cardiovascular disease, including congestive heart failure (CHF), sudden death, or stroke. The secondary endpoint was the occurrence of AF events, which included episodes of paroxysmal AF or symptomatic persistent AF (such as fast-rate persistent AF and, occasionally, slow AF that necessitated medical attention). Data on the progression from paroxysmal to persistent AF were also gathered. The patients were followed for a median of 20.6 months, with follow-up conducted via clinic visits or telephone calls to assess the occurrence of the primary outcome. In cases where direct contact with patients was not possible, information was obtained from their relatives or verified through the National Health Institute of Bulgaria.

2.3. E**thics Approval

The study was approved by the Ethics Committee of Research in Bulgaria and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent before participating in the study.

2.4. Cluster and statistical analysis

We performed hierarchical cluster analysis using Ward's minimum variance method to minimize total within-cluster variance. Only dichotomous variables were selected for this analysis. Ward's method calculates the distance between clusters, where a cluster may be an individual patient or a group of patients, based on squared Euclidean distance. Clusters are merged if their distance is sufficiently small; otherwise, a new grouping is started, and the process continues. The goal was to identify the optimal number of clusters that are homogenous and clinically relevant for AtCM patients, without prior knowledge of outcomes.

For selecting variables for the clustering, we focused on identifying relevant clinical phenotypes of AtCM. Specifically, we selected clinical variables associated with the most common etiological factors for AtCM. Additionally, we conducted Chi-square tests to assess significant relationships between the variables and the clusters and included the relevant binary variables in the cluster analysis. A priori, we selected 11 clinical variables: hypertension, diabetes mellitus, heart failure, obesity, obstructive sleep apnea, cancer, coronary artery disease, sinus node dysfunction or atrioventricular block, implanted pacemaker, ischemic stroke, and atrial fibrillation. We excluded variables such as sex and age to focus on clinical factors rather than demographic ones. Concomitant medications were also excluded to avoid bias related to treatment indications. All variables were treated as categorical (present or absent).

To determine the optimal number of clusters, we first applied K-means clustering using the Elbow method. Based on the results, we selected the optimal number of clusters and then performed hierarchical clustering using this number. The dendrogram was used to visually confirm our choice. We found that the 4-cluster model revealed clearer patterns among patient groups, which we adopted for further analysis (Fig. 1).

Continuous variables were reported as mean and standard deviation. Differences across clusters were assessed using one-way analysis of variance (ANOVA) or Kruskal-Wallis one-way ANOVA, as appropriate. Categorical variables were presented as counts and percentages, with differences evaluated using the chi-squared test or Fisher's exact test when applicable.

Mortality differences between the clusters, along with differences in AF events, were analyzed using the log-rank test and depicted with Kaplan-Meier curves. To investigate the association between cluster phenotypes, mortality, and AF events, Cox regression analysis was performed. Multivariable Cox regression was then used to identify predictors of mortality.

All analyses were conducted using IBM SPSS Statistics Version 30.0. Statistical significance was determined at a 2-sided p-value $<$ 0.05.

3. Results

Of 724 consecutive patients with a dilated left atrium, only 196 met the criteria for severe atrial cardiomyopathy. The mean age of the participants was 73.98 $\pm$ 9.82 years (range 46–100), and 58 % were women. Hypertension was present in 93 % of the patients, diabetes in 26 %, AF in 79 %. 59 % had heart failure, 20 % had cancer, and 23 % were with SND or AV block. The mean LV ejection fraction was 56.1 $\pm$ 5.0 %, and the mean LAVI was 55.2 $\pm$ 7.1 mL/m^2. The analysis identified four clusters of patients with similar clinical characteristics.

Baseline clinical characteristics, medications, and echocardiographic parameters across the four clusters are compared and presented in Tables 1, 2, and 3.

3.1. Demographic and clinical characteristics of the clusters, and their treatment

Cluster 1 (n = 70, 36 %): Younger overweight patients with paroxysmal atrial fibrillation. This was the largest cluster, with the lowest mean age (71.8 $\pm$ 9.1 years) and 61 % women. All patients had hypertension, 58 % were obese, and 70 % were either obese or overweight. The mean BMI was 30.4 $\pm$ 5.6 kg/m^2, and 21 % of the patients had obstructive sleep apnea (OSA). This cluster had the highest percentage of paroxysmal AF, the lowest percentage of CHF, and the lowest CHA2DS2-VA score (2.8 $\pm$ 1.3) compared to the other clusters. In terms of treatment, this group had the lowest percentage of diuretic use.

Cluster 2 (n = 55, 28 %): Older patients with CHF and low BMI. This cluster included patients with a mean age of 76.1 $\pm$ 11.3 years, 65

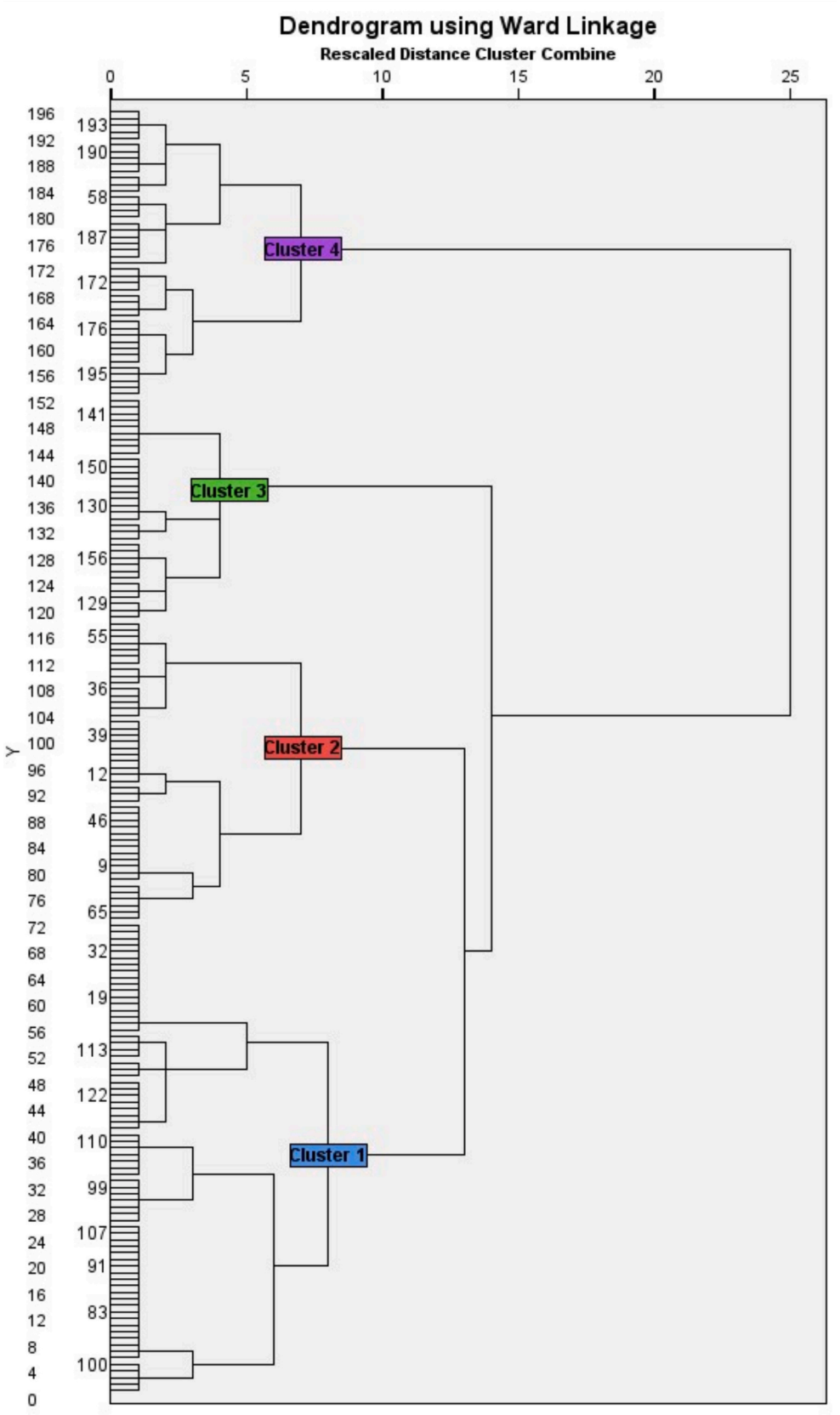

Fig. 1. Dendrogram showing 4 main clusters, generated by hierarchical clustering. The dendrogram depicts the relative degree of similarity between individual patients.

Table 1
Baseline characteristics of patients stratified by clusters.

	Cluster 1 (n = 70) Younger, Overweight, with Paroxysmal AF	Cluster 2 (n = 55) Old patients with CHF and low BMI	Cluster 3 (n = 34) Diabetes with CHF	Cluster 4 (n = 37) Old patients with pacemakers	p-Value (Among Groups)
Age (years)	71.8 ± 9.1*	76.1 ± 11.3*	72.6 ± 10.0	76.2 ± 7.2*	0.36
Female sex (%)	61**	65**	62**	38	0.46
Hypertension (%)	100	93	91	78	<0.001
Diabetes mellitus, type 2 (%)	10	5	100	19	<0.001
CHF (%)	43	69	88	51	<0.001
Obesity (%)	58	3	35	13	<0.001
Overweight and obesity (%)	70	5	38	19	<0.001
OSA (%)	21	4	3	8	0.003
Cancer (%)	10***	29***	26***	19	0.42
CAD (%)	9	9	18[a]	3[a]	0.188
SND or AV block (%)	14	0	0	100	<0.001
Pacemaker (%)	1	0	0	78	<0.001
Stroke (%)	3	29	3	35	<0.001
AF (%)	77	76	79	84	0.839
Paroxysmal AF (%)	40[b]	27	18[b]	22[b]	0.063
Persistent AF (%)	39[d]	49	62[d]	62[d]	0.051
CHA2DS2-VA	2.8 ± 1.3	3.8 ± 1.5	4.4 ± 1.2	3.8 ± 1.2	< 0.001
BMI (kg/m2)	30.4 ± 5.6	24.2 ± 3.7	28.4 ± 5.4	25.9 ± 3.4	<0.001
Smoking (%)	39	27	32	24	0.402
SBP mmHg	127 ± 18[e]	128 ± 21[e]	136 ± 15[e]	128 ± 17	0.094
DBP mmHg	78 ± 11	79 ± 12	82 ± 10	78 ± 11	0.340
HR	72 ± 15[g]	76 ± 13	82 ± 18[g]	71 ± 18[g]	0.013
CRP (mg/dl)	1.7 ± 0.4	1.3 ± 0.4	1.8 ± 0.6	1.4 ± 0.4	0.871
Hemoglobin (g/l)	133.6 ± 18.6	128.8 ± 17.5	126.4 ± 16.9[k]	136.8 ± 26.1[k]	0.091
Creatinine (mcmol/l)	91.4 ± 26.2	95.8 ± 36.4	96.3 ± 15.0	96.7 ± 32.8	0.860
eGRF (ml/min/1.73 m2)	68.7 ± 20.7	65.6 ± 21.9	63.8 ± 20.2	70.0 ± 23.3	0.561
NT-proBNP (pg/ml)	1 504.0 ± 563.4	2 489.9 ± 754.2	3 134.2 ± 1 670.3	937.2 ± 191.0	0.428

AF- atrial fibrillation, CAD- coronary artery disease, CHF- congestive heart failure, OSA- obstructive sleep apnea, CRP- C-reactive protein, NT-proBNP- N-terminal pro-B-type natriuretic peptide, SND- sinus node dysfunction

*The mean difference is significant at the 0.05 level between clusters 1 and 2 (p = 0.015), 1 and 4 (p = 0.027).

** The mean difference is significant at the 0.05 level between clusters 1 and 4 (p = 0.018), 2 and 4 (p = 0.008), and 3 and 4 (p = 0.04).

*** The mean difference is significant at the 0.05 level between clusters 1 and 2 (p = 0.008), 1 and 3 (p = 0.047).

[a]The mean difference is significant at the 0.05 level between clusters 3 and 4 (p = 0.03).

[b]The mean difference is significant at the 0.05 level between clusters 1 and 3 (p = 0.019), and 1 and 4 (p = 0.048).

[d]The mean difference is significant at the 0.05 level between clusters 1 and 3 (p = 0.026), and 1 and 4 (p = 0.020).

[e]The mean difference is significant at the 0.05 level between clusters 1 and 3 (p = 0.016), and 2 and 3 (p = 0.035).

[g]The mean difference is significant at the 0.05 level between clusters 1 and 3 (p = 0.005), and 3 and 4 (p = 0.004).

[k]The mean difference is significant at the 0.05 level between clusters 3 and 4 (p = 0.031).

Table 2
Medications taken according to clusters.

	Cluster 1 (n = 70) Younger, Overweight, with Paroxysmal AF	Cluster 2 (n = 55) Old patients with CHF and low BMI	Cluster 3 (n = 34) Diabetes with CHF	Cluster 4 (n = 37) Old patients with pacemakers	p-Value (Among Groups)
Diuretics (%)	41	65	85	51	<0.001
ACEi/ARB (%)	74	51	85	51	<0.001
B-blocker (%)	76	87	91	59	0.003
Statin (%)	30	29	65	16	<0.001
MRA (%)	26	42	56	19	0.002
SGLT2i (%)	10	5	44	11	<0.001
Digoxin (%)	17	13*	29*	11*	0.142
Antiarrhythmic drug (%)	36**	21	17**	19	0.093
Anticoagulation (%)	71	67	76	76	0.756
Anticoagulation- DOAC (%)	60	54	56	70	0.474
Anticoagulation- Vitamin K antagonist (%)	11	13	18	5	0.445

ACEi/ARB- angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, DOAC- direct oral anticoagulants, MRA- mineralocorticoid receptor antagonists, SGLT2i- sodium-glucose cotransporter-2 inhibitor.

*The mean difference is significant at the 0.05 level between clusters 2 and 3 (p = 0.042), and 3 and 4 (p = 0.037).

**The mean difference is significant at the 0.05 level between clusters 1 and 3 (p = 0.044).

Table 3
Echocardiographic characteristics according to clusters.

	Cluster 1 (n = 70) Younger, Overweight, with Paroxysmal AF	Cluster 2 (n = 55) Old patients with CHF and low BMI	Cluster 3 (n = 34) Diabetes with CHF	Cluster 4 (n = 37) Old patients with pacemakers	p-Value (Among Groups)
LV EF (%)	56.9 ± 4.7	55.9 ± 4.6	55.5 ± 4.8	55.6 ± 6.2	0.433
GLS LV (%)	−16.8 ± 3.3*	−15.8 ± 4.0	−14.9 ± 4.3*	−15.8 ± 3.8	0.107
E/e′ m	13.5 ± 4.4	14.3 ± 5.2	16.4 ± 5.2	14.0 ± 4.9	**0.047**
E/e′ l	10.9 ± 3.4	11.3 ± 3.8	13.6 ± 3.8	11.1 ± 3.8	**0.005**
RVFWLS (%)	−21.2 ± 5.6**	−18.8 ± 6.5**	−20.1 ± 5.4	−19.7 ± 5.8	0.144
RVGLS (%)	−17.6 ± 6.0	−16.5 ± 5.1	−17.4 ± 4.5	−15.7 ± 7.6	0.387
LAVI ml/m2	54.0 ± 5.1	57.5 ± 9.1	54.5 ± 6.2	55.3 ± 8.9	0.533
LASr (%)	19.8 ± 9.6	15.9 ± 8.5	15.0 ± 9.7	15.0 ± 7.1	**0.011**
LAScd (%)	−13.3 ± 5.3	−10.7 ± 6.0	−10.8 ± 5.1	−10.9 ± 3.8	**0.018**
LASct (%)	−6.5 ± 5.9	−4.8 ± 4.6	−4.1 ± 5.3	−4.1 ± 4.9	0.054
RAVI ml/m2	34.8 ± 15.7	35.7 ± 14.9	34.5 ± 12.9	40.2 ± 14.9	0.610
RASr (%)	20.2 ± 9.8	18.3 ± 10.6	18.8 ± 10.1	16.5 ± 7.6	0.486
RAScd (%)	−13.6 ± 7.5	−12.2 ± 6.5	−11.0 ± 9.3	−12.4 ± 4.3	0.532
RASct (%)	−5.2 ± 5.5	−6.3 ± 5.2	−5.6 ± 5.5	−4.0 ± 4.2	0.420
PASP mmHg	39.9 ± 14.6	40.8 ± 13.4	41.9 ± 11.1	38.4 ± 13.5	0.714
MR > mild (%)	31	45	35	30	0.337
Severe MR (%)	3	4	0	3	0.762
TR > mild (%)	34***	53***	50	54***	0.110
Severe TR (%)	17	24	23	19	0.789

E/e′ m – E/e′ ratio of medial mitral annulus, E/e′ l – E/e′ ratio of lateral mitral annulus, GLS LV- global longitudinal strain of left ventricle, LAVI – left atrium volume index, LASr – left atrial reservoir strain, LAScd- left atrial conduit strain, LASct- left atrial contractile strain, LV EF- left ventricular ejection fraction, MR-mitral regurgitation, PASP – pulmonary artery systolic pressure, RAVI- right atrium volume index, RASr- right atrial reservoir strain, RAScd – right atrial conduit strain, RASct – right atrial contractile strain, RVFWLS- right ventricular free wall longitudinal strain, RVGLS- right ventricular global longitudinal strain, TR- tricuspid regurgitation

* The mean difference is significant at the 0.05 level between clusters 1 and 3 (p = 0.017).

** The mean difference is significant at the 0.05 level between clusters 1 and 2 (p = 0.022).

*** The mean difference is significant at the 0.05 level between clusters 1 and 2 (p = 0.04), and clusters 1 and 4 (p = 0.05).

% of whom were women. Sixty nine percent had CHF, and this group had the highest percentage of cancer (29 %) and the lowest mean BMI (24.2 ± 3.7 kg/m^2). The percentage of stroke was also high (29 %). Despite the presence of AF in 76 % of the patients, this cluster had the lowest percentage of anticoagulant use (67 %).

Cluster 3 (n = 34, 17 %): Diabetic patients with CHF. This cluster included patients with a mean age of 72.6 ± 10.0 years, with 62 % of whom being women. All patients had diabetes, 35 % were obese, and the mean BMI was 28.4 ± 5.4 kg/m^2. This cluster had the highest prevalence of CHF (88 %) and coronary artery disease (CAD) (18 %), and 26 % had cancer. This was the cluster with the highest CHA2DS2-VA score (4.4 ± 1.2). It was characterized by the highest values of systolic blood pressure (136 ± 15 mmHg), heart rate (82 ± 18 bpm), and NT-proBNP (3,134.2 ± 1,670.3 pg/ml). This cluster also had the highest percentages of treatment with diuretics, mineralocorticoid receptor antagonists (MRA), beta-blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB), and sodium-glucose cotransporter-2 inhibitors (SGLT2i), as well as digoxin.

Cluster 4 (n = 37, 19 %): Older patients with tachycardia-bradycardia syndrome and implanted pacemakers. This cluster included patients with a mean age of 76.2 ± 7.2 years, with a majority being men (62 %). All patients had sinus node dysfunction or AV block, and 78 % had implanted pacemakers. This cluster had the lowest prevalence of hypertension (78 %) and the highest percentages of permanent AF (62 %) and stroke (35 %). It was characterized by the lowest NT-proBNP levels (937.2 ± 191.0 pg/ml) and had the lowest rates of treatment with beta-blockers, ACEi/ARB, MRA, statins, and digoxin.

3.2. Echocardiographic characteristics of the clusters

Patients in **Cluster 1** had the highest values of global longitudinal strain (GLS) of the left ventricle (−16.8 ± 3.3 %) and of the free wall longitudinal strain of the right ventricle (RVFWLS) (−21.2 ± 5.6 %), as well as the lowest E/e' ratio. They also exhibited the lowest LAVI and right atrial volume index (RAVI) values, with the highest peak strain of the LA and right atrium (RA) (19.8 ± 9.6 % and 34.8 ± 15.7 %, respectively). Additionally, this cluster had the lowest rate of more than mild tricuspid regurgitation.

Patients in **Cluster 2** had the lowest RVFWLS (−18.8 ± 6.5 %) and the largest volume of the left atrium (mean LAVI: 57.5 ± 9.1 ml/m^2). This cluster also had the highest percentages of more than mild mitral and tricuspid regurgitation (45 % and 53 %, respectively).

Cluster 3 was characterized by the lowest GLS of the left ventricle (−14.9 ± 4.3 %), the highest E/e' ratio at the medial and lateral mitral annulus (16.4 ± 5.2 and 13.6 ± 3.8, respectively), and the highest estimated by echocardiography pulmonary artery systolic pressure (41.9 ± 11.1 mmHg).

Patients in **Cluster 4** had the largest right atrium, with a mean RAVI of 40.2 ± 14.9 ml/m^2, and the lowest peak RA strain (16.5 ± 7.6 %). This cluster also had a high prevalence of more than mild tricuspid regurgitation (54 %).

Phenotype groups are schematically presented in Fig. 2.

3.3. Clusters and mortality risk

During a median follow-up of 20.6 ± 9.6 (range 1–39) months, 35 deaths were recorded. Cluster 2 had the highest mortality rate at 29.1 % (16 deaths), followed by Cluster 3 with a mortality rate of 20.6 % (7 deaths). Clusters 1 and 4 had significantly lower mortality rates, at 11.4 % and 10.8 %, respectively. Kaplan–Meier curves illustrating the differences in mortality incidence among the clusters are presented in Fig. 3, with a log-rank test showing a statistically significant difference in mortality rates between clusters (p = 0.045).

Multivariable Cox proportional hazards regression analysis revealed that the following factors were strongly associated with mortality: the presence of heart failure (Hazard Ratio [HR] = 4.4, 95 % Confidence Interval [CI] 1.5 ÷ 12.7, p = 0.006), the presence of cancer (HR = 3.3, 95 % CI 1.6 ÷ 6.9, p = 0.002), and the presence of severe tricuspid regurgitation (HR = 5.4, 95 % CI 2.6 ÷ 11.3, p < 0.001).

Regarding the impact of AF pattern on mortality, the presence of paroxysmal AF was associated with a lower mortality risk (HR = 0.39, 95 % CI 0.21 ÷ 0.99, p = 0.05) compared to persistent AF, which was linked to an increased risk, although without reaching statistical significance (HR = 1.6, 95 % CI 0.9 ÷ 3.1, p = 0.085). In the multivariable

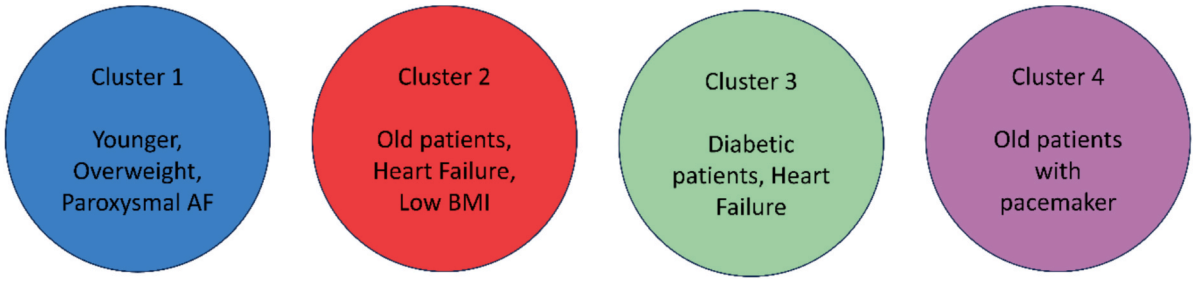

Fig. 2. Clinical phenotypes of atrial cardiomyopathy.

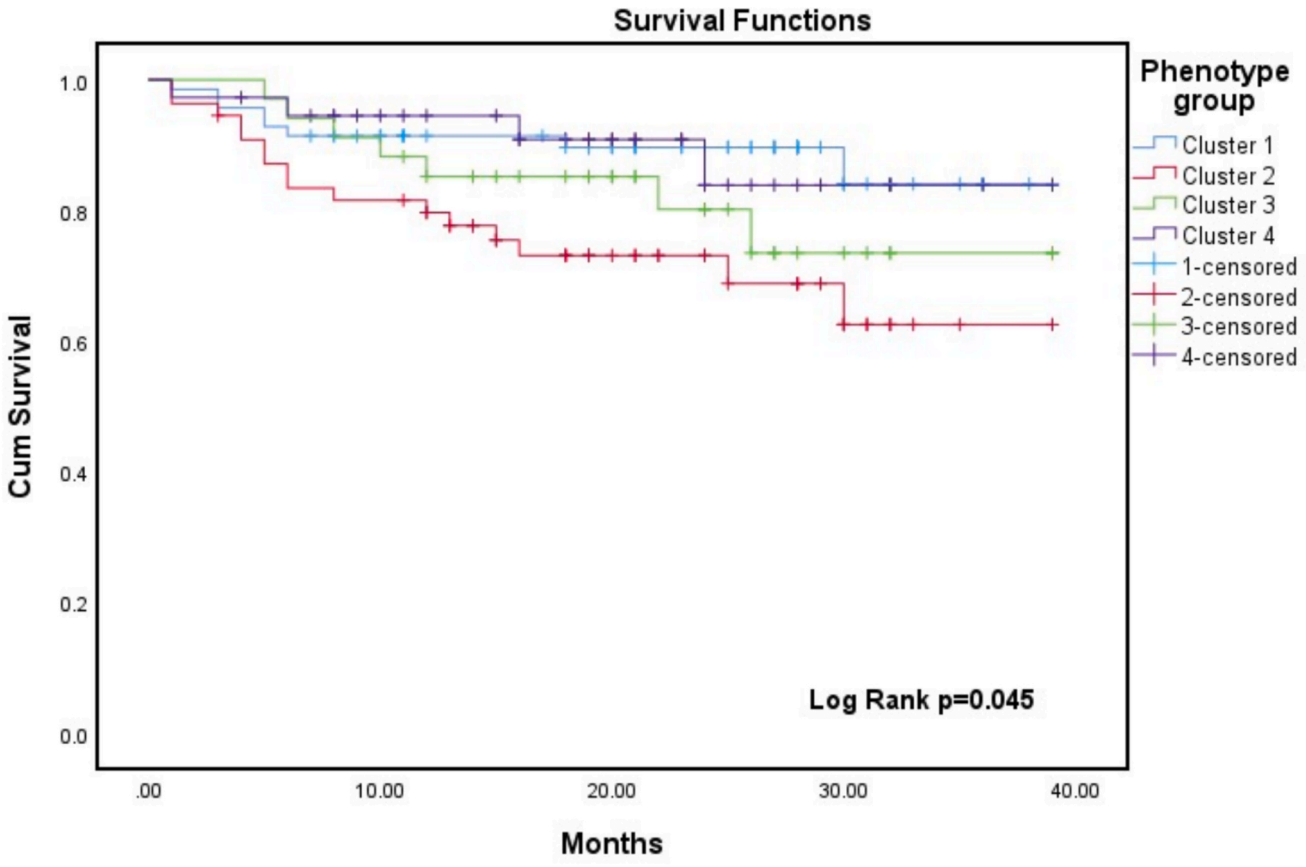

Fig. 3. Kaplan-Meier curves present different mortality rates between cluster 1 to 4 (log-rank test p = 0.045).

model, the CHA2DS-VASc score did not have a statistically significant impact on mortality (HR = 1.2, 95 % CI 0.9 ÷ 1.5, p = 0.228) in patients with severe AtCM.

3.4. Clusters and AF events

During the follow-up, 58 symptomatic AF events were recorded. Cluster 1 had the highest incidence of AF events at 37 % (26 events), primarily due to episodes of paroxysmal AF, followed closely by Cluster 3 at 35 % (12 events), mainly due to symptomatic fast-rate persistent AF episodes. In Cluster 2, the cumulative incidence of AF events was 24 % (13 events), primarily due to fast-rate AF episodes. Cluster 4 had the lowest AF event rate, with 19 % (7 events). Kaplan–Meier curves illustrating the differences in cumulative incidence of AF events among the clusters are presented in Fig. 4, with a log-rank test showing no statistically significant difference in AF event rates between the clusters (p = 0.309).

When progression from paroxysmal to persistent AF was studied among the clusters, 9 % of patients in Cluster 1 progressed to persistent AF, 5 % in Cluster 2, 14 % in Cluster 3, and 5 % in Cluster 4 (p = 0.417).

4. Discussion

To our knowledge, this is the first study employing cluster analysis specifically for patients with atrial cardiomyopathy, distinguishing it from previous studies that focused primarily on atrial fibrillation patients.

We applied cluster analysis to a cohort of patients with severe atrial cardiomyopathy to identify distinct clinical phenotypes. Our key findings are: 1. We identified four clinically relevant and distinct phenotypes within the cohort. 2. Treatment approaches differed among the clusters based on the main comorbidities, though anticoagulant and rhythm or rate control strategies were consistent across groups. 3. Echocardiographic parameters varied significantly among the clusters. 4. The distinct clusters were associated with varying risks of mortality but similar risks of symptomatic AF events.

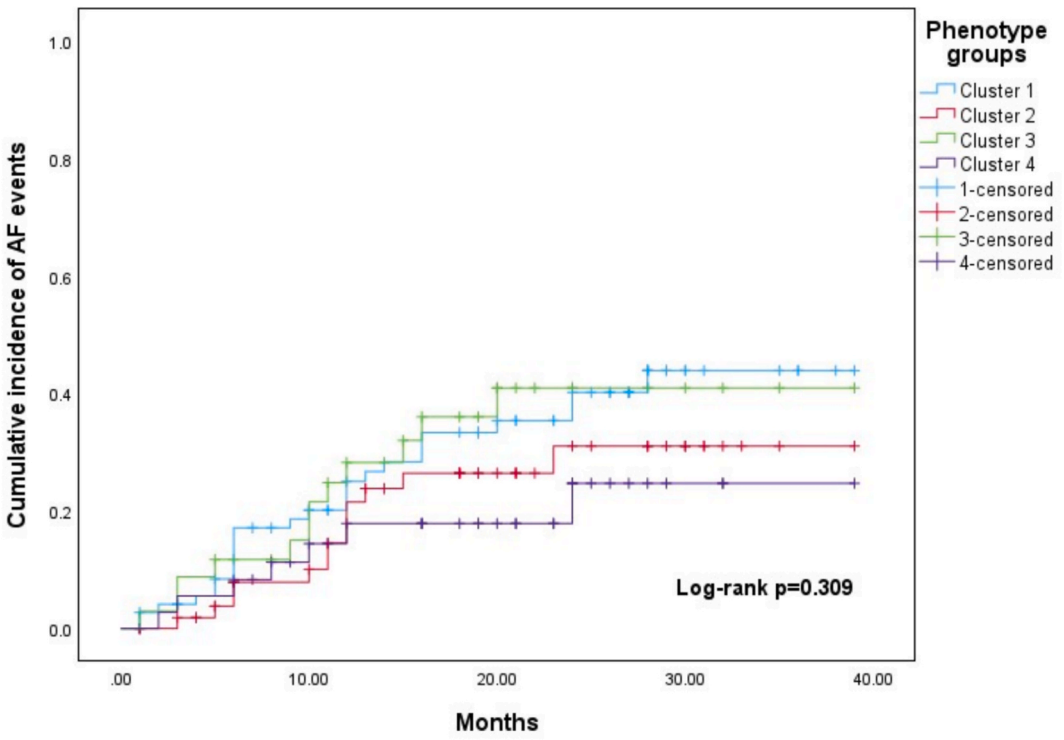

Fig. 4. Kaplan-Meier curves depict the incidence rates of atrial fibrillation events across cluster 1 to 4 (Log-rank test p = 0.309).

The four clusters exhibited distinct clinical characteristics. **Cluster 1**, which consisted of the youngest patients with overweight and obesity, had a higher prevalence of paroxysmal AF compared to the other clusters. It also exhibited the highest rate of symptomatic AF events, primarily due to episodes of paroxysmal AF, but had the lowest mortality rate. The lower mortality risk associated with paroxysmal AF versus persistent AF was noted in the post hoc analysis of the ENGAGE AF-TIMI 48 Trial [13]. Additionally, this cluster had a higher proportion of obese patients. Notably, a U-shaped relationship between body weight and mortality in AF patients has been observed, suggesting that both low and high body weights are associated with increased mortality risk [14].

Cluster 2 predominantly comprised women with heart failure and a significant proportion of cancer cases, leading to the highest mortality rate among the clusters. The association between cancer and increased mortality in patients with AF is well-documented [15,16]. The cluster's higher percentage of patients with low BMI supports previous findings of a U-shaped relationship between body weight and mortality in AF [14]. The substantial presence of heart failure (88 %) underscores its critical role as a leading cause of death in AF patients, surpassing even ischemic stroke [17,18].

This cluster also exhibited the lowest RV strain values. Although the prognostic value of RV strain in atrial cardiomyopathy remains uncertain, it is a recognized predictor of mortality in heart failure, pulmonary hypertension, and valvular heart disease [19–23]. Additionally, Cluster 2 had the highest prevalence of significant tricuspid regurgitation, which has been associated with poorer survival outcomes in AF patients [24,25].

Cluster 3 was characterized by patients with diabetes, a high prevalence of heart failure, and high BMI. This cluster had the highest rate of coronary artery disease and a relatively high incidence of cancer. Notably, this cluster also had a very high prevalence of persistent AF and a high rate of symptomatic AF events. It showed the highest rate of progression to persistent AF and the second-highest mortality rate among the clusters. This aligns with previous findings that persistent forms of AF are associated with worse outcomes [26,27].

A defining feature of this cluster is the lowest GLS of the left ventricle. Several studies have highlighted the prognostic importance of GLS in patients with acute and chronic systolic heart failure, post-myocardial infarction, and ischemic cardiomyopathy [28–31]. GLS of the LV is a significant predictor of cardiovascular events in patients with AF [32]. Additionally, this cluster exhibited the highest E/e' ratio, a known predictor of mortality in patients with non-valvular atrial fibrillation who have preserved left ventricular systolic function [33].

Cluster 4 consisted of the oldest patients, predominantly men, with tachycardia-bradycardia syndrome who had received pacemakers (78 %) due to SND or AV block. This cluster had the highest prevalence of ischemic stroke and permanent AF. The lower prevalence of obesity in this cluster may reflect the association of sarcopenia with advancing age. Surprisingly, and contrary to previous cluster analyses, this group exhibited the lowest symptomatic AF event rate and a relatively low mortality rate.

Thus far, cluster analysis in atrial fibrillation patients has been conducted primarily in a few large observational studies, such as the 'Outcomes Registry for Better Informed Treatment of Atrial Fibrillation' and the 'Keio Interhospital Cardiovascular Studies for AF' registry, which include US and Japanese cohorts, respectively [9,10]. The clinical characteristics of these studied populations differ notably from those in our study. For instance, the Japanese cohort comprised relatively younger patients with a low prevalence of hypertension, a key etiological factor in atrial cardiomyopathy.

More recently, two additional cluster analyses of large AF datasets have been published [34,35]. One prominent study, the ESC-EHRA EURObservational Research Programme in AF (EORP-AF), focused on European AF patients [36]. Our clusters align most closely with those identified in the Italian START (Survey on anTicoagulated pAtients RegisTer) registry, which analyzed a cohort of 5,171 patients. Consistent with their findings, our study also found that the highest mortality rate was in the cluster of elderly women (similar to cluster 4 in their study), followed by the cluster of diabetic patients (comparable to cluster 3 in their study) [11].

The variation in clusters identified across different analyses highlights the significant heterogeneity among atrial fibrillation patients, as

well as regional differences between registries. Notably, most previous cluster analyses of AF patients did not consider cancer as a factor in cluster formation, except for one study. Including cancer in our analysis is crucial, as it may represent a specific subgroup of AF patients with unique characteristics. Additionally, while previous studies primarily focused on echocardiographic markers such as left ventricular ejection fraction and left atrial size, our analysis is the first to incorporate a comprehensive range of echocardiographic parameters. By comparing these parameters across different clusters, we have provided a more detailed phenotypic characterization of severe atrial cardiomyopathy.

4.1. Limitations

Our study has several limitations that should be considered when interpreting the results. First, according to the new definition proposed in 2024 by Goette et al. [2], severe AtCM is characterized by atrial systolic failure (severely reduced left atrial ejection fraction $\leq$ 35 %), significantly impaired atrial contractility (flow velocities $\leq$ 20 cm/sec within the left atrial appendage, or reduced tissue strain), and/or major degrees ($\geq$35 % of LA wall volume) of interstitial alterations (e.g., atrial fibrosis, fatty infiltrates, amyloid infiltration, and inflammation), and/or severe atrial enlargement (LA diameter $\geq$ 5.0 cm, LA volume index $\geq$ 50 mL/m^2), and/or long-standing persistent/permanent atrial fibrillation [2].

It is evident that this proposed definition is much more complex than our inclusion criteria for severe AtCM. Although we did not evaluate left atrial ejection fraction, we assessed other important functional parameters, such as left atrial reservoir strain, which was severely reduced in our cohort (mean value of 16.9 $\pm$ 9.1 %).

A second limitation of our study is the relatively small sample size, which may impact the generalizability and robustness of the findings. Third, different clustering and linkage methods can produce varying results, and there is no consensus on the optimal approach. This variability could influence the clustering outcomes and their interpretations. Fourth, the choice of four clusters was made based on the investigators' discretion; incorporating more clusters might reveal different groupings but could also reduce the statistical power to detect meaningful differences. Fifth, the study population consisted of patients with advanced atrial cardiomyopathy from a hospital setting, characterized by older age and multiple comorbidities. Consequently, the findings may not be applicable to younger, healthier patients with milder forms of atrial cardiomyopathy seen in outpatient settings. Sixth, the results are specific to the Bulgarian population, and further research is needed to explore atrial cardiomyopathy across diverse populations and settings to enhance our understanding of its heterogeneity.

Future research should aim to validate these findings in larger, multicenter cohorts and diverse populations. Additionally, exploring whether phenotype-specific treatment strategies could improve outcomes would be a valuable next step. Future studies should also employ more comprehensive survival analysis techniques, incorporating both parametric and semiparametric methods, to provide more accurate estimates of survival probabilities.

5. Conclusion

In patients with severe atrial cardiomyopathy, we identified four distinct clusters, each characterized by different comorbidities and mortality rates, but similar rates of symptomatic atrial fibrillation events. Our analysis revealed that clinical and echocardiographic parameters significantly influence mortality risk. Specifically, heart failure, cancer, and severe tricuspid regurgitation were strongly associated with worse outcomes. This study provides a foundation for future research in the field and underscores the potential value of phenotype-based approaches.

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CRediT authorship contribution statement

R. Ilieva: Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **P. Kalaydzhiev:** Writing – review & editing, Visualization, Conceptualization. **B. Slavchev:** Writing – original draft, Methodology, Data curation, Conceptualization. **N. Spasova:** Writing – review & editing, Formal analysis, Conceptualization. **E. Kinova:** Writing – review & editing, Supervision, Conceptualization. **A. Goudev:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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