







Arrhythmic risk stratification in patients with left ventricular ring-like scar

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Aims

Left ventricular (LV) ring-like scar on cardiac magnetic resonance (CMR) has been linked to malignant arrhythmias in patients with non-ischæmic cardiomyopathy. This study aimed to perform a comprehensive evaluation of this phenotype and to identify risk factors for life-threatening arrhythmic events (LAEs), a composite of sudden cardiac death (SCD), aborted SCD, and sustained ventricular tachycardia.

Methods and results

One hundred and fifteen patients [median age 39 (interquartile range, IQR, 28–52), 42% females] were identified at 6 referral centres. Inclusion criteria were ring-like LV scar [≥ 3 contiguous segments with sub-epicardial/midwall late gadolinium enhancement (LGE) in the same slice] and one among: pathogenic/likely pathogenic genetic variant, family history for cardiomyopathy, or arrhythmogenic cardiomyopathy diagnosis. During the study follow-up, survival free from LAEs was 60% (3.8 events/100 patients/year); at a median follow-up of 4.6 years (IQR 1.7–8.4) it was 84%. On multivariable analysis, anterior Q waves [hazard ratio (HR): 1.030, 95% confidence intervals (CI): 1.014–1.046, $P < 0.001$], QRS width (HR: 4.642, 95% CI: 1.296–16.628, $P = 0.018$), and LV end-diastolic volume index (LVEDVi; HR: 1.011, 95% CI: 1.001–1.021, per mL/m² increase, $P = 0.040$) were independently associated with LAEs; with good discrimination power (Harrell's C-index = 0.796). Three risk categories were identified: normal electrocardiogram (ECG), abnormal ECG and no LAEs predictive variables, abnormal ECG and ≥ 1 LAEs predictive variables, with a decreasing survival from 100 to 65% and 49%, respectively (Log-rank test = 0.015).

Conclusion

In this study, the LV ring-like scar phenotype was associated with a high rate of malignant arrhythmias in presence of anterior Q waves, QRS prolongation, and increased LVEDVi. A normal ECG identified a lower risk sub-group.

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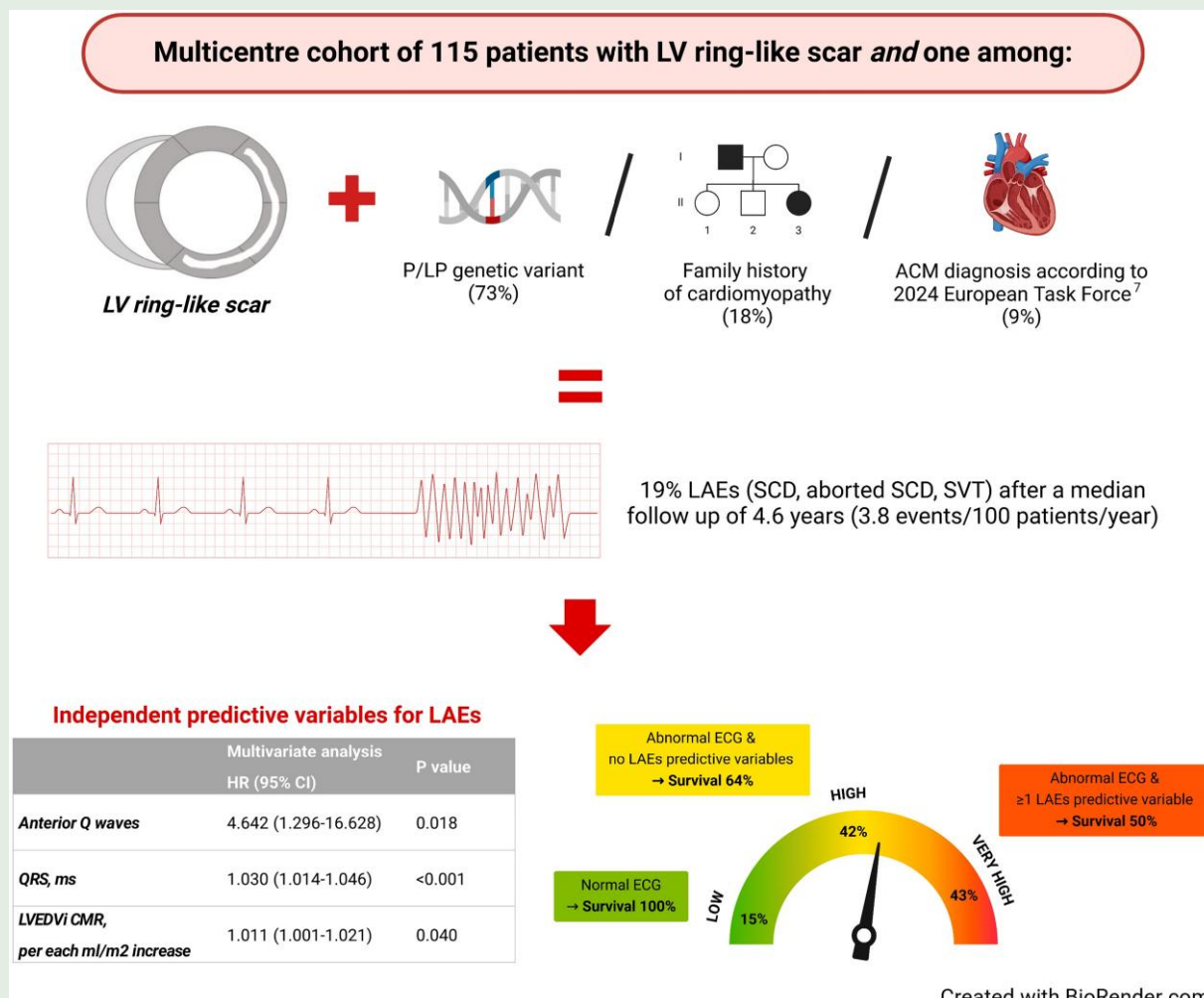
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Lay summary

Left ventricular (LV) ring-like scar represents the cardiac magnetic resonance expression of different genetic substrates and several clinical scenarios. Arrhythmic risk stratification predictors are still not well understood. In this study,

- LV ring-like scar exhibits a high rate of ventricular arrhythmias, particularly in the presence of electrocardiogram abnormalities (anterior Q waves and QRS enlargement) together with increased LV volumes
- Other commonly used risk predictors (such as LV systolic function) did not add significant prognostic information

Graphical Abstract



ACM, arrhythmogenic cardiomyopathy; LAEs, major adverse arrhythmic cardiac events; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; P/LP, pathogenic/likely pathogenic; SCD, sudden cardiac death, SVT, sustained ventricular tachycardia.

Keywords

Cardiomyopathy • Ring-like scar • Cardiac magnetic resonance • Electrocardiogram • Prognosis • Risk stratification • Arrhythmias

Introduction

Contrast-enhanced cardiac magnetic resonance (CMR) imaging has become a mainstay in cardiological clinical practice, particularly concerning cardiomyopathies, with implications for diagnosis and prognosis. Many studies and meta-analyses have shown that the presence, extent, and pattern of distribution of myocardial fibrosis detected by late gadolinium enhancement (LGE), provide independent prognostic

information beyond left ventricular ejection fraction (LVEF) in non-ischaemic cardiomyopathies¹⁻⁴. In addition, the greater use of CMR has resulted in the identification of a new spectrum of heart muscle disease phenotypes. One such phenotype, the 'ring-like scar pattern' affecting contiguous segments of the left ventricle (LV) has attracted particular attention. Initially described as the phenotypic manifestation of a specific genetic substrate, represented by desmoplakin (*DSP*) and filamin C (*FLNC*) mutations,⁵ emerging data have shown that the genetic

basis of this phenotype may be more heterogeneous.⁶ Nowadays, the LV ring-like scar is considered a highly specific characteristic of LV arrhythmogenic cardiomyopathy, and represents a major diagnostic criterion in the recently published European Task Force Consensus Report.⁷ This approach focuses the attention to inherited heart muscle diseases with a genetic substrate and familial involvement. Furthermore, ring-like LV scars are associated with an increased risk of ventricular arrhythmias in patients with dilated non-ischaemic cardiomyopathy (DCM),⁸ as well as non-dilated LV phenotypes.⁹ However, whether it is possible to further stratify the arrhythmic risk among patients showing this CMR-based phenotype has not been investigated so far.

Against this background, we aimed to perform a comprehensive characterization of patients with LV ring-like scar, in terms of clinical, instrumental, and genetic features, to ultimately evaluate whether specific risk factors of life-threatening arrhythmic events (LAEs) exist in individuals with this peculiar entity.

Methods

This was a multicentre, retrospective, observational study evaluating patients with non-ischaemic cardiomyopathy from 6 different tertiary care referral Centres: IRCCS University Hospital of Bologna (Italy); St Bartholomew's Hospital, London (UK); IRCCS Istituto Auxologico Italiano, Milan (Italy); University Hospital of Trieste (Italy); Careggi University Hospital, Florence (Italy); Sant' Andrea Hospital, Sapienza University, Rome (Italy).

The study included patients with a ring-like LV scar pattern detected with CMR, defined as ≥ 3 contiguous segments with sub-epicardial/midwall LGE in the same slice (with or without fatty infiltration) and at least one of the following criteria: a positive genetic test for a cardiomyopathy associated gene;¹⁰ ≥ 1 patient in the same family with a cardiomyopathy diagnosis (either DCM, arrhythmogenic right ventricular (RV) cardiomyopathy, or LV ring-like scar); borderline/definitive arrhythmogenic cardiomyopathy diagnosis (right, left, or biventricular) according to 2024 European Task Force report.⁷ Patients with a major arrhythmic event [sudden cardiac death (SCD) as first presentation, sustained ventricular tachycardia (VT) requiring emergency department admission, aborted SCD due to ventricular fibrillation] before the date of the study entry were excluded.

Ischaemic heart disease was ruled out with a pre-test probability assessment including patient risk factors and non-invasive or invasive test, when necessary, according to the accepted current clinical recommendations.¹¹ Phenocopies (such as cardiac sarcoidosis, systemic sclerosis) were excluded based on a comprehensive clinical/multimodality evaluation and even with myocardial biopsy when needed. Patients with a previous episode of acute myocarditis were included if they fulfilled the study inclusion criteria.

Baseline demographic characteristics, medical history, symptoms, 12-lead electrocardiogram, transthoracic echocardiogram, genetic analysis, CMR, device therapy, and follow-up information were extracted at all the participating centres from clinical datasets sharing the same methodology. Follow-up started from the date of LV ring-like scar diagnosis. A minimum follow-up length was not required.

All the electrocardiograms (ECGs) were retrospectively analysed by expert cardiologist at each centre, blinded to clinical and outcome data. Among conventional ECG parameters, rhythm, heart rate, QRS axis, PR, QRS, Bazett-corrected QT (QTc) intervals, and bundle branch block were evaluated. Pre-specified ECG abnormalities were also recorded: negative T waves; epsilon waves;¹² low QRS voltages (defined as nadir-to-peak QRS amplitudes <10 mm in all precordial leads and as nadir-to-peak QRS amplitudes <5 mm in all the limb leads); pathologic Q waves, defined as $\geq 1/3$ of R wave in depth and/or ≥ 0.04 s in duration in at least two contiguous leads; QRS fragmentation, a RsR' pattern ≤ 120 ms in two contiguous leads, and/or R/S waves notching. QRS duration was considered broad if QRS ≥ 110 ms.¹³

Based on echocardiographic features, patients were stratified as follows: normal/minor alterations (LVEF $> 50\%$ and LV end-diastolic volume index, LVEDVi < 74 mL/m² for males and < 61 mL/m² for females, respectively); hypokinetic non-dilated LV (HNDLV, LVEF $\leq 50\%$ and LVEDVi < 74 mL/m² for males and LVEDVi < 61 mL/m² for females); DCM (LVEF $\leq 50\%$ and LVEDVi ≥ 74 mL/m² for males and LVEDVi ≥ 61 mL/m² for females).^{14,15}

Cardiac magnetic resonance was performed using a 1.5T or 3T cardiac-phased array receiver coil, ECG gating, and breath-hold technique, according to standardized protocols.¹⁶ Cine images were obtained using steady-state free precession (SSFP) pulse sequence. Intramyocardial fatty infiltration was assessed by T1 or proton density weighted imaging, while T2-weighted images were used for the detection of myocardial oedema. LGE imaging was acquired 10 min after intravenous administration of 0.1–0.2 mmol/kg of gadolinium-based contrast agent, using segmented T1-weighted inversion recovery gradient echo or phase sensitive pulse sequences, individually adjusting the inversion time to optimize nulling of normal myocardium. Non-ischaemic LV fibrosis was assessed by expert readers and defined as areas with increased signal intensity following administration of contrast medium in two phase-encoding directions in two orthogonal planes and localized in sub-epicardium/midwall. LGE location was described according to the 17-segment model from the American Heart Association.¹⁷ The number of involved segments was counted. Right ventricular LGE was reported as either present or absent.

All patients underwent genetic testing, which was performed using different sequencing technologies and gene panels reflecting the standard practice at the time of testing in each centre. DNA variants were interpreted according to the current American College of Medical Genetics and Genomics criteria.¹⁰ Patients harbouring pathogenic or likely pathogenic variants (P/LP) were considered genotype positive.

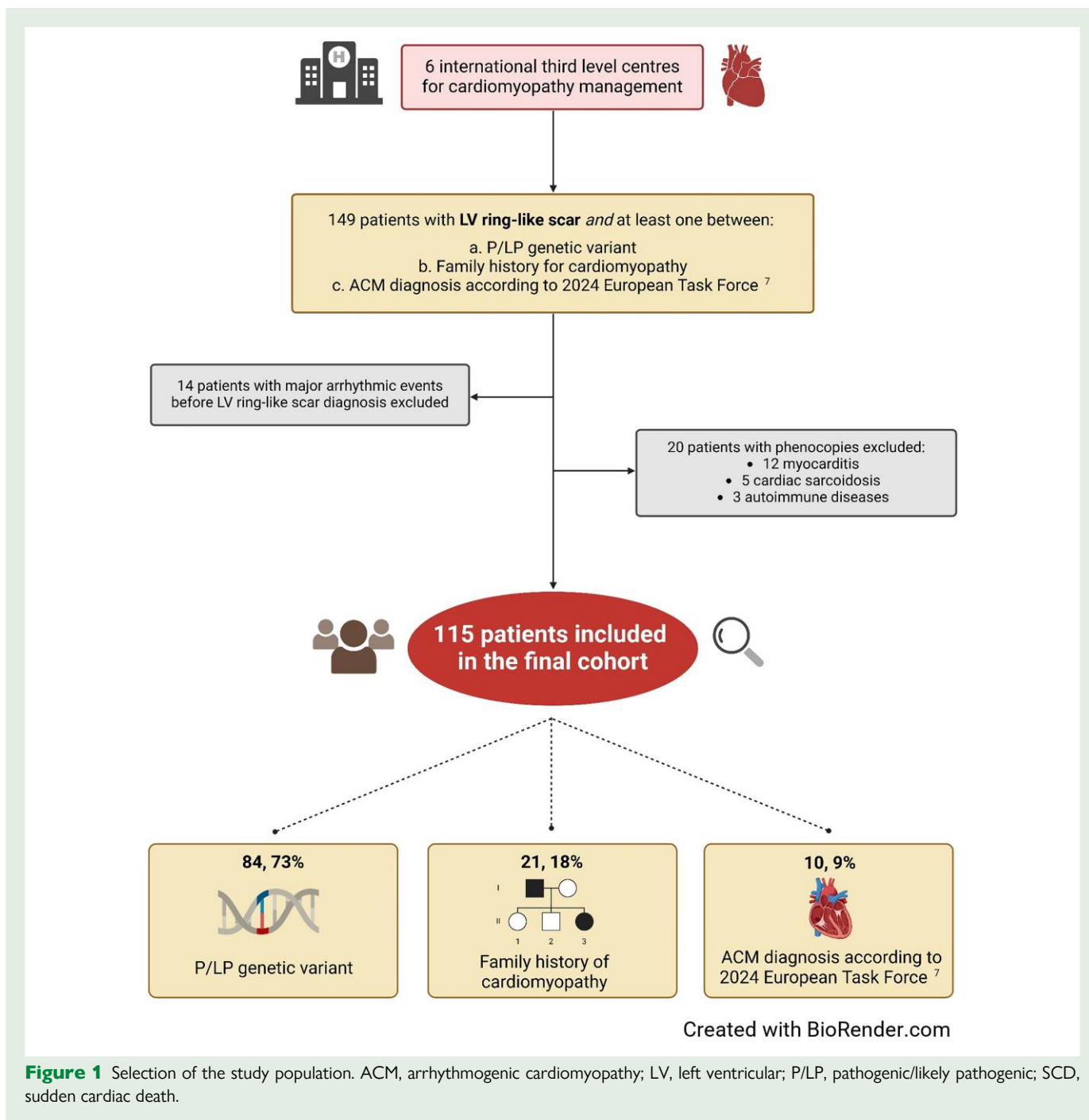
All patients gave written informed consent. The study was approved by the local Ethics Committee of the participating centres and was conducted in accordance with the principles of the most recent revision of the Declaration of Helsinki.

Endpoint

The study endpoint was defined as a composite of LAEs including: (i) SCD, an unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy subject (or when the victim was in good health 24 h before the event, if not witnessed); (ii) aborted SCD, an appropriate implantable cardioverter-defibrillator (ICD) intervention (shock or anti-tachycardia pacing) for ventricular arrhythmias or a non-fatal ventricular fibrillation; and (iii) sustained VT, a ventricular rhythm lasting at least 30 s and/or causing haemodynamic instability (i.e. severe hypotension with systolic blood pressure < 90 mmHg and syncope) and requiring cardioversion. Follow-up ended at the date of primary endpoint or on 31 December 2022.

Statistical analysis

Distribution of continuous variables was assessed by the Shapiro–Wilk test. All were not normally distributed. Accordingly, continuous variables are expressed as median [interquartile range (IQR)]; groups were compared using the Mann–Whitney *U* test or the Kruskal–Wallis test, as appropriate. Categorical variables are expressed as counts (percentage) and were compared with χ^2 or Fisher's test as appropriate. Event-free survival for the study endpoint was estimated using the Kaplan–Meier method and survival between groups was compared by means of the log-rank test. Multivariable Cox proportional hazard model was used to identify independent predictors for the study endpoint. Candidate variables were selected by a multivariable stepwise backward method entering those variables statistically significant ($P < 0.05$) on univariable analysis. Those variables retained were then entered in the final multivariable Cox proportional hazard model. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The discriminatory power of the model was reported as Harrell's *C* statistic. Two-tailed *P*-values ≤ 0.05 defined the statistical



significance. All analyses were performed with STATA 14.0 software (STATA Corporation, College Station, TX, USA).

Results

Overall cohort

One hundred and forty-nine patients were evaluated; after exclusions, the final study cohort was composed of 115 patients (Figure 1 shows the study flow chart). Baseline clinical, ECG, and CMR characteristics of the entire population and according to the endpoint status are listed in Table 1. Supplementary material online, Table S1 shows main baseline

characteristics according to the inclusion criteria for study entry. Overall, 48 patients were females (42%), median age at diagnosis was 39 years (IQR 28–52); half of the patients (53%) were probands. Fifteen patients had a history of myocarditis before the LV ring-like scar diagnosis. The median LVEF at CMR was 48% (IQR 38–57); LVEF was normal in 51 (44%) patients, mildly reduced in 40 patients (35%), and severely reduced in 24 (21%). The median CMR LV end-diastolic indexed volume (LVEDVi) was 101 mL/m² (IQR 81–122). Wall motion abnormalities were present in the LV in 63% and in the RV in 34%. Late gadolinium enhancement involved more frequently the LV inferior, inferolateral, and anterolateral segments. Right ventricular LGE was present in 17% of the cases, while LV or RV fatty

Table 1 Baseline clinical, electrocardiogram, cardiac magnetic resonance, and genetic characteristics of the study population

	Overall (n = 115)	No LAEs (n = 93)	LAEs (n = 22)	P-value
Clinical				
Age, years	39 (28–52)	37 (28–51)	43.5 (28–54)	0.606
Females, n (%)	48 (42)	42 (45)	6 (27)	0.126
Proband status, n (%)	61 (53)	53 (57)	8 (36)	0.081
NYHA class >1, n (%)	26 (23)	16 (17)	10 (45)	0.004
24 h Holter ECG, n (%)				0.230
<1000 VEBs	40 (35)	34 (37)	6 (28)	
≥1000 VEBs	21 (18)	19 (20)	2 (9)	
NSVT	49 (43)	37 (40)	12 (55)	
Echocardiographic phenotype, n (%)				0.014
Normal	53 (46)	47 (51)	6 (28)	
HNLDV	16 (14)	15 (16)	1 (4)	
DCM	46 (40)	31 (33)	15 (68)	
ECG characteristics				
Normal ECG, n (%)	17 (15)	17 (18)	0	0.040
Atrial fibrillation, n (%)	2 (2)	1 (1)	1 (5)	0.347
AV block, first degree, n (%)	6 (5)	3 (3)	3 (14)	0.083
QRS axis, n (%)				0.027
Normal	80 (70)	69 (74)	11 (50)	
Abnormal	35 (30)	24 (26)	11 (50)	
QRS interval (ms)	98 (90–110)	98 (88–106)	106 (98–122)	<0.001
QRS interval ≥120 ms	15 (13)	9 (10)	6 (27)	0.028
QRS interval ≥110 ms	29 (25)	19 (20)	10 (45)	0.015
Pathologic QTcB interval	16 (14)	10 (11)	6 (27)	0.044
RBBB, n (%)	6 (5)	3 (3)	3 (14)	0.083
Non-specific IV delay, n (%)	36 (31)	32 (34)	4 (18)	0.221
LAFB, n (%)	14 (12)	9 (10)	5 (23)	0.139
LBBB, n (%)	5 (4)	3 (3)	2 (9)	0.243
LVH at ECG, n (%)	3 (3)	2 (2)	1 (5)	0.474
TWI, n (%)				
Any localization	83 (72)	67 (72)	16 (72)	0.949
Anterior	7 (6)	6 (6)	1 (5)	1.00
V4–V6	5 (4)	3 (3)	2 (9)	0.243
IaVL	14 (12)	10 (11)	4 (18)	0.466
Lateral	10 (9)	8 (9)	2 (9)	1.00
Inferior	8 (7)	7 (8)	1 (5)	1.00
Inferolateral	17 (15)	13 (14)	4 (18)	0.738
Anterolateral	5 (4)	5 (5)	0	0.581
Inferoanterior	4 (3)	3 (3)	1 (5)	0.578
Diffuse	10 (9)	9 (10)	1 (5)	0.684
QRS fragmentation, n (%)				
Any localization	24 (21)	17 (18)	7 (32)	0.160
Q waves, n (%)				
Any localization	39 (34)	30 (32)	9 (41)	0.441
Inferior	26 (23)	20 (22)	6 (27)	0.561
Anterior	6 (5)	3 (3)	3 (14)	0.083
Lateral	11 (10)	10 (11)	1 (5)	0.688
Epsilon waves, n (%)	2 (2)	2 (2)	0	1.00
Low QRS voltages, n (%)				
Limb leads	55 (48)	44 (47)	11 (50)	0.820

Continued

Table 1 Continued

	Overall (n = 115)	No LAEs (n = 93)	LAEs (n = 22)	P-value
Precordial leads	17 (15)	16 (17)	1 (5)	0.188
Diffuse	15 (13)	15 (16)	0	0.071
CMR				
LVEF	48 (38–57)	49 (39–58)	40 (31–52)	0.016
LVEF, n (%)				0.036
≥50%	51 (44)	44 (47)	7 (32)	
36–49%	40 (35)	34 (37)	6 (27)	
≤35%	24 (21)	15 (16)	9 (41)	
LVEDVi (mL/m ²)	101 (81–122)	95 (79–114)	122 (93–140)	0.007
LVEDVi ≥ sex-specific cut-off ^a , n (%)	24 (30)	22 (24)	12 (55)	
LV WMA, n (%)	72 (63)	55 (59)	17 (77)	0.114
RV WMA, n (%)	39 (34)	31 (33)	8 (36)	0.787
LGE total number of segments	8 (6–12)	9 (6–12)	7 (5–11)	0.673
Genetic findings				
NoP/LP genetic variant	31 (27)	22 (24)	9 (41)	0.066
DSP P/LP variant	53 (46)	48 (52)	5 (23)	
FLNC P/LP variant	18 (16)	14 (14)	4 (18)	
Other gene P/LP variant	13 (11)	9 (10)	4 (18)	

AV, atrioventricular; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; DSP, desmoplakin; FLNC, filamin C; HNDLV, hypokinetic non-dilated left ventricle; LV, intraventricular; LAEs, life-threatening arrhythmic events; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVH, left ventricular hypertrophy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; P/LP, pathogenic/likely pathogenic; RBBB, right bundle branch block; RV, right ventricle; TWI, T-wave inversion; VEBs, ventricular ectopic beats; WMA, wall motion abnormalities.

^aLVEDVi was categorized based on the median values of patients reaching the study endpoint (≥123 mL/m² in men and ≥103 mL/m² in women).

infiltration was observed in 34% and 8% of the patients, respectively. Signs of myocardial inflammation at T₂-weighted images were reported in 15 patients.

Most of the population (84 patients, 73%) harboured a P/LP variant and were considered genotype positive: the most frequent involved genes were *DSP* and *FLNC* (64% and 21%, respectively); the rest had other desmosomal or non-desmosomal P/LP variants (plakophilin-2, *PKP2*: n = 3; desmoglein-2, *DSG2*: n = 3; desmin, *DES*: n = 3; myosin heavy chain 7 *MYH7*: n = 2; ryanodine receptor-2 *RYR2*, dystrophin *DMD* n = 1). [Supplementary material online, Table S2](#) shows the P/LP variants list.

Predictors of study endpoint and risk stratification

During the study follow-up, endpoint-free survival estimate was 60% (95% CI 0.441–0.734; see [Supplementary material online, Figure S1](#)). At a median follow-up of 4.6 years (IQR 1.7–8.4), survival free from LAEs was 84% (95% CI 0.75–0.95). Twenty-two patients (19%) experienced LAEs (3.8 events/100 patients/years): 2 patients had SCD, 2 aborted SCD, 2 patients had sustained VT with haemodynamic instability, and 16 of the 78 patients with an ICD (20%) were appropriately treated for ventricular arrhythmias (13 with ICD shock and 3 exclusively with anti-tachycardia pacing). Six patients with an ICD experienced device-related complications, including inappropriate ICD therapies (8%). One patient who met the study endpoint due to an episode of sustained VT died later because of cancer.

Patients who experienced LAEs were more likely to have a DCM phenotype, to have been diagnosed with HF, and to be symptomatic at baseline [New York Heart Association (NYHA) functional class

>1]. The 17 patients (15%) who had a normal ECG did not experienced LAEs during follow-up. Patients with LAEs had a lower LVEF (49 vs. 40%, *P* = 0.016) and a larger LVEDVi (95 vs. 122 mL/m², *P* = 0.007). The rate of LGE involvement for each cardiac segment was similar between patients experiencing and not experiencing LAEs ([Figure 2A](#)); no significant differences in terms of circumferential LGE distribution (all the six segments in the same LV short axis slice) were observed. No significant associations were found between LGE longitudinal distribution and LAEs (*P* = 0.112; [Figure 2B](#)). There was no association between the genotype and the study endpoint ([Table 1](#)).

[Table 2](#) shows the variables related to the occurrence of LAEs. After a backward stepwise method selection, entering only variables statistically significant on univariable analysis, three variables were selected. On multivariable analysis, the presence of Q waves in anterior leads, QRS length, and LVEDVi at CMR, were associated to the risk of LAEs (HR 1.030, 95% CI 1.014–1.046, *P* < 0.001; HR 4.642, 95% CI 1.296–16.628, *P* = 0.018; HR 1.011, 95% CI 1.001–1.021 per mL/m² increase, *P* = 0.040, respectively), with Harrell's C index of 0.796 ([Table 3](#)).

According to the study results, the population was then divided into three categories of risk, as follows: Group 1, normal ECG; Group 2, abnormal ECG and no LAEs predictive variables; Group 3, abnormal ECG and at least one LAEs predictive variable (anterior Q waves, QRS ≥ 110 ms), LVEDVi ≥ the sex-specific cut-off based on the median LVEDVi of the population (≥123 mL/m² in males and ≥103 mL/m² in females). Kaplan–Meier survival curves showed significantly different event-free survival (log-rank test = 0.015) in the three groups: patients with a normal ECG had 100% survival at the end of the study follow-up, patients with no LAEs predictive variables had 64% (95% CI 0.360–0.8267) survival, and patients with at least 1 LAEs predictive variable

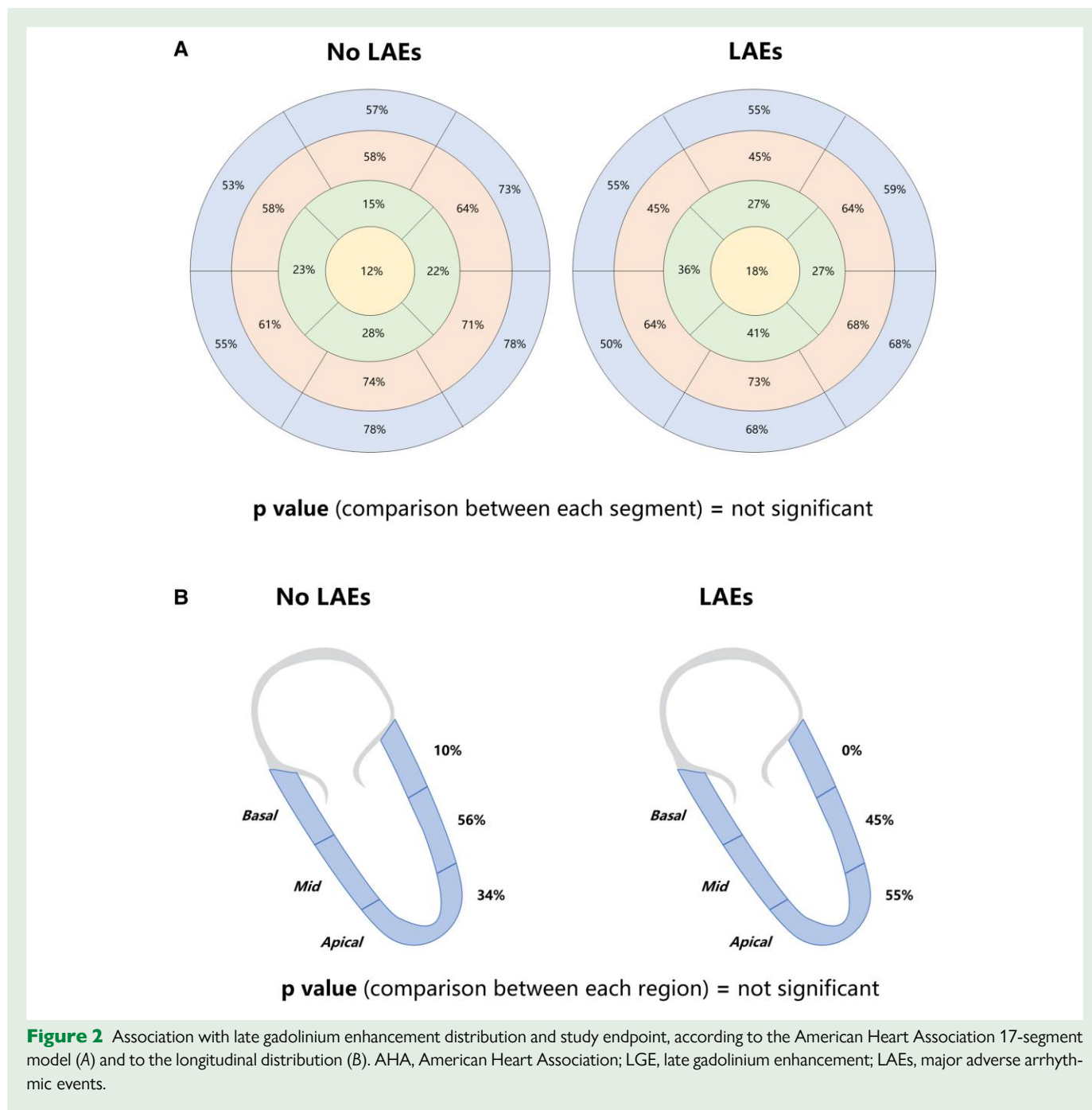


Figure 2 Association with late gadolinium enhancement distribution and study endpoint, according to the American Heart Association 17-segment model (A) and to the longitudinal distribution (B). AHA, American Heart Association; LGE, late gadolinium enhancement; LAEs, major adverse arrhythmic events.

had 50% (95% CI 0.297–0.678) survival (Figure 3). Group 3 had an increased risk of LAEs compared with Group 2 (HR 2.767, 95% CI 1.082–7.078, $P = 0.034$). Supplementary material online, Table S3 shows, as expected, that Group 3 had a worse clinical profile in terms of NYHA class and LV function; however, it is worth noting that both LGE extension and follow-up were comparable between the three study Groups.

Discussion

This is the first study to explore predictors of arrhythmic events in genotyped patients with a LV ring-like scar phenotype. Patients with this phenotype exhibited a high rate of major arrhythmic events, but those

with a normal ECG had none. Independent predictors of LAEs included anterior Q waves, QRS length, and LVEDVi.

The high proportion of patients experiencing arrhythmic events in our cohort is consistent with previous studies. In a recent evaluation of 1673 patients with non-ischaemic DCM (almost 40% with an LVEF <35%), the reported 5-year cumulative incidence of the composite endpoint of SCD or appropriate ICD shock was 12% in those with LGE, compared with 5% of those without LGE.¹⁸ In another cohort with DCM and mild-to-moderate LV systolic dysfunction¹⁹ there was a 9-fold increased risk of SCD in the group with midwall LGE. More recently, the prognostic significance of the LV ring-like pattern of fibrosis was evaluated in patients with apparently idiopathic non-sustained VT.⁹ Compared to individuals without LGE and to those with a non-ring like

Table 2 Univariable analysis for the predictors of the study endpoint

	Univariate analysis HR (95% CI)	P-value
Age, years	1.014 (0.984–1.046)	0.356
Females, n (%)	0.401 (0.156–1.032)	0.058
Proband status	2.316 (0.969–5.532)	0.059
NYHA class >1 first contact ^a	2.520 (1.086–5.845)	0.031
24 h Holter ECG		
<1000 VEBs	1.761 (0.757–4.096)	0.189
≥1000 VEBs		
NSVT		
Echocardiographic phenotype		0.397
Normal	0.400 (0.048–3.334)	
HNDLV	2.648 (1.026–6.830)	
DCM ^a		0.044
Atrial fibrillation	1.801 (0.239–13.549)	0.567
AV block, first degree ^a	3.616 (1.059–12.340)	0.040
QRS interval, ms ^a	1.03 (1.015–1.044)	<0.001
QRS interval ≥120 ms	2.294 (0.896–5.873)	0.083
QRS interval ≥110 ms	2.863 (1.233–6.643)	0.014
QTcB ≥450 ms	2.061 (0.804–5.282)	0.132
QRS axis, normal	2.282 (0.986–5.282)	0.054
RBBB ^a	4.818 (1.413–16.427)	0.012
TWI		
Any localization	0.863 (0.337–2.210)	0.760
Anterior	0.716 (0.096–5.333)	0.745
V4–V6	2.065 (0.480–8.871)	0.329
I-aVL	1.508 (0.506–4.486)	0.460
Lateral	0.809 (0.188–3.483)	0.777
Inferior	0.684 (0.091–5.110)	0.711
Inferolateral	1.257 (0.424–3.725)	0.679
Inferoanterior	1.274 (0.171–9.496)	0.813
Diffuse	0.587 (0.078–4.387)	0.604
Low QRS voltages		
Limb leads	0.794 (0.340–1.852)	0.594
Precordial leads	0.147 (0.019–1.105)	0.063
Q waves		
Any localization	1.248 (0.531–2.934)	0.611
Inferior	1.169 (0.457–2.993)	0.743
Anterior ^a	4.431 (1.285–15.271)	0.018
Lateral	0.316 (0.0422–3.57)	0.262
QRS fragmentation		
Any localization	1.921 (0.781–4.725)	0.155
LVEF CMR, per each % increase ^a	0.964 (0.932–0.997)	0.033
LVEF CMR ≤35%	2.868 (1.224–6.716)	0.015
LVEDVi CMR, per each mL/m ² increase ^a	1.012 (1.003–1.020)	0.004
LVEDVi CMR according to sex ^b	2.64 (1.141–6.125)	0.023
LV WMA CMR	2.229 (0.821–6.051)	0.115
RV WMA CMR	1.147 (0.481–2.735)	0.757
LGE apex	1.662 (0.716–3.856)	0.236
LGE circumferential	0.905 (0.333–2.460)	0.846
LGE extension	0.870 (0.551–1.373)	0.551
Sub-epicardial		
Midwall		
Both		

Continued

Table 2 Continued

	Univariate analysis HR (95% CI)	P-value
LGE total number of segments	0.946 (0.834–1.072)	0.388
P/LP genetic variant		
DSP P/LP variant ^a	0.286 (0.095–0.854)	0.025
FLNC P/LP variant	0.630 (0.193–2.051)	0.443
Other gene P/LP variant	1.703 (0.512–5.658)	0.385

AV, atrioventricular; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; DSP, desmoplakin; FLNC, filamin C; HNDLV, hypokinetic non-dilated left ventricle; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVH, left ventricular hypertrophy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; P/LP, pathogenic/likely pathogenic; RBBB, right bundle branch block; RV, right ventricle; TWI, T-wave inversion; VEBs, ventricular ectopic beats; WMA, wall motion abnormalities.

^aVariables entered in the backward stepwise Cox regression selection method.

^bLVEDVi was categorized based on the median values of patients reaching the study endpoint (≥ 123 mL/m² in men and ≥ 103 mL/m² in women).

Table 3 Multivariate analysis for the predictors of the study endpoint

	Multivariate analysis HR (95% CI)	P-value
Anterior Q waves	4.642 (1.296–16.628)	0.018
QRS, ms	1.030 (1.014–1.046)	<0.001
LVEDVi CMR, per each mL/m ² increase	1.011 (1.001–1.021)	0.040

QRS interval and LVEDVi are modelled as continuous variables.

CMR, cardiac magnetic resonance; LVEDVi, left ventricular end-diastolic volume index.

pattern, patients with sub-epicardial/midwall LV ring-like scar had an almost 3-fold increase in the incidence of the composite endpoint of all-cause death and malignant arrhythmic events.

Electrocardiographic pathological Q waves are observed in 20–30% of patients with DCM, mostly in anterior and lateral leads.²⁰ In a cohort of nearly 6000 autopsied SCD victims from the Fingesture study,²¹ pathological Q waves, wider and fragmented QRS complexes, and TWI were associated with the amount of myocardial fibrosis in both ischaemic and non-ischaemic heart disease. Moreover, Pelli *et al.*²² demonstrated that pathological Q waves, and specifically anterior Q waves, were strongly associated with higher benefit from ICD treatment and were predictors of a lower all-cause mortality.

The role of QRS width in risk stratification of DCM is well recognized, and it is included in risk models for predicting life-threatening arrhythmias.²³ Recently, Marume *et al.*²⁴ showed that in the subset of patients with LVEF $\leq 35\%$, the combination of LGE and wide QRS (defined in that study as QRS ≥ 120 ms) provided additional information over myocardial fibrosis alone, improving the selection for primary prevention ICD implantation. In our population, we observed a less severe degree of cardiac remodelling, expressed in terms of LV volumes and QRS width.

In our study, LV size (in terms of LVEDVi) was independently associated with LAEs, either as a continuous variable or corrected for sex. Comparable results were observed by Guaricci *et al.*²⁵ who described the multicentre cohort from the DERIVATE registry and evaluated the additional prognostic value of a CMR-based risk score in patients with

LVEF $< 50\%$. The authors found that only male sex, midwall LGE in > 3 segments and increased LVEDVi were independent predictors of the arrhythmic endpoint, while age and LVEF were poor predictors. In this context, increased LVEDVi may be a marker of adverse LV remodelling, which carries a higher arrhythmic potential by itself, even without systolic dysfunction.²⁶ Recently, Balaban *et al.*²⁷ investigated a three-dimensional (3D) computational approach to quantify the LV remodelling in a cohort of 156 patients with DCM and LGE and derived a novel shape score (LV arrhythmic score), which was predictive of arrhythmic events, even after adjustment for LVEF, NYHA functional class, ICD, and CRT treatment.

In a cohort of 1000 patients with non-ischaemic dilated cardiomyopathy, Klem *et al.*²⁸ observed that whereas LVEF and myocardial scar were both strong independent predictors of all-cause death, cardiac death, and HF events, only LGE remained a strong independent predictor of SCD. Chen *et al.*⁸ reported a higher incidence of VT with LV ring-like scar compared with other LGE patterns and demonstrated no correlation between the incidence of VT and LVEF, underlying the inadequacy of LVEF as a predictor of SCD. Our study expands these concepts, evaluating a specific subset of patients with a significant fibrotic burden, and confirms that there is a cohort of patients without significant LV systolic dysfunction at risk of malignant arrhythmias.

In our population, no significant associations with LAEs were found regarding LV scar localization and extension. This could be explained by the homogeneous and high total burden of LGE with a preferential involvement of inferolateral segments. Moreover, other mechanisms of arrhythmic instability beyond fibrosis could be assumed.

As far as we know, this is the first study examining the relation between LV ring-like scar, genotype, and arrhythmic outcomes. In our cohort, DSP and FLNC were the most frequently involved genes, a result in line with the genotype-phenotype correlations already described by Augusto *et al.*⁵ who reported the 'ring of fibrosis' as a specific imaging hallmark for DSP/FLNC genotypes. These genes are both associated with higher rate of malignant ventricular arrhythmias and SCD,^{29,30} even with only mild-to-moderate systolic dysfunction.^{31,32} We did not find any relevant associations between genetic status and LAEs. In particular, the lower rate of LAEs observed in DSP/FLNC patients in our study should not be considered contradictory, since our population is different from those of previous investigations including patients with LV ring-like scar. On the contrary, our findings highlight that the LV ring-like scar phenotype may be shared by a heterogenous

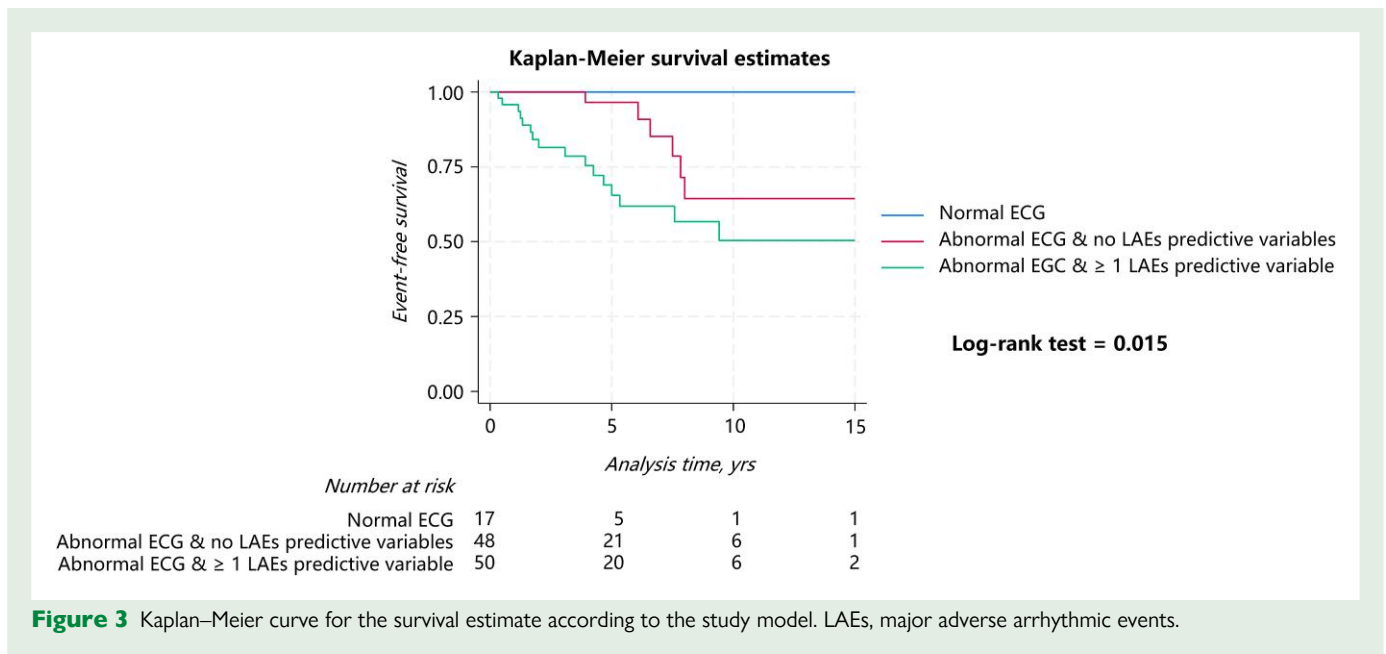


Figure 3 Kaplan–Meier curve for the survival estimate according to the study model. LAEs, major adverse arrhythmic events.

genetic substrate, and emphasize the need to identify new arrhythmic risk factors of this peculiar entity.

Finally, a considerable proportion of patients from our population had a normal ECG (15%), consistently with another cohort of patients with LVEF < 50%.³³ In a recent study from Brunetti *et al.*³⁴ including 75 athletes with normal ECG/echocardiogram and undergoing CMR for ventricular arrhythmia evaluation, the prevalence of LV scar was 40% ($n = 30$) and its presence could be predicted by ventricular arrhythmia reproducibility at exercise test. Taken together, these findings underline that a normal ECG does not exclude the presence of significant myocardial structural alterations, an important consideration in relatives, in whom the absence of ECG alterations should not obviate the need for a complete cardiological evaluation including CMR. In our study, patients with no ECG abnormalities showed a good prognosis. However, in these patients a regular ECG monitoring could be useful to detect disease progression.

Limitations

The results of the present study should be interpreted in light of some limitations. Due to its retrospective nature, it is not immune to sources of biases.

The study involved tertiary referral centres for cardiomyopathies management, potentially leading to selection and/or referral bias in patients characteristics.

Moreover, site-based bias in the scoring of CMR findings cannot be ruled out. Yet, the absence of a core lab for CMR assessment prevented us from performing a deeper LV scar evaluations, such as the total scar mass or border zone mass analysis.

Similarly to previous investigations, our study presents a certain degree of heterogeneity in the genetic next-generation sequencing panels, reflecting both differences between centres and changes in the knowledge of genetics overtime. However, all patients underwent an extensive gene panel analysis, including not only desmosomal genes but also other genes known to be associated with a dilated/arrhythmogenic phenotype.

Finally, due to the limited sample size the study might be underpowered to detect other significant relationships with the endpoint. For example, patients with only basal LV LGE did not experience any LAEs

during the study follow-up, whereas those with any LV apical involvement showed higher rate of the study endpoint, although not statistically significant. Moreover, the limited cohort size hindered us from conducting sub-group analysis that included the 3 study risk factors independently. Yet, although we used a restrictive approach for variable selection, due to the relative low rate of events in our study the risk of model overfitting cannot be ruled out. However, to our knowledge, no previous data were available regarding risk stratification among patients with the LV ring-like scar phenotype.

Conclusions

Left ventricular ring-like scar represents a CMR-based feature common to different genetic substrates, which includes several clinical presentations and a broad spectrum of phenotypes. In this study, the LV ring-like scar was associated with a high rate of malignant arrhythmias events, especially in the presence of anterior Q waves, QRS enlargement, and increased LVEDVi, whereas a normal ECG seemed to identify those at lower risk of arrhythmic events. On the other hand, LVEF and other commonly used risk factors did not add prognostic information.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

V.P., M.G., E.B., F.P., and R.D. contributed to the conception and design of the work. V.P., A.D.L., G.T., M.T., M.R.C., A.R.M., C.T., and J.B.A. contributed

to the acquisition of data for the work. N.T. and E.N. contributed to the interpretation and analysis of results. V.P. and M.G. drafted the manuscript. L.R.L., F.P., L.L., N.G., L.C., A.G., M.B., C.A., M.M., I.O., G.S., P.M.E., and E.B. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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