

# Major arrhythmias in non-dilated left ventricular cardiomyopathy: a novel prediction score

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## Abstract

**Background and Aims** The prediction of the first major arrhythmic event (MAE) is still an unmet need in the recently defined scenario of non-dilated left ventricular cardiomyopathy (NDLVC).

**Methods** A cohort of 337 patients with NDLVC and no history of MAE was retrospectively identified at two large centres. Patient-tailored diagnostic workup included cardiac magnetic resonance (CMR), endomyocardial biopsy, and genetic testing. The

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primary endpoint was the occurrence of the first MAE, including sustained ventricular tachycardia (VT), ventricular fibrillation, or appropriate implantable cardioverter-defibrillator therapy, by 60-month follow-up. A pool of 216 NDLVC patients from 11 European centres served as a validation cohort.

## Results

In the study cohort (mean age  $37 \pm 15$  years, 62% male), the mean left ventricular ejection fraction (LVEF) was  $52 \pm 8\%$ , and 79% of patients had late gadolinium enhancement (LGE) at baseline CMR. By 60-month follow-up, 51 patients (15%) experienced a MAE. The primary endpoint was predicted by male sex [hazard ratio (HR) 2.4, 95% confidence interval (CI) 1.3–4.4,  $P = .007$ ], baseline non-sustained VT (HR 3.1, 95% CI 1.7–5.6,  $P < .001$ ), LVEF  $< 45\%$  (HR 5.5, 95% CI 2.7–11.0,  $P < .001$ ), septal (HR 2.0, 95% CI 1.0–4.0,  $P = .046$ ) and ring-like pattern of LGE (HR 1.3, 95% CI .6–2.6,  $P = .54$ ), pathogenic/likely pathogenic variants in guideline-defined high-risk genes (HR 4.6, 95% CI 2.3–9.1,  $P < .001$ ), and biopsy/CMR-proven myocardial inflammation (HR 15.7, 95% CI 6.1–40.3,  $P < .001$ ). The results were confirmed in the validation cohort (Uno's C-index 0.81, 95% CI .75–.88). A novel risk score was subsequently derived.

## Conclusions

In NDLVC, male sex, non-sustained VT, LVEF  $< 45\%$ , septal and ring-like LGE, high-risk genotypes, and myocardial inflammation predicted the first episode of MAE by 60 months.

## Structured Graphical Abstract

### Key Question

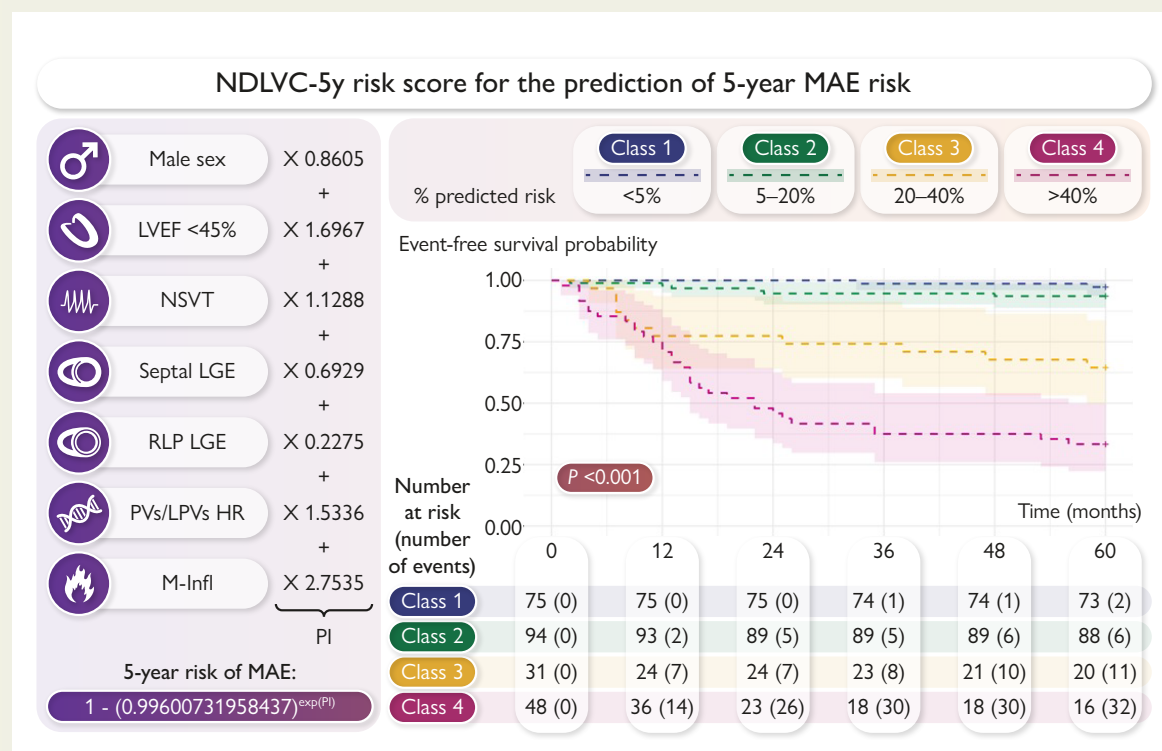
What predicts the occurrence of the first major arrhythmic event (MAE) in non-dilated left ventricular cardiomyopathy (NDLVC)?

### Key Finding

In NDLVC, male sex, non-sustained ventricular tachycardia, left ventricular ejection fraction  $< 45\%$ , septal and ring-like late gadolinium enhancement, high-risk genotypes, and myocardial inflammation predicted the first episode of MAE by 60 months. A new risk score (NDLVC-5y) was subsequently derived.

### Take Home Message

A multi-parametric approach improves the arrhythmic risk stratification of NDLVC.



The main study results are summarized. The key risk factors contributing to the NDLVC-5y risk score are shown, along with the Kaplan–Meier curves for MAE-free survival by 60 months (5 years) within the derivation cohort. Number at risk and number of events are shown under the chart for each of the four risk classes (1 = low risk; 2 = mid-low risk; 3 = mid-high risk; 4 = high risk). LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NDLVC, non-dilated left ventricular cardiomyopathy; M-Infl, myocardial inflammation; MAE, major arrhythmic event; NSVT, non-sustained ventricular tachycardia; PV/LPV HR, pathogenic/likely pathogenic variant in high-risk genes (i.e. *LMNA*, *FLNC*, *TMEM43*, *PLN*, *DSP*, and *RBM20*); RLP, ring-like pattern.

## Keywords

Cardiomyopathy • NDLVC • Ventricular arrhythmia • Sudden cardiac death • Inflammation • Risk stratification

## Introduction

In 2023, the European Society of Cardiology (ESC) guidelines introduced the expression 'non-dilated left ventricular cardiomyopathy' (NDLVC) phenotype, to refer to 'the presence of non-ischaemic left ventricular (LV) scarring or fatty replacement in the absence of LV dilatation, with or without global or regional wall motion abnormalities, or isolated global LV hypokinesia without scarring (as assessed by the presence of late gadolinium enhancement [LGE] on cardiac magnetic resonance [CMR]) that is unexplained solely by abnormal loading conditions (hypertension, valve diseases) or coronary artery disease'.<sup>1</sup>

The NDLVC definition encompasses a spectrum of possible aetiologies, whose identification is guided by an advanced diagnostic workup, which frequently includes genetic testing and histology on top of CMR.<sup>2,3</sup> Except for defined clinical settings (i.e. specific genetic cardiomyopathies), there are currently no definite specific tools available for guiding risk stratification and the primary prevention of sudden cardiac death (SCD) in NDLVC. Previous studies on non-ischaemic cardiomyopathies have suggested a prognostic role for both myocardial inflammation (M-Infl)<sup>4</sup> and distinct genotypes.<sup>5–7</sup>

In response to the call of the ESC guidelines,<sup>1</sup> we aimed to identify the predictors of the first major arrhythmic event (MAE) in a cohort of patients with NDLVC.

## Methods

### Study population

This is a retrospective, observational study, taking place at two large centres experienced in the management of cardiomyopathies (San Raffaele Hospital of Milan and Trieste Hospital, Italy). In compliance with the Declaration of Helsinki, all the participants signed a written informed consent for enrolment in local research registries, approved by the local Institutional Review Boards, and aimed to collect clinical data at long-term follow-up. In detail, patients with NDLVC were identified among those with informative baseline characterization and prospectively collected follow-up data. A total of 337 patients between January 2010 and May 2023 were identified based on the following inclusion criteria, as defined by the 2023 ESC guidelines<sup>1</sup>: (i) age  $\geq 18$  years at first cardiological evaluation in the enrolling centre (not preceded by other evaluations in minor centres); (ii) indexed left ventricular end-diastolic volume (LVEDVi)  $< 62$  mL/m<sup>2</sup> in females and  $< 75$  mL/m<sup>2</sup> in males, at baseline echocardiogram<sup>8</sup>; and (iii) either left ventricular ejection fraction (LVEF)  $< 50\%$  and/or non-ischaemic pattern of LGE at baseline CMR.<sup>1</sup>

The exclusion criteria were (i) presentation with cardiocirculatory arrest (CCA), ventricular fibrillation (VF), or sustained ventricular tachycardia (VT); (ii) history of myocardial infarction or proven obstructive coronary artery disease; (iii) overlapping cardiomyopathies other than NDLVC, according to the ESC classification<sup>1</sup>; (iv) fulminant myocarditis;<sup>9</sup> (v) acute myocarditis proven either by endomyocardial biopsy (EMB) according to the ESC criteria<sup>10</sup> or by CMR according to the updated Lake Louise criteria,<sup>11</sup> in patients with new-onset chest pain accompanied by troponin elevation (infarct-like presentation) and with either proven or suspected viral aetiology (documented pathogenic viral genomes on EMB<sup>10</sup> or history of viral infections over the 30 days preceding the clinical presentation, respectively);<sup>12</sup> (vi) abnormal loading conditions, namely, valvular heart diseases of moderate to severe degree, congenital heart disease, and uncontrolled hypertension<sup>13</sup>; (vii) known exposure to exogenous pathogenic noxae (COVID-19 vaccination or other vaccines, alcohol, drugs, toxic agents, or prior chemo/radio/immunotherapy); (viii) systemic rheumatologic diseases; (ix) sarcoidosis; and (x) asymptomatic genotype-positive relatives identified by family screening. The study flowchart is shown in [Figure 1](#).

A de-identified database from the participating centres was used for data collection. A multicentre cohort of 216 patients with NDLVC meeting the

same inclusion and exclusion criteria was employed for validation purposes from 11 European centres (Ancona, Arezzo, Athens, Barcelona Bellvitge, Barcelona Sant Pau, Berlin, Florence Careggi, Florence Don Gnocchi, Maastricht, Padua, Valencia—details in the [Supplementary data](#)). The data supporting the study findings will be made available upon reasonable request.

### Diagnostic workup

For the study purposes, the baseline characterization of NDLVC included echocardiogram and, whenever available, CMR with LGE sequences.<sup>14</sup> In detail, LGE was defined as a non-ischaemic stria pattern involving at least two consecutive segments of the left ventricle.<sup>15,16</sup> Late gadolinium enhancement short- and long-axis images were analysed in terms of distribution (subepicardial, midwall, both), extension (number of LV segments involved, from 1 to 17, with visual thresholding), and localization (i.e. either isolated or dominant septal involvement). In addition, the presence of a ring-like pattern (RLP), i.e. presence of LGE involving at least three contiguous segments within the same short-axis slice,<sup>17,18</sup> was systematically evaluated and reviewed at each participating centre (derivation and validation), by personnel blinded to the study design and outcomes.

Either right septal or left ventricular EMB was performed with a patient-tailored indication. Myocardial inflammation was defined by 3 months of clinical presentation, as follows: (i) EMB-proven: based on the ESC definition of virus-negative myocarditis,<sup>10</sup> including histological (inflammatory infiltrates of non-ischaemic origin, either with or without necrosis), immunohistochemical ( $\geq 14$  leucocytes/mm<sup>2</sup> including up to 4 CD68+ monocytes/mm<sup>2</sup> and  $\geq 7$  CD3+ T lymphocytes/mm<sup>2</sup>), and molecular analyses (absence of intra-myocardial pathogenic viral genomes), and (ii) CMR-proven: based on the updated Lake Louise criteria.<sup>11</sup> In detail, T2-weighted images included black blood T2-short tau inversion recovery sequences on two orthogonal planes and parametric T2 mapping with previously defined cut-off values.<sup>19</sup> For patients undergoing both CMR and EMB within a 3-month time frame, histology results were prioritized in the event of discordant findings.

Ventricular tachycardia episodes were classified into sustained or non-sustained (NSVT) according to recommended criteria.<sup>20</sup>

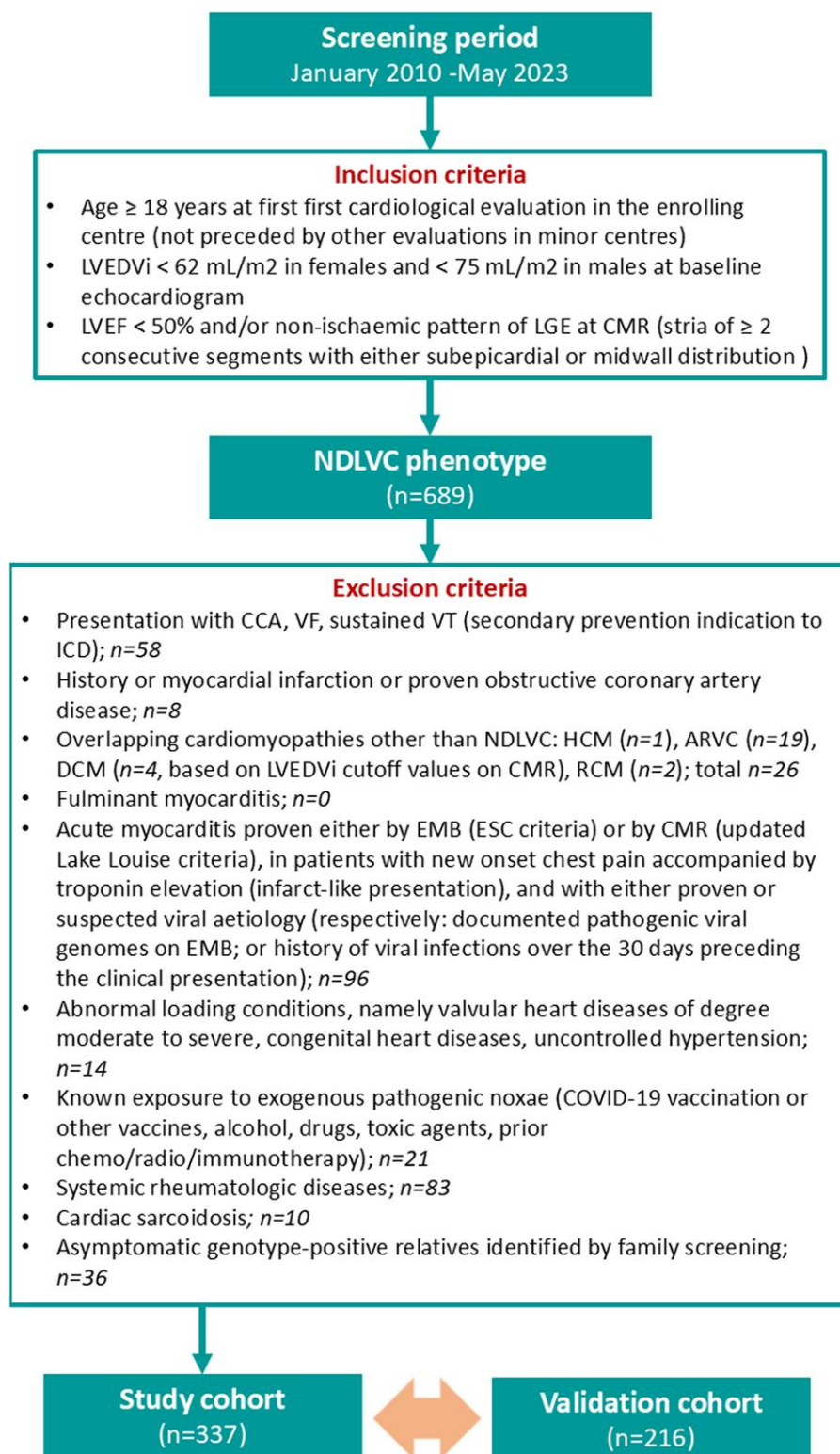
At both leading centres, genetic testing was performed by the Illumina TruSight One-Sequence panel (Illumina, Redwood City, California). A panel of cardiomyopathy-associated genes was analysed (see [Supplementary data online, Table S1](#)). Variants were filtered and prioritized based on information available in public databases and classified according to the American College of Medical Genetics and Genomics guidelines.<sup>21</sup> For risk stratification purposes, only pathogenic and likely pathogenic variants (PVs/LPVs) were considered on the so-called 'high-risk' genes, including *LMNA*, *FLNC*, *TMEM43*, *PLN*, *DSP*, and *RBM20*, as recommended by the ESC.<sup>1</sup>

### Treatment and follow-up

Treatment choices, including antiarrhythmic drugs and implantable cardioverter-defibrillator (ICD) placement, were clinically driven and in keeping with prior ESC guidelines.<sup>20,22</sup> The use of immunomodulatory therapy to target EMB-proven M-Infl was patient-tailored. Follow-up clinical data were prospectively collected during in-person clinical visits, occurring every 6 or 12 months from the time of NDLVC diagnosis, at the discretion of the site investigator, and included clinical reassessment, ambulatory Holter ECG monitoring, transthoracic echocardiography, and telemetric interrogations in cardiac device carriers. For patients without the planned in-person evaluation, information regarding vital status and symptoms was obtained from medical records and telephone calls. For each patient, follow-up ended at the last clinical contact or on 1<sup>st</sup> March 2024.

### Endpoints

The primary endpoint of the study was the occurrence of MAE, including SCD, sustained VT, VF, or appropriate ICD therapy [anti-tachycardia pacing (ATP), or shock] by 60-month follow-up. For the study purposes, the



**Figure 1** Study flowchart. ARVC, arrhythmogenic right ventricular cardiomyopathy; CCA, cardiocirculatory arrest; CMR, cardiac magnetic resonance; DCM, dilated left ventricular cardiomyopathy; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; n, number; NDLCV, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy; VF, ventricular fibrillation; VT, ventricular tachycardia



minimal ventricular rate to define arrhythmic events was set at 167 b.p.m.<sup>23,24</sup> Event times were measured from the date of NDLVC diagnosis. The complete definitions of events are reported in the [Supplementary data](#).

## Statistical analysis

All analyses and graphics were performed in R environment (ver. 4.4.2) and SPSS Version 20 (IBM Corp., Armonk, NY, USA). Missing data were managed by multiple imputation with random forest imputation.<sup>25,26</sup> Continuous variables were compared by t-type Welch's test statistic. Dependencies between dichotomic categorical variables were compared by using Fisher's exact test. Survival curves were fitted by the Kaplan–Meier estimator and compared by the log-rank test. Cox proportional hazard model was selected by LASSO procedure, to identify the risk factors for the primary outcome, among those priorly selected based on the known clinical relevance. Optimal LASSO  $\lambda$  parameter was fitted by 10-fold cross-validation.<sup>27</sup> Validation was performed by computing Uno's C-index by 10-times 10-fold cross-validation.<sup>28</sup> To further investigate how different independent variables affect the risk score, a sensitivity analysis was performed on the fitted model. A risk score (NDLVC-5y), version 1 ('v1') was derived from the global model described above. To reflect the heterogeneity of diagnostic tools available in the real world, a restricted model was built based on the minimal diagnostic workup to fulfil the definition of NDLVC (i.e. CMR and echocardiography in the absence of M-Infl and genetics). The restricted model was selected by the same LASSO procedure described for the global model. Based on the fitted 5-year probability of the event, we identified four risk classes: class 1 (low) = 0–5%; class 2 (mid-low) = 5–20%; class 3 (mid-high) = 20–40%; and class 4 (high) = > 40%. External validation was computed by applying the fitted model and risk classes to the independent validation cohort, without refitting.<sup>29</sup> The model was refined using calibration plots with bootstrap procedure (B = 10000). A calibration analysis of both global and restricted models was performed.

Two-sided  $P < .05$  were considered statistically significant. Accordingly, the confidence level for intervals (CI) was set at 95%. All  $P$ -values were computed by permutation methods to avoid any distributional assumption or asymptotic approximation.

## Results

### General features of the population

The study cohort is composed of 337 patients with NDLVC (mean age  $37 \pm 15$  years, 62% male), of whom 297 (88%) had symptoms mainly including palpitations ([Table 1](#)). The mean LVEF at presentation was  $52 \pm 8\%$ , with LV systolic dysfunction (LVEF < 50%) documented in 135 patients (40%) and at least one NSVT episode recorded at baseline in 99 cases (29%).

Delayed-enhanced CMR was performed in 296 patients (88%) and was remarkable for LGE in 233 cases (79%), of whom 81 (35%) and 42 (18%) showed septal localization and the RLP, respectively. Endomyocardial biopsy (91% right ventricular septum sampling) was performed in 126 symptomatic patients, mainly because of persistent arrhythmias (58%), LV systolic dysfunction (26%), or non-informative CMR (9%). Signs of M-Infl were detected in 130 patients (39%), including CMR ( $n = 108$ ), histology ( $n = 66$ ), or both techniques ( $n = 44$ ).

Of the 208 genotyped patients, 109 (52%) had PVs/LPVs in cardiomyopathy-associated genes, of whom 64 (59%) had the high-risk genotype (see [Supplementary data online, Table S2](#)). Specifically, the high-risk genes mainly included *DSP* ( $n = 24$ ), *LMNA* ( $n = 20$ ), and *FLNC* ( $n = 17$ ), whereas *TTN* accounted for most of the remaining ones ( $n = 26$ ). The comparison among clinically relevant subgroups identified by multimodality diagnostic workup is shown in [Supplementary data online, Table S3](#).

**Table 1** Baseline features of the study population ( $n = 337$ )

Parameter	
Baseline features	
Age, years, mean $\pm$ SD	$37 \pm 15$
Male sex, $n$ (%)	209 (62)
Caucasian, $n$ (%)	327 (97)
Family history of SCD/CM, $n$ (%)	120 (36)
Clinical presentation	
Syncope, $n$ (%)	19 (6)
Palpitation, $n$ (%)	216 (64)
Dyspnoea, $n$ (%)	29 (9)
Chest pain, $n$ (%)	33 (10)
Asymptomatic <sup>a</sup> , $n$ (%)	40 (12)
NYHA class, q2 (range)	1 (1–2)
Electrocardiogram and telemonitoring	
First-degree AVB, $n$ (%)	51 (15)
IVCD, $n$ (%)	124 (37)
ST/T abnormalities, $n$ (%)	172 (51)
Second/third-degree AVB, $n$ (%)	6 (2)
Supraventricular arrhythmias, $n$ (%)	23 (7)
NSVT, $n$ (%)	99 (29)
Daily PVC, $n \cdot 10^3$ , q2 (q1–q3)	349 (3–3578)
Blood exams	
Elevated troponin, $n$ (%)	70 (21)
Elevated natriuretic peptides, $n$ (%)	130 (39)
Elevated C-reactive protein, fraction (%)	15/289 (5)
Transthoracic echocardiogram	
LVEDVi, mL/m <sup>2</sup> , mean $\pm$ SD	$60 \pm 9$
LVEF, %, mean $\pm$ SD	$52 \pm 8$
LVEF < 50%, $n$ (%)	135 (40)
LVEF < 45%, $n$ (%)	46 (14)
LVEF < 35%, $n$ (%)	0 (0)
Diastolic dysfunction, $n$ (%)	124 (37)
RV dilation, $n$ (%)	9 (3)
RV systolic dysfunction, $n$ (%)	2 (1)
Cardiac magnetic resonance	
LGE presence fraction (%)	233/296 (79)
No. of LGE segments, mean $\pm$ SD	$5 \pm 2$
Subepicardial LGE, fraction (%)	192/296 (65)
Septal LGE, fraction (%)	81/296 (27)
Ring-like LGE, fraction (%)	42/296 (14)

Continued

**Table 1 Continued**

Parameter	
Abnormal T2-weighted sequences (M-Infl), fraction (%)	108/296 (36)
Fatty replacement, fraction (%)	13/114 (11)
FDG-PET scan, fraction (%)	
Abnormal FDG uptake	22/46 (48)
Endomyocardial biopsy, fraction (%)	
CD3+ > 7/mm <sup>2</sup> (M-Infl)	66/126 (52)
With histology-proven necrosis	25/126 (20)
Without histology-proven necrosis	41/126 (32)
Reactive fibrosis	86/126 (68)
Cardiomyopathic features <sup>b</sup>	95/126 (75)
Genetic test, fraction (%)	
Any variant	155/208 (75)
PVs/LPVs	109/208 (52)
PVs/LPVs in high-risk genes <sup>c</sup>	64/208 (31)

AVB, atrioventricular block; CD, cluster of differentiation; CM, cardiomyopathy; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; IVCD, intraventricular conduction delay; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; M-Infl, myocardial inflammation; NDLC, non-dilated left ventricular cardiomyopathy; NYHA, New York Heart Association; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complexes; q, quartile; PV/LPV, pathogenic/likely pathogenic variant in cardiomyopathy-associated genes; RV, right ventricular; SCD, sudden cardiac death; SD, standard deviation.

<sup>a</sup>Asymptomatic patients were identified by routine medical evaluation: in most cases ( $n = 33/40$ , 83%), patients showed electrocardiogram abnormalities and/or arrhythmias at pre-participation screening for sports activity.

<sup>b</sup>Features suggesting chronic cardiomyopathy included cardiac myocyte hypertrophy, sarcoplasmic vacuolization, and nuclear atypia.

<sup>c</sup>High-risk genes include *LMNA* ( $n = 20$ ), *FLNC* ( $n = 17$ ), *TMEM43* ( $n = 1$ ), *PLN* ( $n = 0$ ), *DSP* ( $n = 24$ ), and *RBM20* ( $n = 2$ ).

**Table 2 Events by 60-month follow-up**

Parameter	
Major adverse outcomes	
All cause death <sup>a</sup> , $n$ (%)	4 (1)
Cardiac death <sup>a</sup> , $n$ (%)	3 (1)
Heart transplant, $n$ (%)	7 (2)
For VT storms	3 (1)
For mechanical failure	4 (1)
Timing, months, median (range)	38 (11–55)
MAE, $n$ (%)	51 (15)
MAE detail, $n$ (%)	
VF or SCD	2 (1)
Sustained VT	3 (1)
ICD therapy—ATP	10 (3)
ICD therapy—shock	36 (11)
Other endpoints, $n$ (%)	
Cardiac hospitalization	58 (17)
Urgent/for symptoms	19 (5)
For diagnostic workup	13 (4)
For treatment upgrade	26 (8)
VT below the threshold of ICD detection	2 (1)
LVEF < 35%	15 (4)
LVEF < 50%	78 (23)
Catheter ablation of VT	8 (2)

ATP, anti-tachycardia pacing; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MAE, major arrhythmic event; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

<sup>a</sup>Cardiac death included electrical storm from fast VT/VF in an ICD carrier ( $n = 1$ ), SCD from VF in a pacemaker carrier ( $n = 1$ ), and device-related infectious endocarditis ( $n = 1$ ); non-cardiac death was due to malignancy ( $n = 1$ ).

## Treatment

Medical treatment included beta-blockers (78%), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (72%), angiotensin receptor–neprilysin inhibitors (10%), sodium–glucose cotransporter-2 inhibitors (12%), and diuretics (18%). In addition, immunomodulatory strategies were used in 83 of the 130 patients (64%) with documented M-Infl (see [Supplementary data online, Table S3](#)). For the primary prevention of SCD, 180 patients (53%) underwent ICD implantation. In addition, one patient (<1%) received a pacemaker and 71 (21%) had a loop recorder. Additional data on treatment strategies are shown in [Supplementary data online, Table S4](#).

## Endpoints

The median follow-up of the study was 85 (IQR 53–120) months, and 2 patients (< 1%) were lost to follow-up. Overall, 4 patients died (1%; SCD or VF,  $n = 2$ ; device-related infectious endocarditis,  $n = 1$ ; malignancy,  $n = 1$ ), and 7 (2%) underwent heart transplant.

By 60-month follow-up, MAE occurred in 51 patients (15%), including appropriate ICD shocks in 36 (11%). Eight patients (2%) underwent

VT catheter ablation. Additional data about outcomes are reported in [Table 2](#). Major arrhythmic event occurred earlier in patients with M-Infl as compared with those carrying PVs/LPVs (see [Supplementary data online, Figure S1](#)).

## Risk stratification

We report no missing data regarding the candidate risk factors for MAE. As shown in [Table 3](#), univariable Cox's regression analysis identified baseline NSVT, RLP of LGE, PVs/LPVs in high-risk genes, and M-Infl, as the four main predictors of MAE by 60 months (all  $P < .001$ ).

In multivariable analysis (global model), the primary endpoint was independently predicted by male sex [hazard ratio (HR) 2.4, 95% CI 1.3–4.4,  $P = .007$ ], baseline NSVT (HR 3.1, 95% CI 1.7–5.6,  $P < .001$ ), baseline LVEF < 45% (HR 5.5, 95% CI 2.7–11.0,  $P < .001$ ), septal localization of LGE (HR 2.0, 95% CI 1.0–4.0,  $P = .046$ ), RLP (HR 1.3, 95% CI .6–2.6,  $P = .54$ ), PVs/LPVs in high-risk genes (HR 4.6, 95% CI 2.3–9.1,  $P$

**Table 3** Risk stratification

Candidate risk factor	Univariable Cox's		Multivariable Cox's		Performance
	HR (95% CI)	P-value	HR (95% CI)	P-value	
Age > 30 years	1.3 (.7–2.3)	.40			Uno's C = 0.81 (95% CI .75–.88)
Male sex	1.5 (.8–2.6)	.19	2.4 (1.3–4.4)	.007	
Non-Caucasian ethnicity	1.8 (.4–7.3)	.42			
Syncope at presentation	2.4 (1.1–5.0)	.02			
IVCD	1.5 (.9–2.7)	.12			
Second/third-degree AVB	1.3 (.7–2.5)	.47			
Baseline NSVT	3.8 (.8–2.9)	<.001	3.1 (1.7–5.6)	<.001	
Baseline PVC > 5000/24 h	1.3 (.7–1.9)	.68			
LVEF < 50%	1.1 (.7–1.7)	.89			
LVEF < 45%	2.3 (1.4–2.3)	.008	5.5 (2.7–11.0)	<.001	
LVEF < 40%	0.9 (.5–1.9)	.73			
LGE	2.2 (.9–5.0)	.08			
Septal LGE	2.5 (1.5–4.4)	.001	2.0 (1.0–4.0)	.046	
Ring-like pattern LGE	5.8 (2.8–8.3)	<.001	1.3 (.6–2.6)	.54	
Cardiomyopathic PV/LPVs	1.2 (.7–2.1)	.55			
PV/LPVs in high-risk genes <sup>a</sup>	2.5 (1.4–4.3)	<.001	4.6 (2.3–9.1)	<.001	
M-Infl	4.1 (2.3–10.2)	<.001	15.7 (6.1–40.3)	<.001	

AVB, atrioventricular block; CI, confidence intervals; HR, hazard ratio; IVCD, intraventricular conduction delay; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; M-Infl, myocardial inflammation; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complexes.

<sup>a</sup>High-risk genes include *LMNA*, *FLNC*, *TMEM43*, *PLN*, *DSP*, and *RBM20*.

<.001), and M-Infl (HR 15.7, 95% CI 6.1–40.3,  $P < .001$ ). The Kaplan–Meier curves for the single predictors are shown in [Figure 2](#). Irrespective of the diagnostic technique (i.e. EMB and/or CMR), M-Infl showed a high negative predictive value for MAE (see [Supplementary data online, Table S5](#) and [Figure S2](#)).

In the restricted model not accounting for genetics and M-Infl, the primary endpoint was better predicted by a RLP of LGE and baseline NSVT (see [Supplementary data online, Table S6](#)). Within the derivation cohort, the global model had a greater accuracy than the restricted one (see [Supplementary data online, Figure S3](#)).

## Validation cohort

The clinical features of the validation cohort are presented in [Supplementary data online, Table S7](#). While clinical profiles at presentation were similar to the study group, the proportion of cases undergoing genetic testing and search for M-Infl was significantly lower in validation as compared with the study cohort [63/216 (29%) vs 208/337 (62%) and 81/216 (38%) vs 301/337 (89%); both  $P < .001$ ]. However, the relative proportion of high-risk genotypes and M-Infl was comparable (see [Supplementary data online, Table S7](#)). By 60-month follow-up, MAE occurred in 41 patients (19%, vs 15% in the study cohort,  $P = .24$ ). Both models were verified in the validation cohort (global model: Uno's C 0.81, 95% CI .75–.88; restricted model: Uno's C 0.79, 95% CI .71–.88).

## Risk score

The formula to estimate the NDLVC-5y score, version 1 ('v1'), derived from the global multivariable model presented above, is calculated according to the following equation:

$$5 - \text{year risk of MAE} = 1 - (0.99600731958437)^{\exp(\text{PI})}$$

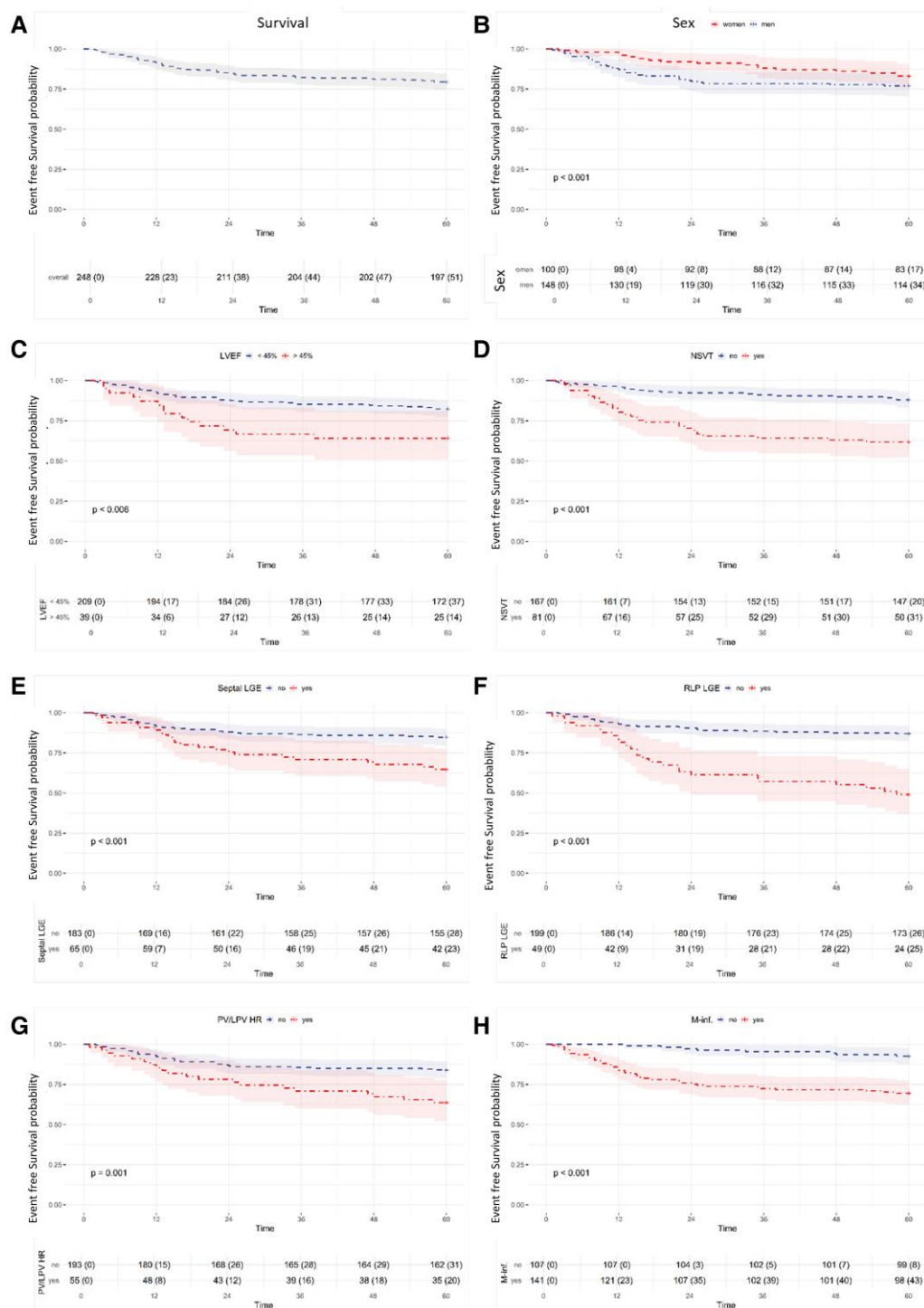
Here, PI represents the prognostic index, which is calculated according to the equation  $PI = 0.8605I_{\text{male sex}} + 1.6967I_{\text{LVEF} < 45\%} + 1.1288I_{\text{NSVT}} + 0.6929I_{\text{Septal LGE}} + 0.2275I_{\text{RLP LGE}} + 1.5336I_{\text{PVs/LPVs HR}} + 2.7535I_{\text{M-infl}}$ . The functions  $I_*$  are defined to take value 1 (if the predictor \* is present) or 0 (if the predictor \* is absent), and 0.99600731958437 is the fitted survival at baseline.

The Kaplan–Meier curves for risk classes 1–4 are shown in [Figure 3](#). The results of the application of the NDLVC-5y score to the validation cohort are presented in [Figure 4](#).

## Discussion

### Main study findings

In response to the recently issued call of the ESC guidelines,<sup>1</sup> our study sought to address the gap in arrhythmic risk stratification in NDLVC. The main elements of novelty of our paper are as follows:

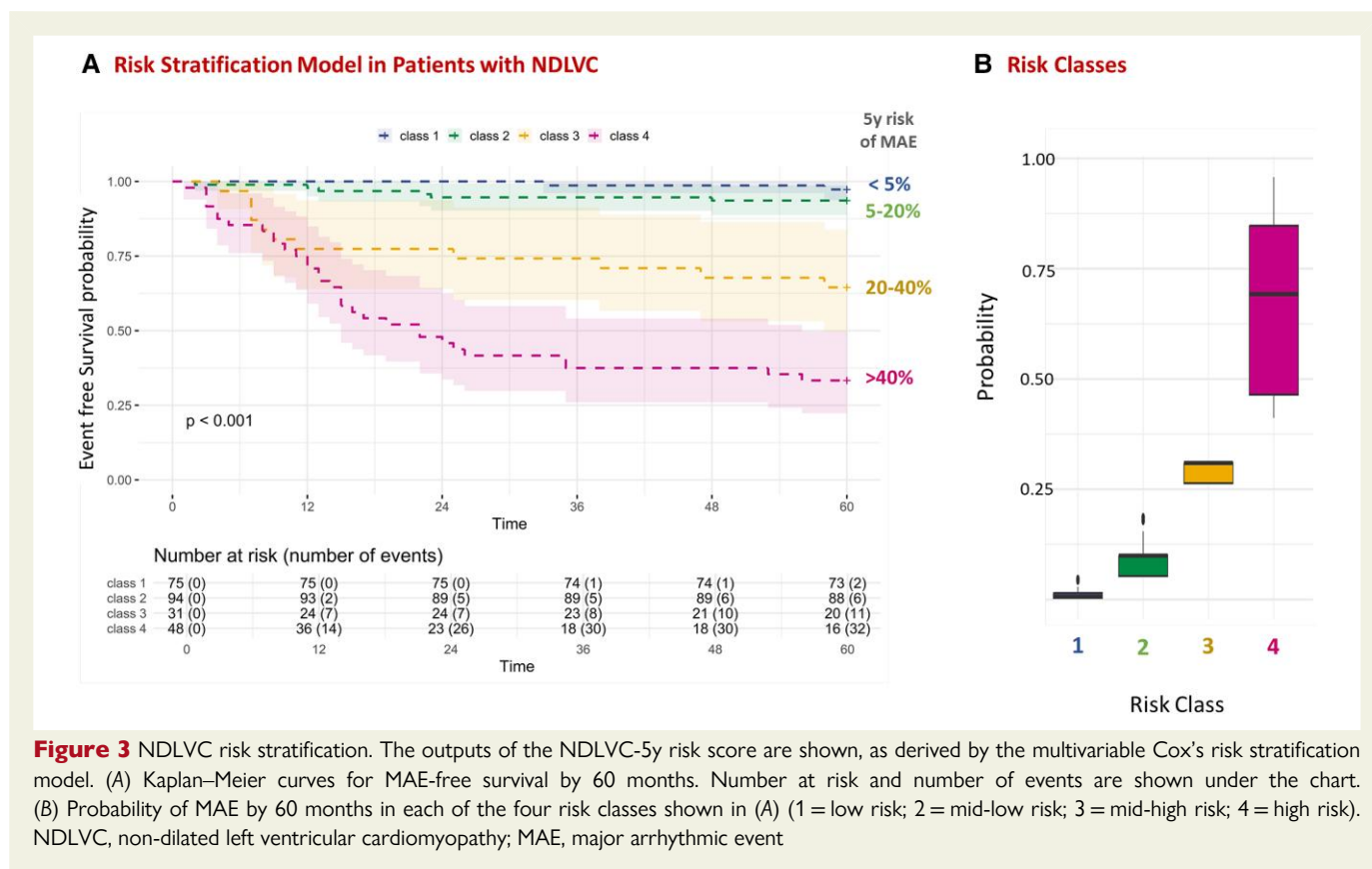


**Figure 2** Predictors of MAE. Kaplan–Meier curves are shown for the freedom from MAE by 60 months, in groups defined by the presence/absence of each of the predictors identified by multivariable analyses. Numbers at risk are shown under each chart. LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MAE, major arrhythmic event; M-Infl, myocardial inflammation; NSVT, non-sustained ventricular tachycardia; PV/LPV HR, pathogenic/likely pathogenic variants in high-risk genes (i.e. *LMNA*, *FLNC*, *TMEM43*, *PLN*, *DSP*, and *RBM20*); RLP, ring-like pattern

(i) the validation of many dilated cardiomyopathy-derived candidate risk factors for MAE (i.e. LVEF, NSVT, distinct patterns of LGE, high-risk genotypes) in the novel setting of NDLVC<sup>1</sup>; (ii) the identification of M-Infl as an additional critical predictor of MAE, which prompts the

relevant role of T2-weighted CMR and EMB in NDLVC workup; and (iii) the creation of a novel risk score for NDLVC (NDLVC-5y), offering a practical instrument to predict MAE in daily clinical practice (*Structured Graphical Abstract*). Considering the ESC definition, we





**Figure 3** NDLVC risk stratification. The outputs of the NDLVC-5y risk score are shown, as derived by the multivariable Cox's risk stratification model. (A) Kaplan–Meier curves for MAE-free survival by 60 months. Number at risk and number of events are shown under the chart. (B) Probability of MAE by 60 months in each of the four risk classes shown in (A) (1 = low risk; 2 = mid-low risk; 3 = mid-high risk; 4 = high risk). NDLVC, non-dilated left ventricular cardiomyopathy; MAE, major arrhythmic event

presented also a restricted risk stratification model for NDLVC (i.e. without genetics and search for M-Infl), to favour widespread applicability of our findings.

## Non-dilated left ventricular cardiomyopathy aetiology

Based on the phenotype-based definition of the ESC, which relies solely on transthoracic echocardiography and delayed-enhanced CMR,<sup>1</sup> NDLVC encompasses a broad spectrum of aetiologies, including chronic myocarditis, early-stage dilated cardiomyopathy, and either isolated or left-dominant arrhythmogenic cardiomyopathy variants.<sup>30</sup> In this setting, genetic testing and histology may help to identify the disease aetiology and to subsequently guide the clinical decisions: examples of beneficial effects range from early diagnosis of genetic diseases in asymptomatic relatives<sup>1,21</sup> to the safe use of immunosuppressive therapy for EMB-proven virus-negative myocarditis.<sup>10</sup> On the other hand, we described a consistent proportion of cases with non-diagnostic findings even following advanced diagnostic workup (genetic test, histology, CMR), as well as patients with overlapping genetic and inflammatory features (see [Supplementary data online, Table S3](#)). In light of the above, high-risk genotypes and M-Infl were hereby used for risk stratification purposes as merely descriptive terms, without any claim of defining NDLVC aetiology.

## Risk stratification

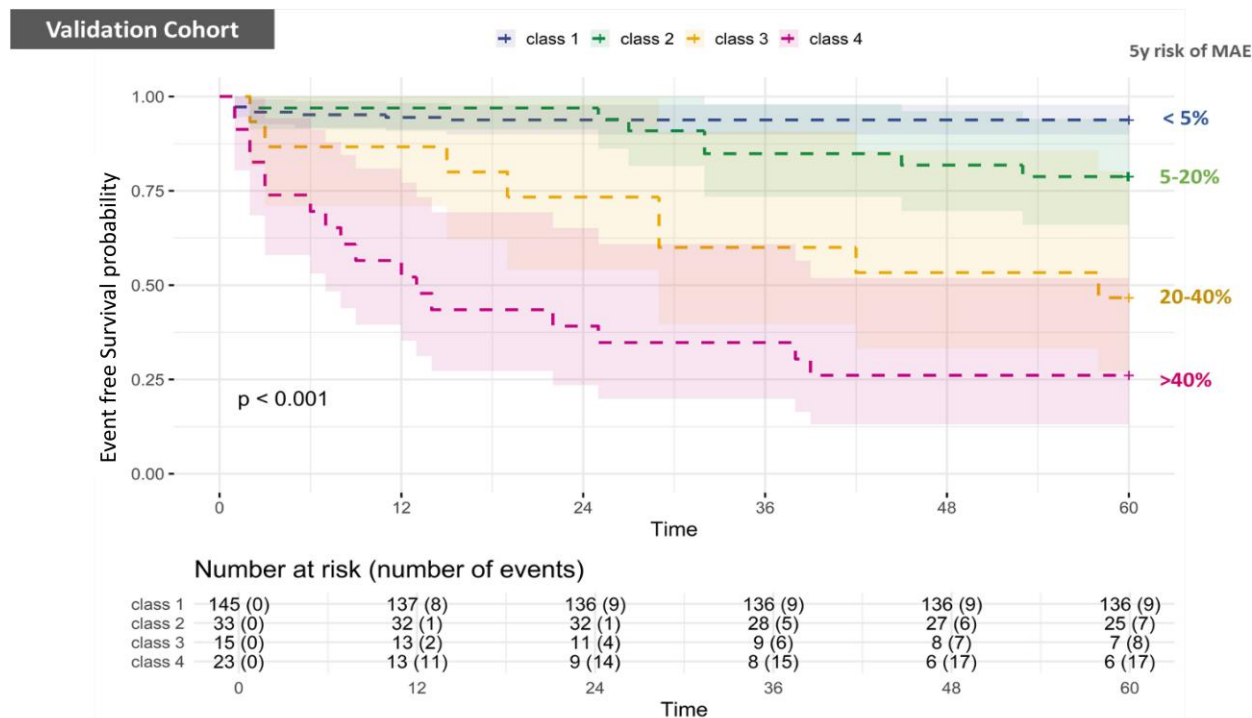
Our study primarily aimed to improve the prediction of the first MAE in NDLVC. Our inclusive study design offered the unique opportunity of comparing outcomes within a broad spectrum of genetic and inflammatory diseases, including undefined and overlapping cases. As suggested

by the ESC guidelines,<sup>1</sup> both echocardiogram-derived LVEF < 45% and baseline NSVT were confirmed as relevant risk factors.<sup>31–36</sup> In addition, we demonstrated that the septal localization and RLP of LGE were capable of predicting MAE more efficiently than other CMR-derived parameters such as LGE presence and extension.<sup>18,37,38</sup> Our results were probably influenced by the high prevalence of LGE (79% within the study cohort, with a mean of 5 segments per patient, [Table 1](#)), but do not contradict pre-existing evidence.<sup>18,39,40</sup> Among genotypes, the association with MAE was hereby proven not for any kind PVs/LPVs ([Table 3](#)), but only for the guideline-defined high-risk genes.<sup>5,41</sup> The known association between the RLP and high-risk genes such as *DSP* and *FLNC*<sup>3</sup> may have accounted for the higher predictivity of RLP in the restricted model (see [Supplementary data online, Table S3](#)). Importantly, no prior studies to our knowledge described the prognostic value of M-Infl. We showed that M-Infl was a strong predictor of MAE ([Table 3](#)), notable for a high rule-out value (see [Supplementary data online, Figure S2](#)), in both EMB- and CMR-proven settings (see [Supplementary data online, Table S5](#)), and at a shorter term than high-risk genotypes (see [Supplementary data online, Figure S1](#)). Our findings call for a wider application of both genetic testing and search for M-Infl to the diagnostic workup of NDLVC.

## Clinical implications

We showed that genotyping and search for M-Infl are critical to improve the selection of candidates to ICD implant. The genetic and inflammatory subgroups were also more prone to cardiac death and heart transplant (see [Supplementary data online, Table S3](#)).

In our experience, arrhythmic presentation was the main driver for both genetic testing ([Table 1](#)) and frequent choice of EMB over



**Figure 4** Application of the NDLVC-5y score to the validation cohort. The Kaplan–Meier curves for MAE-free survival by 60 months are shown, as derived by the application of the NDLVC-5y risk score to the validation cohort. Number at risk and number of events are shown under the chart for each of the four risk classes (1 = low risk; 2 = mid-low risk; 3 = mid-high risk; 4 = high risk). NDLVC, non-dilated left ventricular cardiomyopathy; MAE, major arrhythmic event

T2-weighted CMR to detect M-Infl.<sup>42</sup> However, we highlight the complementarity between EMB and CMR and recommend a patient-tailored approach aimed to maximize their clinical value, i.e. for CMR, panoramic view, non-invasiveness, and restaging of M-Infl during follow-up, and for EMB, gold standard diagnosis, definition of histotype, and guidance to aetiology-driven therapy.<sup>10,12</sup>

In light of the potential overlaps, we also suggest considering genetic testing in patients with recurrent/arrhythmic myocarditis and EMB in genetic cardiomyopathies displaying suitable targets for immunomodulation (i.e. persistence of arrhythmias, low LVEF, or symptomatic troponin release).<sup>43,44</sup> In such clinically demanding scenarios, clinicians may consider genetic testing and EMB as parallel exams downstream CMR. In the event of unavailable local resources (T2-weighted CMR, performance and interpretation of EMB), referral to third-level centres within a hub-and-spoke network<sup>20,45,46</sup> is advisable. Importantly, our findings enhance the importance of multidisciplinary interactions to manage NDLCV.<sup>47</sup>

## Risk score in clinical practice

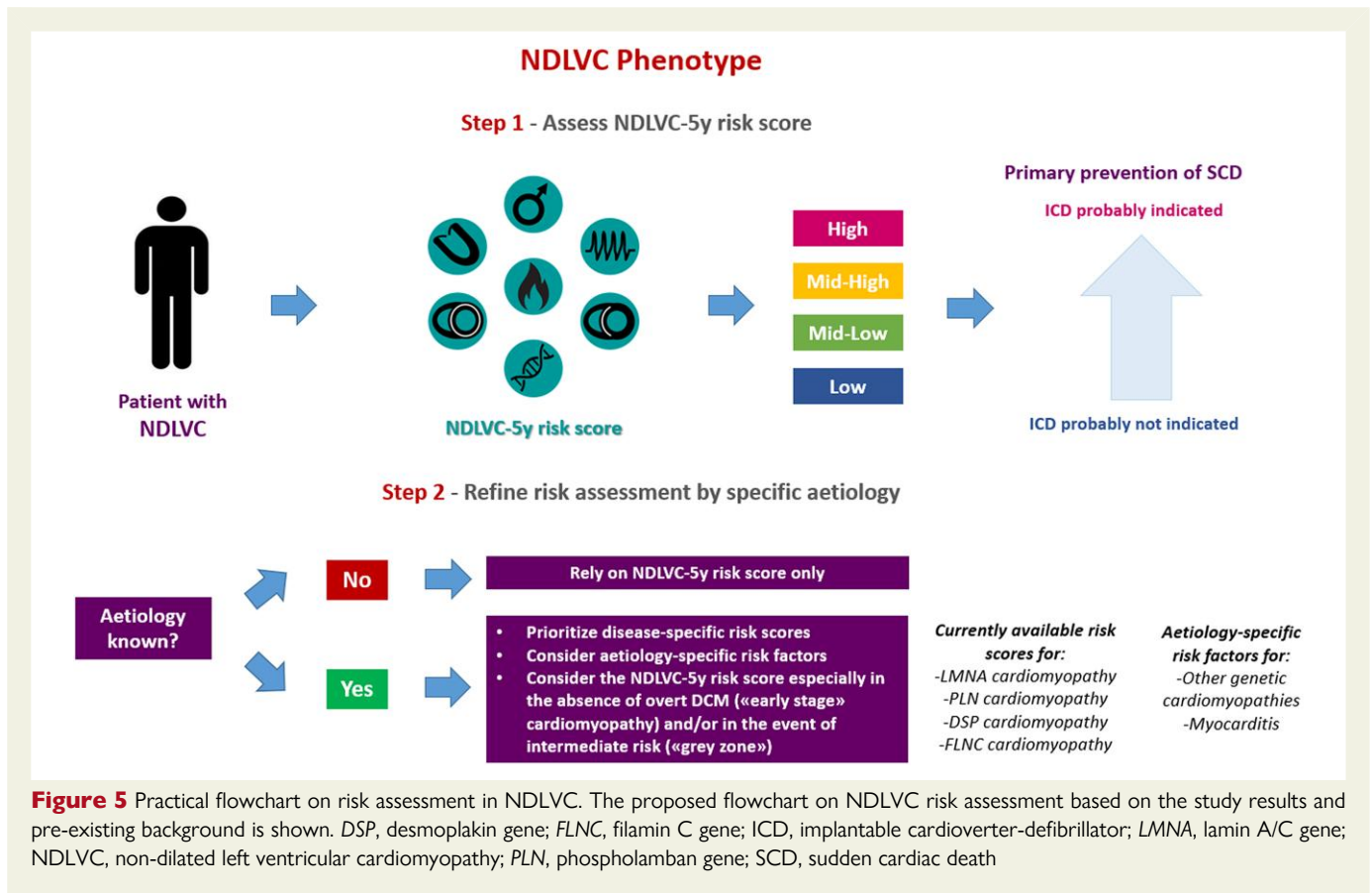
The NDLCV-5y risk score offers an actionable tool to guide arrhythmic risk stratification in daily clinical practice. Aimed to make the study results adaptable to patients with NDLCV investigated through delayed-enhanced CMR only, we presented a restrictive risk stratification model; however, we derived the risk score from the global model in light of its greater accuracy in predicting MAE (see [Supplementary data online, Figure S3](#)). Consistently with other disease-specific scores,<sup>32,35,48–50</sup> we defined distinct risk groups with a 5-year probability of events, hereby ranging from <5% to >40%.

The NDLCV-5y risk score is not meant to replace the existing ones, but just to enable the prediction of the first MAE in patients manifesting the ESC-defined NDLCV phenotype. Once a specific diagnosis is met, as well as if a distinct aetiology is known at baseline, the use of dedicated risk scores should be the first choice, as recommended.<sup>1</sup> However, the NDLCV-5y risk score is expected maximally helpful in more demanding clinical scenarios, such as patients with (i) NDLCV of undefined aetiology, (ii) known aetiology in the absence of overt DCM ('early stage'), or (iii) disease-specific scores resulting into an intermediate risk ('grey zone'). To assess arrhythmic risk in patients with NDLCV, we propose to follow the stepwise approach shown in [Figure 5](#).

The novel NDLCV-5y risk score deserves further validation by larger studies.

## Limitations

We presented a small-sized ( $n = 337$ ) retrospective study led by two centres only and validated in a geographically localized cohort: our risk score, currently labelled as 'v1' (version 1), calls for external validation. Reflecting the local practice and available resources, a selection bias applies to diagnostic tests and treatment strategies offered at the leading institutes: consistently, validating our global model was challenged by the limited investigation of M-Infl (EMB in particular) and genotypes in the other centres. A broad spectrum of NDLCV aetiologies were included in this study. Cardiac magnetic resonance was missing in 12% of NDLCV cases, and data were not reviewed in a core lab: the uniform inclusion of CMR with centralized analysis is advised for external validation purposes in the future. Cardiac magnetic resonance and quantitative data on cardiac biomarkers were not uniformly available. Also, while all patients were screened for



the high-risk genes (see [Supplementary data online, Table S1](#)), genetic re-testing was not performed. Importantly, the definition of M-Infl was heterogeneous, as assessed by histology and/or CMR: in particular, while most patients had concordant findings (see [Supplementary data online, Table S3](#)), we acknowledge that T2-weighted sequences on CMR may not equal M-Infl<sup>51</sup> and that EMB is biased by sampling errors.<sup>52</sup> While our definition of M-Infl was supported by recognized criteria in both techniques,<sup>10,11</sup> our study was underpowered to test the equivalence between CMR and EMB: dedicated studies are needed to this purpose. We also acknowledge that therapy might have modified the risk of MAE: however, the treatment unbalances between the cohorts (see [Supplementary data online, Table S7](#)) made this study unsuitable to investigate the mitigating effects of immunomodulation on arrhythmic risk. Finally, our risk stratification models have not been tested in patients with any degree of LV dilation or decompensated heart failure.

## Conclusion

Our findings suggest that male sex, baseline NSVT, LVEF < 45%, septal LGE, ring-like LGE, PVs/LPVs in high-risk genes, and M-Infl are critical predictors of MAE in patients with NDLVC. The NDLVC-5y is a novel risk score, designed to predict the first MAE by 60 months in NDLVC. Our results deserve confirmatory evidence and may change the prognostic assessment of patients with the NDLVC spectrum.

## Acknowledgements

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the Heart Rhythm Society. B.H. is a participant in the Berlin Institute of Health-Charité Advanced Clinician Scientist Pilot Program funded by the Charité-Universitätsmedizin Berlin and the Berlin Institute of Health.

## Supplementary data

[Supplementary data](#) are available at *European Heart Journal* online.

## Declarations

### Disclosure of Interest

G.P. received speaker fees from Abbott. M.Ca. received speaker fees from Abbott and Biosense Webster. B.H. is an inventor of patents that use RNA for the diagnosis of myocarditis (patent protection is being processed for MCG for diagnosis and measurement of therapy response in inflammatory cardiomyopathy and for cytokines as therapy targets in inflammatory cardiomyopathy). P.D.B. is a consultant for Abbott and Biosense and has received research grants from Abbott, Biosense, Biotronik, and Boston Scientific. The other authors report no disclosures.

### Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Funding

All authors declare no funding for this contribution.

## Ethical Approval

In compliance with the Declaration of Helsinki, all the participants signed a written informed consent for enrolment in local research registries, approved by the local Institutional Review Boards, and aimed to collect clinical data at long-term follow-up.

## Pre-registered Clinical Trial Number

None supplied.

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