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Magnetic Resonance Imaging Characterization and Clinical Outcomes of Dilated and Arrhythmogenic Left Ventricular Cardiomyopathies

Matteo Castrichini, MD[a,b,c,*], **Antonio De Luca, MD, PhD**[a,*], **Giulia De Angelis, MD**[a], **Raquel Neves, MD**[b], **Alessia Paldino, MD**[a], **Matteo Dal Ferro, MD**[a], **Giulia Barbati, PhD**[d], **Kristen Medo, MS**[c], **Andrea Barison, MD, PhD**[e], **Chrysanthos Grigoratos, MD, PhD**[e], **Marta Gigli, MD**[a], **Davide Stolfo, MD, PhD**[a,f], **Francesca Brun, MD**[a], **Daniel W. Groves, MD**[c], **Robert Quaife, MD**[c], **Ramone Eldemire, MD**[c], **Sharon Graw, PhD**[c], **Jeffrey Addison, MD**[c], **Giancarlo Todiere, MD, PhD**[e], **Ignazio Alessio Gueli, MD**[e], **Nicoletta Botto, BSc**[e], **Michele Emdin, MD, PhD**[e,g], **Giovanni Donato Aquaro, MD**[h], **Ramin Garmany, BS**[b], **Naveen L. Pereira, MD**[b], **Matthew R.G. Taylor, MD, PhD**[c], **Michael J. Ackerman, MD, PhD**[b], **Gianfranco Sinagra, MD**[a], **Luisa Mestroni, MD**[c], **John R. Giudicessi, MD, PhD**[b,†], **Marco Merlo, MD**[a,†]

[a]Cardiothoracovascular Department, Division of Cardiology, Azienda Sanitaria Universitaria Giuliano Isontina, University of Trieste, Trieste, Italy, member of European Reference Network for Rare, Low-Prevalence, or Complex Diseases of the Heart (ERN GUARD-Heart)

[b]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA

[c]University of Colorado Cardiovascular Institute, Anschutz Medical Campus, Aurora, Colorado, USA

[d]Biostatistics Unit, Department of Medical Sciences, University of Trieste, Trieste, Italy

[e]Fondazione CNR-Regione Toscana G. Monasterio, Pisa, Italy

[f]Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

[g]Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy

[h]Academic Radiology Unit, Department of Surgical, Medical and Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy.

Abstract

BACKGROUND—Nondilated left ventricular cardiomyopathy (NDLVC) has been recently differentiated from dilated cardiomyopathy (DCM). A comprehensive characterization of these 2 entities using cardiac magnetic resonance (CMR) and genetic testing has never been performed.

ADDRESS FOR CORRESPONDENCE: Dr Marco Merlo, Cardiothoracovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, University of Trieste, Via Valdoni, 7 34149 Trieste, Italy. marco.merlo@asugi.sanita.fvg.it.

*Drs Castrichini and De Luca contributed equally to this work and share first authorship.

†Drs Giudicessi and Merlo contributed equally to this work and share senior authorship.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

APPENDIX For supplemental tables and figures, please see the online version of this paper.

OBJECTIVES—This study sought to provide a thorough characterization and assess clinical outcomes in a large multicenter cohort of patients with DCM and NDLVC.

METHODS—A total of 462 patients with DCM (227) or NDLVC (235) with CMR data from 4 different referral centers were retrospectively analyzed. The study endpoint was a composite of sudden cardiac death or major ventricular arrhythmias.

RESULTS—In comparison to DCM, NDLVC had a higher prevalence of pathogenic or likely pathogenic variants of arrhythmogenic genes (40% vs 23%; $P < 0.001$), higher left ventricular (LV) systolic function (LV ejection fraction: 51% ± 12% vs 36% ± 15%; $P < 0.001$) and higher prevalence of free-wall late gadolinium enhancement (LGE) (27% vs 14%; $P < 0.001$). Conversely, DCM showed higher prevalence of pathogenic or likely pathogenic variants of nonarrhythmogenic genes (23% vs 12%; $P = 0.002$) and septal LGE (45% vs 32%; $P = 0.004$). Over a median follow-up of 81 months (Q1-Q3: 40-132 months), the study outcome occurred in 98 (21%) patients. LGE with septal location (HR: 1.929; 95% CI: 1.033-3.601; $P = 0.039$) was independently associated with the risk of sudden cardiac death or major ventricular arrhythmias together with LV dilatation, older age, advanced NYHA functional class, frequent ventricular ectopic activity, and nonsustained ventricular tachycardia.

CONCLUSIONS—In a multicenter cohort of patients with DCM and NDLVC, septal LGE together with LV dilatation, age, advanced disease, and frequent and repetitive ventricular arrhythmias were powerful predictors of major arrhythmic events.

Keywords

arrhythmias; dilated cardiomyopathy; LGE; nondilated left ventricular cardiomyopathy; SCD

Dilated cardiomyopathy (DCM) is a primary heart muscle disease characterized by left ventricular (LV) dilatation and systolic dysfunction in the absence of either pressure or volume overload or significant coronary artery disease (CAD).[1]

Recently, the 2023 European Society of Cardiology (ESC) guidelines for the management of cardiomyopathies introduced a new phenotype called nondilated LV cardiomyopathy (NDLVC). This new entity embraces different conditions characterized by LV hypokinesia without dilatation and LV scarring or fatty replacement regardless of LV function,[1] thus also including what was previously referred to as arrhythmogenic cardiomyopathy (ACM) with LV involvement.

Cardiac magnetic resonance (CMR) and genetic testing play a crucial role in the diagnosis and prognostic stratification of left-sided cardiomyopathies. In particular, CMR is able to identify myocardial scarring, which has been recognized as a strong predictor of major arrhythmic events.[2-5] Similarly, specific genotypes have been associated with greater arrhythmic risk.[6,7]

The role of CMR and genetic testing for the arrhythmic risk stratification in a cohort of patients with DCM and NDLVC has not been explored. Therefore, the aim of the present study was to provide a comprehensive characterization and describe clinical outcomes in a large multicenter cohort of patients with DCM and NDLVC.

METHODS

STUDY POPULATION.

In this multicenter, retrospective, observational study, all patients with a diagnosis of DCM or NDLVC who underwent genetic testing and CMR scan between January 1, 2001, and March 31, 2023, at 4 different tertiary care referral centers (University Hospital of Trieste, Trieste, Italy; University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA; Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA; and Fondazione CNR-Regione Toscana G. Monasterio, Pisa, Italy) were consecutively enrolled (Supplemental Table 1).

DCM was defined as the presence of LV dilatation and regional or global systolic dysfunction (LV ejection fraction [LVEF]: ≤50%) unexplained solely by abnormal loading conditions or significant CAD.[1] Right ventricular (RV) dilatation and dysfunction could be present but were not necessary for the diagnosis. Significant CAD (ie, stenosis of ≥50% in any major epicardial vessel) was systematically ruled out. Alternative causes of systolic dysfunction, such as active viral or sarcoid myocarditis, were also excluded.

NDLVC was defined as the presence of nonischemic LV scarring in the absence of LV dilatation, with or without regional or global LV systolic dysfunction. Isolated global LV hypokinesia without scarring was also included.[1] Nonischemic LV scarring was defined by the presence of late gadolinium enhancement (LGE) with subepicardial or intramyocardial distribution in CMR imaging.

LV dilatation by CMR was defined as increased LV end-diastolic volume index (ie, LVEDVi of >96 mL/m^2 for female patients and >105 mL/m^2 for male patients) according to an expert consensus document of the European Association of Cardiovascular Imaging.[8]

Demographic and clinical data were collected at baseline evaluation. Detailed information regarding family history of cardiomyopathies and sudden cardiac death (SCD), with a ≥3-generation pedigree, were recorded. Data from 12-lead electrocardiogram (ECG) and Holter ECG monitoring were also collected. In particular, the number of ventricular ectopic beats during 24-hour evaluation along with the occurrence of nonsustained ventricular tachycardia (NSVT) were evaluated. NSVT was defined as ≥3 consecutive ventricular premature beats with a rate >100 beats/min, lasting <30 seconds, documented during 12-lead ECG or 24-hour Holter ECG monitoring or implantable device detected.

The study was performed according to the criteria set by the Declaration of Helsinki and received Institutional Review Board approval from each institution. When required, patients provided written informed consent.

MOLECULAR GENETICS AND DEFINITION OF GENETIC VARIANTS.

DNA was extracted from blood leukocytes according to standard techniques, and genetic testing was performed by next-generation sequencing, and all variants were validated with bidirectional Sanger sequencing, as previously reported.[7] Next-generation sequencing

was obtained with commercially available cardiomyopathy panels in accredited clinical or research laboratories.

Patients were classified as carriers of pathogenic or likely pathogenic (P/LP) variants, carriers of a variant of uncertain significance (VUS), and negative genetic test result according to the American College of Medical Genetics criteria.[9] In particular, gene variants were classified as VUS if there was insufficient or conflicting evidence regarding a molecular alteration's role in disease.[9] Patients carrying a VUS or with a negative result on genetic testing were considered as a single group (ie, nondiagnostic genetic test).

P/LP variants were further divided into P/LP of arrhythmogenic and nonarrhythmogenic genes (Supplemental Tables 2 and 3). According to the Heart Rhythm Society 2019 Consensus Statement,[10] the following were considered arrhythmogenic genes: *BAG3, DES, DSC2, DSG2, DSP, FLNC, JUP, LDB3, LMNA, NKX2-5, PKP2, PLN, RBM20, SCN5A, TMEM43*.

CMR ACQUISITION PROTOCOL AND IMAGE ANALYSIS.

By protocol, all participants underwent CMR evaluation. CMR studies were performed on 1.5- or 3.0-T magnetic resonance scanners at each center, with a cardiac phased-array receiver surface coil, ECG gating, and breath-hold technique, using a dedicated cardiac software.

Cine images in standard long-axis and short-axis views were acquired using a balanced steady-state, free-precession pulse sequence. Approximately 10 minutes after intravenous administration of 0.1 to 0.2 mmol/kg gadolinium-based contrast agent, LGE images were acquired in the same views using segmented T_1-weighted inversion-recovery prepared gradient-echo or phase-sensitive inversion recovery pulse sequences, individually adjusting inversion time to optimize nulling of apparently normal myocardium.

CMR images were analyzed offline in a blinded manner. LV and RV volume and function were measured using the standard volumetric technique from the cine short-axis stack[11] and indexed to body surface area. Regional wall motion abnormalities were visually assessed and described using a 17-segment model for the LV.[12] In postcontrast images, LGE presence was defined by the identification of areas of increased signal intensity confirmed in 2 orthogonal planes or after phase/frequency direction swapping. LGE pattern was visually classified as subepicardial, intramyocardial, subendocardial, or transmural.[13] LGE location was described as septal (including isolated or combined septal involvement) and nonseptal, when only the free wall was involved. Subtle areas of LGE confined to the RV insertion points were considered paraphysiologic and excluded from both septal and nonseptal LGE.[14]

STUDY ENDPOINTS.

The study endpoint was a composite of SCD or major ventricular arrhythmias (SCD/MVA). SCD was defined as unexpected death due to cardiac causes with or without documented ventricular fibrillation (VF), death within 1 hour of acute symptoms, or nocturnal death with no antecedent history of immediate worsening symptoms.[6] MVAs included

successfully resuscitated VF or ventricular tachycardia (VT), sustained (>30 seconds) VT causing hemodynamic instability or appropriate implantable cardioverter-defibrillator (ICD) interventions, defined as shock or antitachycardia pacing for termination of rapid (>185 beats/min) sustained VT or VF.[15]

The date of the enrollment CMR scan was considered as the baseline evaluation. The end of follow-up was defined as the date of event adjudication or the date of the last available contact with the patient. When multiple events occurred, patients were censored at the time of the first event.

STATISTICAL ANALYSIS.

Summary statistics of clinical and instrumental variables were expressed as mean ± SD, median (Q1-Q3), or n (%), as appropriate. The comparison between groups was performed using the 1-way analysis of variance for gaussian-distributed continuous variables, using the Brown-Forsythe statistic when the assumption of equal variances did not hold or the nonparametric Kruskal-Wallis/Mann-Whitney *U* test for nongaussian continuous variables. The chi-square or Fisher exact test was calculated for discrete variables.

Cumulative incidence function (CIF) curves were estimated and compared by groups considering competing risks of death for other causes or heart transplant, and the appropriate statistical test (ie, R library “cmprsk”) suitable for competing risks was performed. Time was expressed in months; therefore, all events occurring in the first 30 days are represented in the curves at time zero.

Univariable Cox regression models were estimated to explore the association of the variables of interest with the outcome. A Cox multivariable model was used to identify a subset of independent predictors of outcome. LGE was recoded as a categorical variable in 3 levels, considering as a reference level “LGE absent.” A *P* value of <0.05 was considered as statistically significant. The *P* values and 95% CIs have not undergone adjustments for multiplicity, and therefore some observed statistical estimates may be inflated.

Analyses were conducted using SPSS Statistics for Macintosh (IBM), version 28.0, and the software R, version 4.2.3 (R Foundation for Statistical Computing).

RESULTS

STUDY POPULATION.

A total population of 462 patients were enrolled. Among them, 227 (49%) patients had a diagnosis of DCM, and 235 (51%) patients had a diagnosis of NDLVC. Clinical, demographic, genetic, and instrumental characteristics of the total study population and according to cardiac phenotype are shown in Table 1. Mean age at enrollment was 43 ± 15 years, and 58% were male. Mean LVEF was 44% ± 14%. Among the study population, 227 (49%) patients carried P/LP variants. A P/LP variant in an arrhythmogenic gene was found in 146 patients (32% of the whole population). Among these patients, P/LP variants were most frequently unearthed in *DSP*-encoded desmoplakin (n = 44; 10%), *LMNA*-encoded lamin A/C (n = 32; 7%), and *FLNC*-encoded filamin C (n = 22; 5%). Among patients

with a P/LP in a nonarrhythmogenic gene, the most frequently affected gene was *TTN*-encoded titin (n = 60; 13%). LGE was found in 273 (59%) patients. In particular, LGE was present in 142 (60%) patients with nondiagnostic genetic testing, 97 (66%) patients with a P/LP variant in an arrhythmogenic gene, and 34 (42%) patients with P/LP variants in a nonarrhythmogenic gene. The most common LGE pattern was intramyocardial (n = 165; 36%). The interventricular septum was frequently involved (178 patients; 38%), either isolated (n = 48; 10%) or in combination with the free wall (n = 130; 28%) (Supplemental Table 4).

GENETIC AND CMR CORRELATES ACCORDING TO CARDIAC PHENOTYPE.

Compared to DCM, patients with NDLVC more frequently had a family history of SCD (34% vs 25%; $P = 0.02$), a higher prevalence of P/LP variants in arrhythmogenic genes (40% vs 23%; $P < 0.001$), higher LVEF (51% ± 12% vs 36% ± 15%; $P < 0.001$), and a higher prevalence of free-wall LGE (27% vs 14%; $P < 0.001$). Conversely, the frequency of NYHA functional class III or greater at presentation (17% vs 7%; $P < 0.001$), NSVT (46% vs 34%; $P = 0.012$), P/LP variants in nonarrhythmogenic genes (23% vs 12%; $P = 0.002$), and septal LGE (45% vs 32%; $P = 0.004$) was higher in DCM. Whereas the P/LP variants in *DSP*-encoded desmoplakin (14% vs 5%; $P = 0.004$) and *PKP2*-encoded plakophilin-2 (3% vs 0.4%; $P = 0.038$) were more common in NDLVC, the burden of P/LP variants in *TTN*-encoded titin (16% vs 10%; $P = 0.037$) was higher in DCM. No other genotype-specific differences were observed between NDLVC and DCM.

OUTCOME ANALYSIS.

Over a median follow-up of 81 months (Q1-Q3: 40-132 months), the study outcome of SCD/MVA occurred in 98 patients (21%). Univariable and multivariable Cox regression analyses are shown in Table 2. Septal LGE location (HR: 1.929; 95% CI: 1.033-3.601; $P = 0.039$) was independently associated with the study outcome, along with LVEDVi (HR: 1.014; 95% CI: 1.008-1.021; $P < 0.001$); older age (HR: 1.023; 95% CI: 1.006-1.041; $P = 0.008$); advanced NYHA functional class (HR: 2.768; 95% CI: 1.437-5.311; $P = 0.002$); >1,000 ventricular ectopic complexes/24 hours (HR: 2.117; 95% CI: 1.183-3.788; $P = 0.011$); and nonsustained VT (HR: 2.018; 95% CI: 1.167-3.491; $P = 0.012$).

The CIF curve for the occurrence of the study endpoint according to the presence and location of LGE in the overall population is shown in Figure 1. Patients with LGE were at higher risk compared to those without LGE (17% vs 7% risk of SCD/MVA at 5 years and 31% vs 13% at 10 years, respectively; $P < 0.001$). Interestingly, patients with any septal LGE showed a greater risk of events compared to those with free-wall LGE ($P = 0.025$) and without LGE ($P < 0.001$), whereas there was no significant difference between patients with isolated or combined septal LGE ($P = 0.13$).

Figure 2 reports the cumulative incidence of SCD/MVA according to the phenotype. A worse outcome was observed for DCM patients when compared to those with NDLVC ($P = 0.0003$). Interestingly, DCM patients with LGE showed the highest risk of arrhythmic events, whereas NDLVC patients without LGE showed the lowest risk (Figure 3).

Supplemental Figure 1 shows the cumulative incidence of SCD/MVA according to the presence of a P/LP variant and LGE. Patients with LGE showed a greater incidence of events irrespective of the genetic status.

Supplemental Figure 2 describes the cumulative incidence of SCD/MVA according to the genotype. No differences were found based on the presence of P/LP variants (P = 0.950), as well as arrhythmogenic P/LP variants (P = 0.250), in the overall population. However, a different effect of arrhythmogenic P/LP variants was observed at different centers (Supplemental Figure 3).

DISCUSSION

In this study, to our knowledge, we provide the first comprehensive CMR characterization and genetic background analysis in a large cohort of DCM and NDLVC (Central Illustration). We found that the presence of any LGE is associated with a greater risk of major arrhythmic events and that septal LGE is an independent predictor of the study's outcome, independent of the underlying genetic substrate.

In our cohort of 462 patients, LGE was present in almost 60% of patients, with no significant difference between DCM and NDLVC. It is well known that the presence of LGE is associated with major arrhythmic events providing incremental value over conventional risk stratifiers, such as LVEF, particularly in DCM.[2,4,16,17] In our combined population of DCM and NDLVC, we confirmed a 17% risk of MVA or SCD at 5 years associated with the presence of LGE compared to a 7% risk at 5 years when LGE was absent. A more intriguing finding is the different effect of LGE locations in determining the arrhythmic risk. So far, different results have been reported regarding this issue. Halliday et al[4] described a higher risk of SCD or aborted SCD in DCM patients with septal LGE vs nonseptal LGE location. Di Marco et al[2] found that the combination of septal and free-wall LGE conferred a higher risk of MVAs than both isolated septal and isolated free-wall LGE. Barison et al[18] found that a higher risk of ICD interventions was associated with septal and inferior wall LGE. Recently, de Frutos et al[19] described the LGE distribution according to genotype and the risk of MVA in a large multicenter cohort of DCM patients. They observed an increased risk of arrhythmic events for LGE-positive patients, in particular for those with combined LGE patterns.[19] Our study confirms and expands the knowledge in this evolving field. Indeed, we showed that not only the presence of LGE but also its septal location was associated with a higher prevalence of major arrhythmic events compared with the isolated free-wall location in a large cohort of patients including DCM and NDLVC. In fact, septal LGE was associated with a 3.4-fold unadjusted increased risk of MVA or SCD, compared to a 1.9-fold unadjusted increased risk for free-wall LGE. After adjustment for other clinical and instrumental significant features, septal LGE location remained an independent predictor of MVA or SCD. Interestingly, we did not observe a significant difference between isolated and combined septal LGE, suggesting a neutral effect of LGE extension.

Somewhat surprisingly, the presence of P/LP variants in arrhythmogenic genes, despite a trend, was not independently associated with a greater risk of MVA or SCD, a result that is in contrast to some previous studies.[6,7] However, some differences between the

current and previous series need to be considered. First, in previous reports, CMR tissue characterization was not systematically performed, potentially neglecting the effect of LGE, particularly relevant in patients with negative genetic test results. In fact, in our study, LGE was frequently observed in patients with nondiagnostic genetic test as well as in carriers of arrhythmogenic genes variants. Furthermore, patients with LGE and negative genetic test results showed a higher risk of events compared to those with positive genetic test results without LGE. These results confirm that the development of myocardial fibrosis remains a central pathophysiologic mechanism for arrhythmic susceptibility, regardless of the underlying cause. Second, in the present study, we used the list of arrhythmogenic genes proposed by the Heart Rhythm Society 2019 Consensus Statement,[10] whereas a different classification of arrhythmogenic genes was used in other studies, hampering a direct comparison of the results. It should also be considered that some center-specific differences in the patients' characteristics (ie, different prevalence of genetic testing and LGE positivity) may account at least in part for these differences (Supplemental Table 1, Supplemental Figure 3). Further validation studies are needed to confirm these results.

Another interesting finding is that the new phenotypic classification proposed by the 2023 ESC guidelines for the management of cardiomyopathies is effective in predicting arrhythmic outcome. In fact, dilated patients, in particular those with LGE, showed higher risk of arrhythmic events when compared to those with NDLVC. Consistently, LVEDVi emerged as an independent predictor of outcome at multivariable analysis.

In recent years, the implementation of CMR and genetic testing have revealed a significant overlap between DCM and ACM with LV involvement,[7] resulting in a difficult disease classification. The phenotypic classification based on LV dilatation proposed by the 2023 ESC guidelines for the management of cardiomyopathies simplifies the diagnostic approach and appears effective in the arrhythmic risk stratification of these patients. However, it should be considered that DCM and NDLVC may not be 2 mutually exclusive entities but, rather, a continuum of disease with a possible evolution over time. Furthermore, it should be recognized that this classification may include highly heterogeneous conditions, with potentially different etiology, clinical behavior, and treatment.

Of note, DCM and NDLVC showed a different clinical profile. Advanced NYHA functional class, higher arrhythmic burden, and lower biventricular function are common in DCM. On the other hand, patients with NDLVC showed a higher prevalence of arrhythmogenic P/LP variants. Interestingly, the prevalence of LGE was not significantly different between DCM and NDLVC. However, myocardial fibrosis may be the expression of a different pathophysiology in these conditions. In fact, in NDLVC, myocardial scar is a hallmark of disease and could be speculatively related to an arrhythmogenic genetic substrate, whereas in DCM myocardial scar may reflect the progression of disease.

CLINICAL IMPLICATIONS.

Our findings prompt some considerations of the clinical management of patients with DCM and NDLVC. First, LGE appears to be a strong predictor of adverse arrhythmic outcomes independent of LVEF, which emphasizes the need for a systematic CMR-guided characterization because of its prognostic and therapeutic implications. The importance

of CMR in the assessment of cardiomyopathies has been recently stated in the 2023 cardiomyopathy guidelines of the ESC, with a Class I recommendation at baseline and a Class IIa recommendation during follow-up.[1] The presence and location of LGE at CMR, along with other clinical and instrumental variables such as LV dilatation, NYHA functional class, and arrhythmic burden, might help to stratify patients according to their arrhythmic risk and allow the identification of those who may benefit from primary prevention ICD placement, potentially expanding the current indications.[20] Our results confirm the importance of a deep characterization of patients with DCM and NDLVC through CMR imaging, on top of the genetic testing, which is particularly relevant when an elusive result is found, confirming the indications given by the 2023 ESC guidelines on cardiomyopathies.[1] Future studies on larger populations with available CMR and genetic characterization will be needed to further define the distinct role of both variables (including specific LGE distribution pattern and specific gene variants) on patients' outcomes.

STUDY LIMITATIONS.

As with all observational studies, our study has the common bias because of its retrospective design. The study population was enrolled at 4 referral centers for the diagnosis and treatment of cardiomyopathies, thus imposing a selection bias. Moreover, the enrollment of patients who necessarily underwent CMR might have represented an additional selection bias, potentially translating into a population at higher risk of SCD/MVA. This aspect is particularly relevant for individuals with a nondiagnostic genetic test and imposes caution in the interpretation of results regarding the effect of arrhythmogenic variants. Similarly, the different recourse to genetic testing at different centers, with different observed genetic yields, may have influenced the results.

The prognostic impact of genotype in our cohort could not be extended to all affected carriers (eg, those without CMR study). Furthermore, a minor portion of considered genes are not currently validated in ClinGen for the analyzed phenotypes (ie, *MYBPC3, FKRP, KCNJ2*). However, the number of carriers of these genotypes in our cohort is negligible.

For the purposes of this study, truncating variants in TTN-encoded titin were considered as nonarrhythmogenic. However, recent evidence suggests that A-band–localizing truncating variants in TTN-encoded titin may result in an arrhythmic phenotype.[21]

The study population included patients previously diagnosed as having ACM with LV involvement (ie, isolated LV forms and biventricular forms), whereas isolated RV forms were excluded. LV involvement has already been shown to be an independent predictor of major arrhythmic events in ACM, with a significantly worse prognosis than isolated RV forms.[3] Despite common LV involvement, these 2 entities may represent 2 different conditions with different genotypes; structural abnormalities (ie, RV dilatation and dysfunction); and, finally, clinical outcomes.[3] Further research and specific recommendations are needed for a better classification of biventricular forms.

Although the 2023 ESC guidelines define LV dilatation according to echocardiography-based cutoffs,[1] specific CMR cutoffs were used in the present study given its design.

The lack of a single core CMR laboratory for imaging evaluation could be considered a further limitation. Moreover, T_1 and T_2 mapping as well as extracellular volume calculation were not available for most patients given the retrospective nature of the study. Further studies are needed to evaluate the diagnostic and prognostic role of mapping techniques in this setting.

CONCLUSIONS

In our large, multicenter cohort of patients with DCM and NDLVC, the presence and septal location of LGE were powerful predictors of major arrhythmic events. In addition, advancing age, progression of disease, frequent and repetitive ventricular arrhythmias, and LV dilatation were cumulative predictors with LGE of major arrhythmic events. The increased risk was independent of the genetic background.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

ACM	arrhythmogenic cardiomyopathy
CAD	coronary artery disease
CIF	cumulative incidence function
CMR	cardiac magnetic resonance
DCM	dilated cardiomyopathy
ECG	electrocardiogram
ICD	implantable cardioverter-defibrillator
LGE	late gadolinium enhancement
LV	left ventricular
LVEDVi	left ventricular end-diastolic volume index
LVEF	left ventricular ejection fraction
MVA	major ventricular arrhythmia
NDLVC	nondilated left ventricular cardiomyopathy

NSVT	nonsustained ventricular tachycardia
P/LP	pathogenic or likely pathogenic
RV	right ventricular
SCD	sudden cardiac death
VF	ventricular fibrillation
VT	ventricular tachycardia
VUS	variant of uncertain significance

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Late gadolinium enhancement, in particular its septal location, identifies patients with dilated and nondilated left ventricular cardiomyopathies at elevated risk of arrhythmic events.

TRANSLATIONAL OUTLOOK:

Further research is needed to clarify the influence of genetic variants on arrhythmia risk in patients with these and other LV cardiomyopathies, particularly those without LV enlargement or septal LGE.

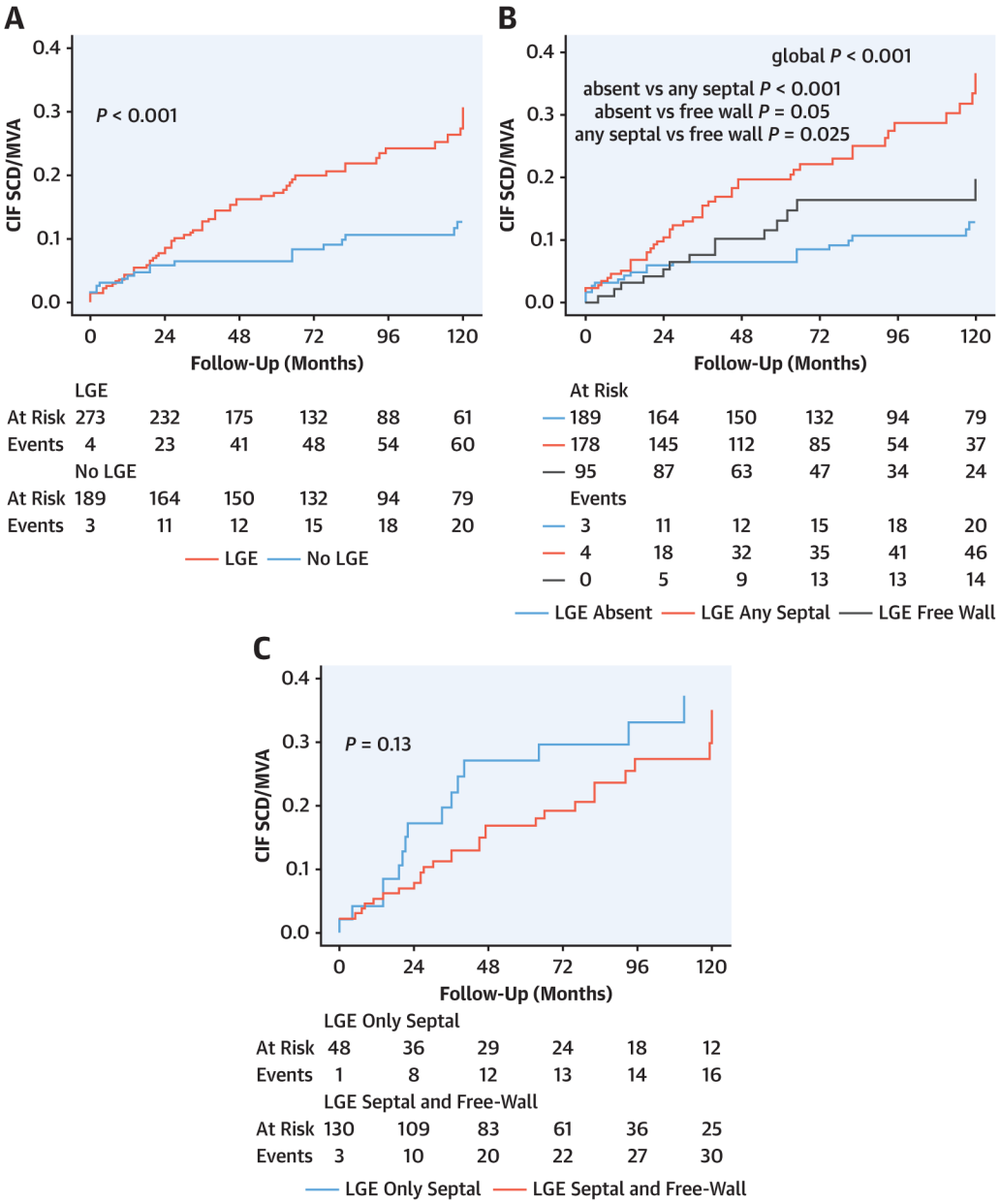


FIGURE 1. Cumulative Incidence of the Composite Endpoint (SCD/MVA) According to LGE

(A) Patients with LGE were at higher risk of events compared to those without LGE ($P <$ 0.001). (B) Patients with any septal LGE showed a greater risk of events compared to those with free-wall LGE ($P = 0.025$) and without LGE ($P < 0.001$). (C) No significant difference between patients with isolated or combined septal LGE ($P = 0.13$). No corrections for multiple testing were applied. CIF = cumulative incidence function; LGE = late gadolinium enhancement; MVA = major ventricular arrhythmias; SCD = sudden cardiac death.

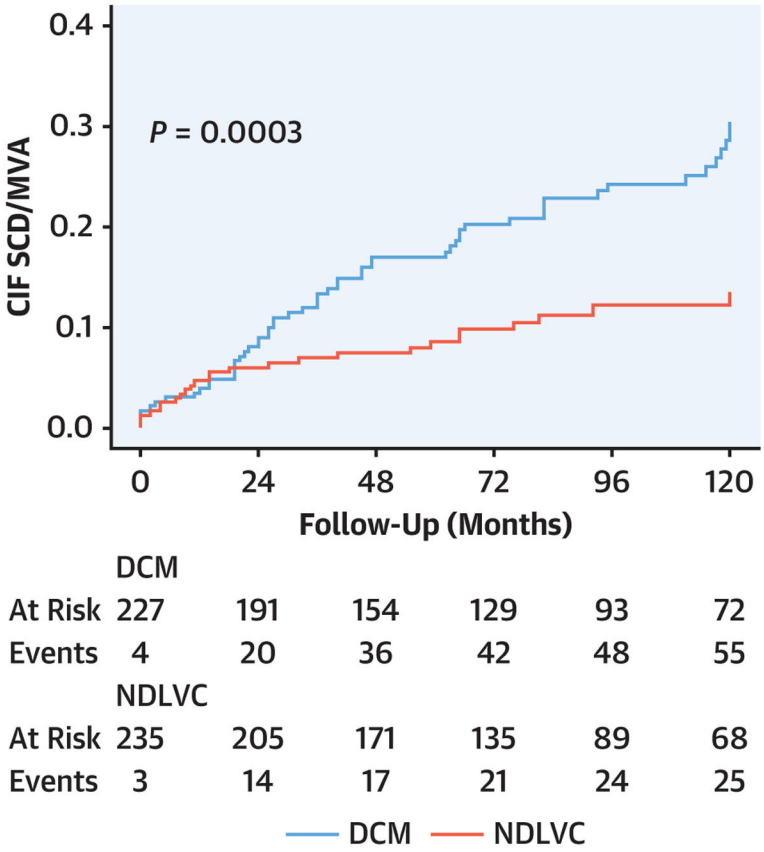


FIGURE 2. Cumulative Incidence of Composite Endpoint (SCD/MVA) Comparing DCM vs NDLVC

A worse outcome was observed for DCM patients when compared to NDLVC patients (*P* = 0.0003). DCM = dilated cardiomyopathy; NDLVC = nondilated left ventricular cardiomyopathy; other abbreviations as in Figure 1.

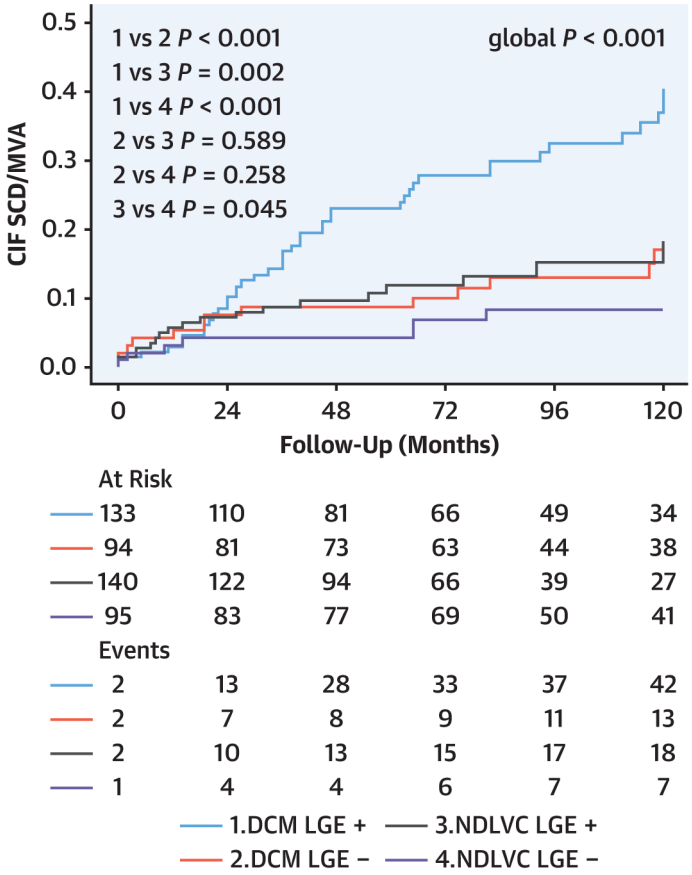
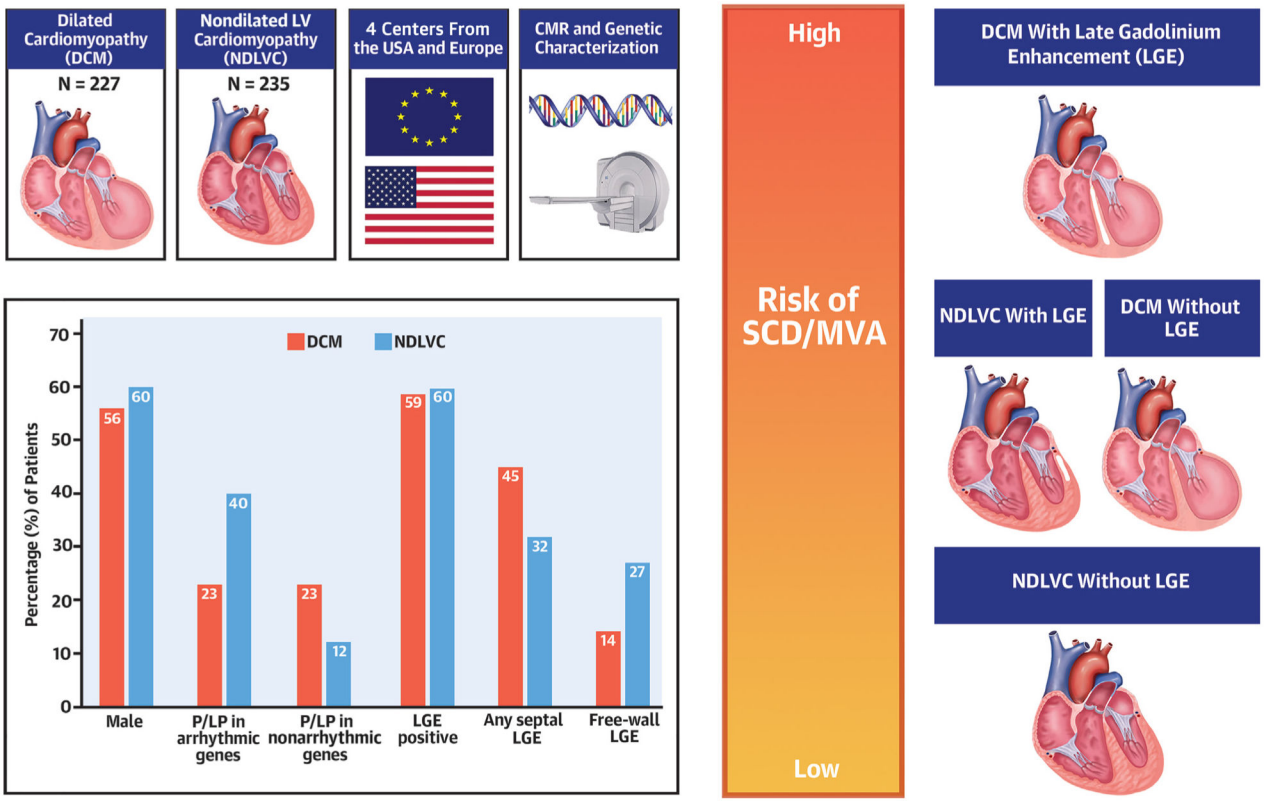


FIGURE 3. Cumulative Incidence of SCD/MVA According to Phenotype and LGE Positivity

DCM patients with LGE showed the highest risk of arrhythmic events, whereas NDLVC patients without LGE showed the lowest risk. No corrections for multiple testing were applied. Abbreviations as in Figure 1 and 2.



CENTRAL ILLUSTRATION. Characterization and Clinical Outcomes of Dilated Cardiomyopathy and Nondilated Left Ventricular Cardiomyopathy

In a multicenter cohort of patients with dilated and nondilated LV cardiomyopathies, LV dilatation as well as the presence and septal location of LGE were independent predictors of major arrhythmic events. Patients with LV dilatation and LGE showed the greater risk of events, whereas those with NDLVC without LGE showed the lowest risk. CMR = cardiac magnetic resonance; DCM = dilated cardiomyopathy; LGE = late gadolinium enhancement; LV = left ventricular; MVA = major ventricular arrhythmias; NDLVC = nondilated left ventricular cardiomyopathy; P/LP = pathogenic or likely pathogenic; SCD = sudden cardiac death.

TABLE 1

Clinical and Demographic Characteristics of the Total Study Population and According to Phenotype

	Total (N = 462)	DCM (n = 227)	NDLVC (n = 235)	*P* Value
Age, y	43 ± 15	43 ± 15	43 ± 16	0.895
Male	268 (58)	128 (56)	140 (60)	0.274
Family history of CMP	183 (42)	88 (40)	95 (43)	0.294
Family history of SCD	**135 (29)**	**56 (25)**	**79 (34)**	**0.020**
NYHA functional class III or IV	**54 (12)**	**39 (17)**	**15 (7)**	**<0.001**
>1,000 VEB/24 h	147 (32)	68 (30)	79 (34)	0.210
NSVT	**183 (40)**	**103 (46)**	**80 (34)**	**0.012**
LBBB	53 (12)	27 (12)	26 (11)	0.446
RBBB	38 (8)	16 (7)	22 (10)	0.401
AV block	65 (18)	29 (19)	36 (17)	0.582
ACEI/ARB/ARNI	**310 (67)**	**174 (77)**	**136 (58)**	**<0.001**
Beta-blockers	**396 (86)**	**203 (90)**	**193 (82)**	**0.017**
ICD	**179 (39)**	**119 (52)**	**60 (26)**	**<0.001**
Genetics				
P/LP variants	227 (49)	105 (46)	122 (52)	0.131
P/LP variants in arrhythmogenic genes	**146 (32)**	**53 (23)**	**93 (40)**	**<0.001**
DSP	**44 (10)**	**12 (5)**	**32 (14)**	**0.004**
LMNA	32 (7)	12 (5)	20 (9)	0.096
FLNC	22 (5)	13 (6)	9 (4)	0.237
RBM20	16 (3)	8 (4)	8 (3)	0.572
DSG2	8 (2)	2 (1)	6 (3)	0.168
PKP2	**8 (2)**	**1 (0.4)**	**7 (3)**	**0.038**
PLN	7 (2)	3 (1)	4 (2)	0.738
DES	4 (1)	1 (0.4)	3 (1)	0.332
SCN5A	3 (1)	1 (0.4)	2 (1)	0.513
DSC2	2 (0.4)	0 (0)	2 (1)	0.258
P/LP variants in nonarrhythmogenic genes	**81 (17)**	**52 (23)**	**29 (12)**	**0.002**
TTN	**60 (13)**	**37 (16)**	**23 (10)**	**0.037**
DMD	6 (1)	5 (2)	1 (0.4)	0.100
MYH7	5 (1)	4 (2)	1 (0.4)	0.176
TNNT2	4 (1)	2 (1)	2 (1)	0.972
FKRP	2 (0.4)	1 (0.4)	1 (0.4)	0.742
MYBPC3	2 (0.4)	1 (0.4)	1 (0.4)	0.742
KCNJ2	1 (0.2)	1 (0.4)	0 (0)	0.491
NEXN	1 (0.2)	1 (0.4)	0 (0)	0.491
Nondiagnostic genetic test	235 (51)	122 (54)	113 (48)	0.131
VUS	99 (21)	49 (22)	50 (21)	0.391
Negative	136 (30)	73 (32)	63 (27)	0.298
CMR				

	Total (N = 462)	DCM (n = 227)	NDLVC (n = 235)	*P* Value
LVEDVi, mL/m^2	**107 ± 36**	**134 ± 32**	**80 ± 14**	**<0.001**
LVEF, %	**44 ± 14**	**36 ± 15**	**51 ± 12**	**<0.001**
RVEDVi, mL/m^2	**86 ± 24**	**93 ± 24**	**79 ± 23**	**<0.001**
RVEF, %	**49 ± 12**	**46 ± 13**	**52 ± 11**	**<0.001**
LGE positive result	273 (59)	133 (59)	140 (60)	0.452
Any septal LGE	**178 (38)**	**102 (45)**	**76 (32)**	**0.004**
Free-wall LGE	**95 (20)**	**31 (14)**	**64 (27)**	**<0.001**
LGE intramyocardial	165 (36)	81 (36)	84 (36)	0.533
LGE subepicardial	**124 (27)**	**50 (22)**	**74(32)**	**0.014**
LGE subendocardial	20 (4)	16 (7)	4 (2)	0.532
LGE transmural	33 (7)	18 (8)	15 (6)	0.321
LGE biventricular	44 (9)	19 (8)	25 (11)	0.251

Values are n (%) or mean ± SE unless noted otherwise. No corrections for multiple testing were applied. **Bold** values indicate statistical significance at the $P < 0.05$ level.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; AV = atrioventricular; CMP = cardiomyopathy; CMR = cardiac magnetic resonance; DCM = dilated cardiomyopathy; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; NDLVC = nondilated left ventricular cardiomyopathy; NSVT = nonsustained ventricular tachycardia; P/LP = pathogenic or likely pathogenic; RBBB = right bundle branch block; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; VEB = ventricular ectopic beats; VUS = variant of uncertain significance.

TABLE 2

Univariable and Multivariable Analyses for the Composite Primary Endpoint of SCD/MVA

	Univariable		Multivariable	
	HR (95% CI)	***P* Value**	**HR (95% CI)**	***P* Value**
Age, y	**1.025 (1.010-1.039)**	**<0.001**	**1.023 (1.006-1.041)**	**0.008**
Male	0.931 (0.761-1.140)	0.490	—	—
Family history of CMP	0.800 (0.523-1.224)	0.300	—	—
Family history of SCD	0.864 (0.543-1.375)	0.553	—	—
NYHA functional class III or IV	**2.790 (1.717-4.534)**	**<0.001**	**2.768 (1.437-5.311)**	**0.002**
>1,000 VEB/24 h	**3.084 (2.067-4.602)**	**<0.001**	**2.117 (1.183-3.788)**	**0.011**
NSVT	**3.781 (2.451-5.831)**	**<0.001**	**2.018 (1.167-3.491)**	**0.012**
LBBB	1.191 (0.683-2.077)	0.545	—	—
RBBB	1.819 (0.966-3.425)	0.085	—	—
AV Block	1.851 (1.151-2.977)	0.11	—	—
P/LP variants	0.967 (0.650-1.438)	0.869	—	—
P/LP variants in arrhythmogenic genes	1.219 (0.804-1.849)	0.352	—	—
P/LP variants in nonarrhythmogenic genes	0.676 (0.376-1.213)	0.169	—	—
LVEDVi, mL/m^2	**1.011 (1.006-1.017)**	**<0.001**	**1.014 (1.008-1.021)**	**<0.001**
LVEF, %	**0.962 (0.947-0.977)**	**<0.001**	—	n.s.
RVEDVi, mL/m^2	1.008 (1.001-1.016)	0.068	—	—
RVEF, %	**0.969 (0.952-0.986)**	**<0.001**	—	n.s.
LGE any septal vs absent	**3.431 (2.105-5.593)**	**<0.001**	**1.929 (1.033-3.601)**	**0.039**
LGE free wall vs absent	**1.912 (1.039-3.518)**	**0.037**	—	n.s.
LGE any septal vs free wall	**1.791 (1.078-3.021)**	**0.028**	—	n.s.

For details regarding the incidence rate, see Supplemental Table 5. **Bold** values indicate statistical significance at the $P < 0.05$ level.

n.s. = not statistically significant; other abbreviations as in Table 1.