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Clinical Research

Predictors of Disease Progression in Patients with Left Ventricular Nondilated Cardiomyopathy

Elena Bacigalupi, MD,[a,‡] Marco Merlo, MD, PhD,[a,h,‡] Giulia Barbati, PhD,[b] Andrea Villatore, MD,[c,d] Lucia Molinari, MD,[c,d] Matteo Dal Ferro, MD,[a,h] Alessia Paldino, MD, PhD,[a,h] Cinzia Radesich, MD,[a,h] Giulia Bassetto, MD,[a,h] Lina Manzi, MD,[a,h] Chiara Di Resta, PhD,[c,e] Maria Perotto, MD,[a,h] Carola Pio Loco detto Gava, MD,[a,h] Simone Sala, MD,[d,f] Antonio Esposito, MD,[c,d,g] Paolo Della Bella, MD,[f] Gianfranco Sinagra, MD,[a,h] and Giovanni Peretto, MD, PhD[c,d,f]

[a] *Cardiothoracovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI) and University of Trieste, Trieste, Italy*

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

[c] *Vita-Salute San Raffaele University, Milan, Italy*

[d] *Disease Unit for Myocarditis and Arrhythmogenic Cardiomyopathies, IRCCS San Raffaele Scientific Institute, Milan, Italy*

[e] *Cardiology Department, IRCCS San Raffaele Scientific Institute, Milan, Italy*

[f] *Cardiac Electrophysiology Department, IRCCS San Raffaele Scientific Institute, Milan, Italy*

[g] *Experimental Imaging Center, Radiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy*

[h] *Member of ERN Guard-HEART Network, Amsterdam, The Netherlands*

ABSTRACT

Background: Nondilated left ventricular cardiomyopathy (NDLVC) is a highly heterogeneous and unexplored category of cardiomyopathies introduced in the 2023 European Society of Cardiology (ESC) guidelines. This study aims to identify factors associated with adverse remodeling in a large multicentre cohort of patients with NDLVC.

Methods: A total of 432 patients with NDLVC (63.4% male, mean age 39.4 ± 14.6 years) with multiparametric characterization were enrolled from January 2010 to May 2023 in 2 high-volume Italian centres. Diagnosis followed ESC criteria. Endpoints were worsening of left ventricular ejection fraction (LVEF) ≥ 10% from the baseline value

RÉSUMÉ

Contexte : La cardiomyopathie ventriculaire gauche non dilatée (CVGND) est une catégorie de cardiomyopathies très hétérogène et encore peu étudiée, introduite dans les recommandations 2023 de la Société européenne de cardiologie (SEC). Cette étude vise à identifier les facteurs associés à un remodelage défavorable dans une vaste cohorte multicentrique de patients atteints de CVGND.

Méthodologie : Au total, 432 patients atteints de CVGND (63,4 % d'hommes, âge moyen 39,4 ± 14,6 ans) avec caractérisation multiparamétrique ont été recrutés entre janvier 2010 et mai 2023 dans deux centres italiens à haut volume clinique. Le diagnostic a été posé

Nondilated left ventricular cardiomyopathy (NDLVC), recently introduced by the 2023 European Society of Cardiology (ESC) guidelines for the management of cardiomyopathies,[1] is defined as the presence of "nonischemic left ventricular (LV) scarring or fatty replacement, in the absence of LV dilation, 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 not solely explained by abnormal loading conditions (hypertension, valve diseases) or coronary artery disease (CAD)."[1]

This phenotype includes a wide spectrum of patients who may have been classified previously as hypokinetic nondilated

Keywords: nondilated left ventricular cardiomyopathy; left ventricular ejection fraction; dilated cardiomyopathy; genetic test; myocardial inflammation

‡These authors equally contributed as first authors.

Corresponding author: Dr Marco Merlo, Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Via P. Valdoni 7, 34149 Trieste, Italy. Tel.: 0039 0403994477.

E-mail: marco.merlo79@gmail.com

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(or group W), evolution to dilated cardiomyopathy (DCM) (or group E), and the concomitant occurrence of both (or group W + E), assessed at the latest available echocardiographic evaluation.

Results: During a median follow-up of 77 months (interquartile range [IQR]: 48-109), 27.3% of patients experienced worsening LVEF, 28.9% progressed to DCM, and 18.3% reached the combined W + E endpoint. A multivariable model including positive genetic testing associated to myocardial inflammation, family history of cardiomyopathies or sudden cardiac death, intraventricular conduction delay, baseline echocardiographic LVEF < 45%, a ring-like late gadolinium enhancement on cardiac magnetic resonance, and nonsustained ventricular tachycardia at baseline had the strongest discrimination power for predicting worsening LVEF (area under the curve [AUC] of 0.8; 95% confidence interval [CI], 0.75-0.86), evolution to DCM (AUC 0.78; 95% CI, 0.73-0.84) and the combined W + E (AUC 0.84; 95% CI, 0.79-0.89). Negative genetic testing reduced the risk across all the endpoints (odds ratio [OR], 0.2; 95% CI, 0.1-0.4; $P < 0.001$; OR, 0.2; 95% CI, 0.1-0.4; $P < 0.001$ and OR, 0.1; 95% CI, 0.04-0.3; $P < 0.001$, respectively).

Conclusions: In this large NDLVC cohort, in which 38% of patients showed an adverse remodelling over long-term follow-up, a multiparametric approach integrating deep phenotyping and genetics effectively identified high-risk patients.

selon les critères de la SEC. Les critères d'évaluation étaient les suivants : (I) dégradation de la fraction d'éjection ventriculaire gauche (FEVG) ≥ 10 % par rapport à la valeur de référence (ou groupe W), (II) évolution vers une cardiomyopathie dilatée (CMD) (ou groupe E), et (III) survenue concomitante des deux (ou groupe W+E), évalués lors de la dernière échocardiographie disponible.

Résultats : Au cours d'un suivi médian de 77 mois (intervalle interquartile : 48-109), 27,3 % des patients ont présenté une aggravation de la FEVG, 28,9 % ont évolué vers une CMD et 18,3 % ont atteint le critère d'évaluation combiné W+E. Un modèle multivarié incluant des tests génétiques positifs associés à une inflammation myocardique, des antécédents familiaux de cardiomyopathies et/ou de mort subite cardiaque, un retard de conduction intraventriculaire, une FEVG échocardiographique de base < 45 %, lésions avec anneau de rehaussement tardif au gadolinium à l'IRM cardiaque et une tachycardie ventriculaire non soutenue à l'inclusion, présentait le pouvoir discriminant le plus fort pour prédire une aggravation de la FEVG [aire sous la courbe [ASC] de 0,8 (intervalle de confiance ([IC] à 95 % : 0,75-0,86)], l'évolution vers une CMD [ASC 0,78 (IC à 95 % : 0,73-0,84)] et la combinaison W+E [ASC 0,84 (IC à 95 % : 0,79-0,89)]. Des tests génétiques négatifs réduisaient le risque pour tous les critères d'évaluation [rapport de cotes [RC] : 0,2, IC à 95 % : 0,1-0,4, $p < 0,001$), (RC : 0,2, IC à 95 % : 0,1-0,4, $p < 0,001$) et (RC : 0,1, IC à 95 % : 0,04-0,3, $p < 0,001$), respectivement].

Conclusions : Dans cette vaste cohorte CVGND, dans laquelle 38 % des patients ont présenté un remodelage défavorable au cours du suivi à long terme, une approche multiparamétrique intégrant un phénotypage approfondi et la génétique a permis d'identifier efficacement les patients à haut risque.

cardiomyopathy,[2] early-stage dilated cardiomyopathy (DCM), arrhythmogenic left ventricular cardiomyopathy (ALVC),[3] healed myocarditis from a previous unrecognized acute event and chronic inflammatory cardiomyopathy, pathologic entities with significant variability in arrhythmic risk, progression of disease, and long-term prognosis.

Previous studies on nonischemic DCM have suggested prognostic implications in progression of disease and arrhythmic risk of specific genotypes,[4] presence and distribution of LGE,[5,6] and myocardial inflammation.[7] In NDLVC, the first data on arrhythmic risk stratification have recently been reported,[8,9] and since the introduction of this definition, prognostic evaluation is being defined. However, to date, no study has specifically investigated the evolution of NDLVC to DCM and the factors associated with adverse LV remodelling.

Therefore, through a comprehensive multimodal approach, integrating clinical, electrocardiographic, imaging, and genetic data, we aimed to identify factors associated to worsening left ventricular ejection fraction (LVEF) and progression to DCM, in a large cohort of patients diagnosed with NDLVC.

Methods

Study design

This retrospective, observational study was conducted at 2 high-volume centres with expertise in cardiomyopathy management (San Raffaele Hospital, Milan and Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina-Trieste).

Patients evaluated between January 2010 and May 2023 were identified from institutional cardiomyopathy databases; these patients had been followed over time in dedicated outpatient clinics and were included if they fulfilled predefined criteria, confirmed by review of imaging data.

All potentially predictive variables were collected as part of the standardized baseline diagnostic workup, including clinical, electrocardiographic, imaging, and genetic parameters, as described in detail in the corresponding sections. The follow-up duration was at least 1 year.

Study population

Inclusion criteria were age ≥ 18 years; indexed left ventricular end-diastolic volume (LVEDVi) < 62 mL/m^2 in female patients and < 75 mL/m^2 in male patients at baseline echocardiogram; either baseline LVEF < 50% or nonischemic pattern of LGE at baseline CMR.[1]

Exclusion criteria were history of myocardial infarction or proven obstructive coronary artery disease by invasive angiography or coronary computed tomography; clinical presentation as infarct-like acute myocarditis of either proven or suspected viral aetiology, confirmed by endomyocardial biopsy (EMB) following Dallas Criteria[10] or by CMR according to the updated Lake Louise Criteria[11]; abnormal loading conditions, defined as moderate to severe valvular heart diseases, congenital heart diseases, uncontrolled hypertension; known exposure to exogenous pathogenic noxae (vaccines, alcohol, drugs, toxic agents, previous chemo/radio/

immunotherapy); systemic rheumatologic diseases or sarcoidosis; diagnostic criteria for other cardiomyopathies according to the ESC definitions. The study flowchart is shown in Supplemental Figure S1.

Diagnostic workup

For the study purposes, the criteria for defining NDLVC were assessed at the time of baseline workup, including echocardiogram and, whenever available, CMR with LGE sequences. All patients had available data of echocardiographic LVEF and LVEDVi at baseline (ie, first contact at referral centre) and during follow-up (ie, last contact at referral centre), as recommended by ESC guidelines and caused by the wider feasibility of echocardiography compared with CMR.

Demographic and clinical information, including heart failure symptoms (New York Heart Association [NYHA] functional class), competitive sport activity, family history of cardiomyopathy (CMPs) or sudden cardiac death (SCD)—assessed with a 3-generation pedigree—were collected at baseline. Data from 12-lead electrocardiogram (ECG) and Holter ECG monitoring including presence of ventricular arrhythmias (sustained and non-sustained ventricular tachycardia [NSVT]), atrial fibrillation/atrial flutter, and atrioventricular blocks were recorded. Intraventricular conduction delay (IVCD) was defined by the presence of complete or incomplete right or left bundle branch blocks, anterior or posterior fascicular blocks, or fragmented QRS complexes.

Echocardiographic LV and right ventricular (RV) dimensions and systolic function were assessed at transthoracic echocardiography.[12] LV systolic dysfunction was defined by LVEF $< 50\%$. Severity of valvulopathies was quantified according to current recommendations.[13]

CMR scan were obtained following international guidelines.[14] All CMR examinations were centrally reviewed and considered as baseline, although their timing varied across the study period: After 2015 they were performed within 3 months from diagnosis, whereas before 2015 they were performed within 9 months. Analysis of LGE short- and long-axis images included assessment of distribution (subepicardial, midwall, subendocardial, or transmural), extension (focal, multifocal, or ring-like), and localization (septal involvement). Ring-like pattern was defined, according to previous works, as LGE in at least 3 contiguous segments within the same short-axis slice[15,16] and was evaluated systematically by trained experts blinded to the study design and outcomes. In addition, the presence of ventricular fibrofatty infiltration, defined as "India ink" sign in steady-state free precession (SSFP) sequences,[17] was evaluated and reported.

EMB was performed in accordance with available consensus documents[18,19] in cardiomyopathies with features of clinical complexity, such as severe LV dysfunction refractory to standard therapy, unexplained life-threatening ventricular arrhythmias, and relapsing or chronic troponin release.

Myocardial inflammation (M-Infl) was identified either with EMB or CMR. EMB-proven inflammation was defined according to the ESC criteria for virus-negative myocarditis, based on histologic and molecular analyses. CMR-proven inflammation was assessed using the updated Lake Louise Criteria, using black-blood T2 short tau inversion recovery (STIR) sequences in 2 orthogonal planes and parametric T2 mapping with predefined cutoff values. In cases of discordant findings between CMR and EMB, histologic results were prioritized.

Genetic testing was conducted using a panel of cardiomyopathy-associated genes (Supplemental Fig. 2). Variants were classified according to American College of Medical Genetics and Genomics guidelines.[20] Only pathogenic and likely pathogenic variants (P/LP) were considered to define the cardiomyopathy as genetically determined, whereas a negative genetic test was defined as the absence of any P/LP variants in the analyzed panel. High-risk genes are defined by ESC guidelines, such as *LMNA*, *FLNC*, *DSP*, *TMEM43*, *PLN*, and *RBM20*.[1]

Based on this comprehensive diagnostic approach, patients were categorized into 5 etiologic groups: inflammatory and genetic (GI), inflammatory only (I), genetic only (G), undefined because of negative findings on both M-Infl and genetic test (U), and undefined because of insufficient diagnostic characterization for both M-Infl and genetic (UU).

To ensure the robustness of our results, a sensitivity analysis was performed on the population with at least 24 months of follow-up (94.3%, n = 399), with the same variables and models applied in the overall cohort. In addition, a prespecified subgroup analysis was conducted on patients with baseline echocardiographic LVEF $\geq 50\%$ (63%, n = 272) to explore outcomes in this specific subset.

Treatment and follow-up

Treatment decision, such as antiarrhythmic drugs, catheter ablation of ventricular arrhythmias, and implantable cardioverter defibrillator (ICD) placement, were clinically-driven and aligned with ESC guidelines.[21,22] Immunomodulatory therapy targeting EMB-proven M-Infl was patient-tailored. Follow-up data were collected during in-person visits, including repeat ECG, imaging, and Holter monitoring according to clinical practice and physician judgement. For patients unable to attend scheduled visits, vital status and symptom information were obtained from medical records and telephone calls. Follow-up concluded at the last clinical contact or on March 1, 2024, for each patient.

Given the retrospective design, major adverse clinical events (all cause death, cardiac transplantation, and major arrhythmic events) were also collected from medical records and reported but were not prespecified study endpoints.

Endpoints

Study endpoints included worsening LVEF, defined as a decrease of at least 10% from baseline LVEF; evolution to a manifest DCM phenotype (LVEDV > 75 mL/m^2 in male patients and > 62 mL/m^2 in female patients); and the concomitant occurrence of both endpoints, referred to as combined W + E.

Statistical analysis

Analyses were performed using the R statistical package, version 4.2.3. and the IBM-SPSS Statistics Software, version 20 (IBM, Armonk, NY). Two-sided P value < 0.05 defined

statistical significance. Accordingly, confidence interval (CI) level was set at 95%.

Variables are expressed as counts (percentages) and mean ± standard deviation (SD) as appropriate. The χ^2 test was used to test possible associations between categorical data. According to the distribution shape of continuous variables, the nonparametric Wilcoxon test or the analysis of variance (ANOVA) test was used to compare continuous data between groups.

Because follow-up echocardiograms were not performed at fixed intervals but rather according to clinical practice, longitudinal repeated data were unavailable and time-to-event analyses (Kaplan-Meier estimates or Cox regression) were not feasible. Endpoints were therefore analyzed at the last available echocardiographic follow-up using logistic regression models (univariable and multivariable). As a consequence, echocardiographic outcomes were inherently subject to immortal time bias, and competing risk analyses could not be performed.

Univariable (UV) logistic regression was used to assess the association between baseline variables and the endpoints of interest. Multivariable (MV) models were constructed with the aim of maximizing the area under the curve (AUC) of the estimated probability. Specifically, starting with an initial list of significant parameters from the univariable analysis and excluding pairs of variables with a high correlation (Spearman rho > 0.5), considering at most 2 parameters per category (demographics, history, etiology, genetics, ECG, echocardiography, CMR) at a time, because of the statistical power with respect to the number of events, a series of MV models were estimated. The subset of parameters that maximized AUCs across the endpoints was then identified. Internal validation of the final models was performed using a bootstrap approach with the R library"rms." Finally, nomograms were created to provide clinicians with a practical tool to derive the probability of the endpoints based on the values of the selected parameters.

Results

Phenotypic characterization at baseline

We included 432 patients diagnosed with NDLVC (63.4% male, mean age 39.4 ± 14.6 years). At first clinical presentation, most patients reported arrhythmia related symptoms (66.7%, n = 288), whereas 14.4% (n = 62) experienced chest pain, 11.6% (n = 50) dyspnea, and 7.4% (n = 32) were asymptomatic. A family history of CMPs or SCD was noted in 8.6% (n = 37) of patients, and 38.7% presented with NSVT; 38.9% (n = 168) exhibited IVCD at baseline ECG. Regarding the initial echocardiographic assessment, mean LVEF was 52.8 ± 8.4 and 63% (n = 272) of patients showed preserved biventricular function.

Tissue characterization was assessed with contrast enhanced CMR in 88% (n = 382) of patients and with EMB in 43.5% (n = 188) of patients. CMR detected LGE in 82.4% (n = 315) of cases, with a ring-like pattern in 16% (n = 61), and septal involvement in 30.4% (n = 116).

Biopsy- or CMR-proven M-Infl was found in 46% (n = 180) of patients. Genetic testing was performed in 70% (n = 301) of patients, identifying P/LP variants in cardiomyopathy-associated genes in 40.9% (n = 123). Of these, 24.3% (n = 73) carried high-risk P/LP mutations according to ESC guidelines.

In terms of etiology, 9% (n = 39) of patients were classified as GI, 19.7% (n = 85) as G, 32.6% (n = 141) as I, 20% (n = 87) as U, and 18.5% (n = 80) as UU.

Medical treatment for heart failure was initiated in 94% (n = 406) of patients, with 82% receiving beta blockers, 66.4% angiotensin converting-enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), 5.6% angiotensin receptor neprilysin inhibitors, and 6.7% sodium-glucose cotransporter-2 inhibitors. Only 13.7% of patients were treated with loop diuretics. In addition, immunomodulatory strategies were used in 39.4% of patients with documented M-Infl, with the immunosuppressive strategy decided case by case by the clinical researchers. During follow-up, 45.9% (n = 198) of patients received ICD placement, mostly in primary prevention (94%, n = 186), and 7.4% (n = 32) underwent catheter ablation for ventricular arrhythmias. Baseline characteristics and treatment strategies are summarized in Table 1.

Clinical outcomes (all cause death, cardiac transplantation, and major arrhythmic events) were reported in Supplemental Table S2, showing worse prognosis in patients with adverse echocardiographic remodelling and highlighting the importance of deep phenotypic characterization in patients with NDLVC.

Study endpoints and prognostic stratification

During a median follow-up at 77 months (IQR: 48-109), 118 patients (27.3%) showed a worsening in LVEF, 125 patients (28.9%) progressed to a DCM phenotype, and 79 patients (18.3%) experienced the combined W + E endopoint. In the subgroup with baseline LVEF ≥ 50%, worsening LVEF was reported in 58 patients (21.3%), evolution in DCM phenotype in 56 patients (20.6%), and the combined W + E endpoint in 31 patients (11.4%).

We assessed baseline factors associated with study endpoints throughout univariate analysis (Table 2). A negative genetic testing emerged as the strongest protective factor against LVEF worsening (odds ratio [OR], 0.2; 95% CI, 0.1-0.4; $P < 0.001$), evolution to DCM (OR, 0.2; 95% CI, 0.1-0.4; $P < 0.001$) and the combined W + E endpoint (OR, 0.1; 95% CI, 0.04-0.3; $P < 0.001$), whereas the coexistence of biopsy- or CMR-proven M-Infl added to a positive genetic etiology (ie, the GI etiology), represented the strongest adverse predictor of LVEF worsening (OR, 6.5; 95% CI, 3.2-13; $P < 0.001$), evolution to DCM (OR, 2; 95% CI, 1-4; $P = 0.03$) and the combined W + E endpoint (OR, 3.6; 95% CI, 1.8-7.3; $P < 0.001$). Family history of CMPs or SCD, IVCD on ECG, ring-like LGE on CMR, and baseline echocardiographic LVEF < 45% emerged as significantly associated to all the endpoints. NSVT at baseline Holter ECG monitoring resulted significantly associated to LVEF worsening and the combined W + E endpoint, but not with evolution to DCM.

Consistent results were observed in the subgroup with at least 24 months follow-up (Supplemental Table 3) and in patients with baseline LVEF ≥ 50% (Supplemental Table 4).

Table 1. Baseline features of the population

	Total n = 432	Worsening LVEF n = 118	Evolution in DCM n = 125	Combined W + E n = 79
Parameter				
Age	39.4 ± 14.6	39.49 ± 14.64	38.55 ± 14.2	38 ± 3.8
Male	274 (63.4%)	76 (64.4%)	73 (58.4%)	51 (64.6%)
Athletes	72 (16.7%)	16 (13.6%)	21 (16.8%)	11 (14%)
Family history of CMPs and/or SCD	37 (8.6%)	16 (13.6%)	16 (12.8%)	11 (14%)
Clinical presentation				
Arrhythmia-related symptoms	288 (66.7%)	82 (69.5%)	82 (65.6%)	55 (69.6%)
Chest pain	62 (14.4%)	17 (14.4%)	18 (14.4%)	10 (12.7%)
Dyspnea	50 (11.6%)	10 (8.5%)	14 (11.2%)	8 (10.1%)
Asymptomatic	32 (7.4%)	8 (6.8%)	10 (8%)	5 (6.3%)
Etiology				
Genetic	85 (19.7%)	36 (30.5%)	39 (31.2%)	27 (34.2%)
Genetic and inflammatory	39 (9%)	26 (22%)	17 (13.6%)	16 (20.3%)
Inflammatory	141 (32.6%)	28 (23.7%)	35 (28%)	19 (24.1%)
Unknown	87 (20%)	15 (12.7%)	21 (16.8%)	10 (12.7%)
Not sufficient tests	80 (18.5%)	13 (11%)	13 (10.4%)	7 (8.9%)
Genetic testing*				
Negative	112 (37.2%)	13 (14%)	14 (15%)	5 (8%)
VUS	66 (22%)	18 (19.4%)	24 (25.8%)	14 (22.6%)
TTN	27 (9%)	8 (8.6%)	11 (11.8%)	5 (8%)
High-risk genotype†	73 (24.3%)	42 (45.2%)	34 (36.6%)	30 (48.4%)
ECG				
AV block (degree 0-3)	64 (14.8%)	28 (23.7%)	27 (21.6%)	19 (24.1%)
IVCD	168 (38.9%)	66 (56%)	62 (49.6%)	46 (58.2%)
Low QRS voltages	51 (11.8%)	14 (11.9%)	17 (13.6%)	11 (14%)
NSVT	167 (38.7%)	57 (48.3%)	55 (44%)	40 (50.6%)
Echocardiogram				
LVEF (%)	52.8 ± 8.4	50.8 ± 8.7	49.7 ± 8.2	49 ± 7.9
LVEDVi (mL/m^2)	59.4 ± 9.2	61.2 ± 9.8	63.6 ± 7.4	64.1 ± 7.7
RV disfunction	25 (5.8%)	10 (8.5%)	9 (7.2%)	6 (7.6%)
RV dilatation	26 (6%)	6 (5.1%)	10 (8%)	6 (7.6%)
CMR				
LVEF (%)	50.7 ± 8.7	47.8 ± 9.3	47.3 ± 8.7	45.6 ± 8.6
RVEF (%)	59.3 ± 7.3	59 ± 6.6	60.8 ± 6.8	60.1 ± 6.7
LGE presence‡	315 (82.4%)	98 (92.4%)	97 (87.4%)	64 (92.8%)
Septal LGE involvement‡	116 (30.4%)	42 (39.6%)	39 (35.1%)	29 (42%)
Ring-like LGE‡	61 (16%)	34 (32%)	25 (22.5%)	22 (32%)
Medications				
Beta blockers	354 (82%)	97 (82%)	104 (83.2%)	64 (81%)
ACE/ARB	287 (66.4%)	79 (67%)	89 (71.2%)	57 (72.2%)
ARNI	24 (5.6%)	15 (12.7%)	17 (13.6%)	13 (16.5%)
SGLT2i	29 (6.7%)	16 (13.6%)	15 (12%)	11 (13.9%)
Loop diuretics	59 (13.7%)	32 (27%)	27 (21.6%)	21 (26.6%)
Immunomodulatory	71 (16.4%)	12 (10.2%)	14 (11.2%)	10 (12.7%)
Catheter ablation VA	32 (7.4%)	8 (6.8%)	10 (8%)	5 (6.3%)
ICD placement	198 (45.9%)	86 (72.9%)	81 (64.8%)	65 (82.3%)

Baseline features of the population are shown for the study groups. Data are expressed as means ± standard deviation for continuous variables and as counts and percentages for categorical variables.

Treatment was started upon drug availability.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; AV, atrioventricular; BMI, body mass index; CMPs, cardiomyopathies; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy; ICD, implantable cardioverter defibrillator; IVCD, intraventricular conduction delay; LGE, late gadolinium enhancement; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVNC, left ventricular non compaction; n, number; NSVT, nonsustained ventricular tachycardia; RV, right ventricular; RVEF, right ventricular ejection fraction; RVEDVi, indexed right ventricular end-diastolic volume; SCD, sudden cardiac death; SGLT2i, sodium-glucose cotransporter-2 inhibitors; TTN, titin; VA, ventricular arrhythmias; VUS, variants of uncertain significance.

* Percentage refer to the group of patients who perform genetic testing.

† "High-risk" genes include *LMNA*, *FLNC*, *TMEM43*, *PLN*, *DSP*, and *RBM20*.

‡ Percentage refer to the group of patients who contrast-enhanced CMR.

The same multivariable model, including the negative genetic testing, the GI etiology, a family history of CMPs or SCD, IVCD, baseline echocardiographic LVEF < 45%, LGE with a ring-like pattern, and NSVT at baseline Holter ECG monitoring, demonstrated the strongest discriminative power across all the endpoints, with AUCs of 0.8 (95% CI, 0.75-0.86) for worsening LVEF, 0.78 (95% CI, 0.73-0.84) for evolution in DCM phenotype, and 0.84 (95% CI, 0.79-0.89) for and the combined W + E endpoint (Table 3). Notably, a negative genetic testing consistently served as a protective factor, whereas the presence of P/LP variants in cardiomyopathies-related genes coupled with inflammatory

Table 2. Univariable analysis of the entire NDLVC population

	Worsening LVEF		Evolution in DCM		Combined W + E	
Parameter	OR (CI 95%)	*P* value	OR (CI 95%)	*P* value	OR (CI 95%)	P value
Age > 30 years	1 (0.6-1.5)	0.84	0.9 (0.6-1.4)	0.6	0.9 (0.5-1.4)	0.59
Male	1.1 (0.7-1.7)	0.6	0.8 (0.5-1.2)	0.2	1.1 (0.7-1.8)	0.71
Athletes	0.7 (0.4-1.3)	0.23	1 (0.6-1.7)	0.9	0.8 (0.4-1.5)	0.42
Family history of CMPs and/or SCD	2.3 (1.1-4.6)	**0.02**	2.1 (1.1-4.2)	**0.03**	2.1 (1-4.5)	**0.05**
Etiology						
Genetic	2.4 (1.5-4)	**< 0.001**	2.6 (1.6-4.3)	**< 0.001**	2.7 (1.6-4.6)	**< 0.001**
Genetic and inflammatory	6.5 (3.2-13)	**< 0.001**	2 (1-4)	**0.03**	3.6 (1.8-7.3)	**< 0.001**
Inflammatory	0.6 (0.3-0.9)	**0.02**	0.7 (0.5-1.1)	0.2	0.6 (0.3-1)	0.07
Unknown	0.5 (0.3-0.9)	**0.02**	0.7 (0.4-1.3)	0.28	0.5 (0.3-1.1)	0.07
Not sufficient tests	0.5 (0.2-0.9)	**0.02**	0.4 (0.2-0.8)	**0.009**	0.4 (0.2-0.9)	**0.02**
Genetic testing						
Negative	0.2 (0.1-0.4)	**< 0.001**	0.2 (0.1-0.4)	**< 0.001**	0.1 (0.04-0.3)	**< 0.001**
VUS	0.8 (0.4-1.4)	0.42	1.4 (0.8-2.4)	0.29	1 (0.5-2)	0.92
TTN	0.9 (0.4-2.2)	0.84	1.6 (0.7-3.6)	0.26	0.9 (0.3-2.4)	0.76
High-risk genotype*	4.9 (2.8-8.5)	**< 0.001**	2.6 (1.5-4.4)	**< 0.001**	4.4 (2.4-8)	**< 0.001**
ECG						
AVB	2.4 (1.4-4)	**0.002**	2 (1.2- 3.5)	**0.01**	2.2 (1.2-4)	**0.01**
QRS > 120 ms	2.5 (1.5-4.4)	**< 0.001**	2.5 (1.4-4.3)	**0.001**	3 (1.7-5.4)	**< 0.001**
Pathologic Q waves	1.3 (0.6-2.9)	0.59	1.2 (0.5-2.7)	0.69	1.5 (0.6-3.7)	0.36
IVCD	2.6 (1.7-4.1)	**< 0.001**	1.9 (1.2-2.8)	**0.004**	2.6 (1.6-4.3)	**< 0.001**
Low QRS voltages	1 (0.5-2)	0.9	1.3 (0.7-2.5)	0.4	1.3 (0.6-2.6)	0.49
NSVT	1.7 (1.1-2.6)	**0.02**	1.3 (0.9-2)	0.2	1.8 (1.1-3)	**0.02**
Echocardiogram						
LVEF < 45%	2.4 (1.5-4)	**< 0.001**	2.9 (1.7-4.7)	**< 0.001**	3.2 (1.9-5.6)	**< 0.001**
RV disfunction	1.8 (0.8-4.1)	0.17	1.4 (0.6-3.3)	0.42	1.4 (0.6-3.7)	0.47
RV dilatation	0.9 (0.4-2.1)	0.72	1.7 (0.8-3.8)	0.19	1.5 (0.6-3.7)	0.36
At least moderate VHD	1.2 (0.7-2.3)	0.52	1.6 (0.9-2.9)	0.14	1.3 (0.6-2.6)	0.53
CMR						
LVEF < 45%	3.6 (2.1-6)	**< 0.001**	4.9 (2.9-8.2)	**< 0.001**	6 (3.4-10.5)	**< 0.001**
RVEF < 45%	0.6 (0.2-2.3)	0.5	0.6 (0.2-2.2)	0.4	0.7 (0.2-3.2)	0.6
Fibrofatty infiltration	1.9 (0.7-5.1)	0.21	0.7 (0.2-2)	0.47	1.2 (0.4-4)	0.77
LGE presence	3.3 (1.5-7.3)	**0.002**	1.7 (0.9-3.2)	0.11	3.2 (1.2-8.2)	**0.02**
Septal LGE involvement	1.8 (1.1-2.9)	**0.01**	1.3 (0.8-2.1)	0.23	1.9 (1.1-3.2)	**0.02**
Focal LGE	0.9 (0.4-2.2)	0.82	0.9 (0.4-2.1)	0.76	1.2 (0.5-3.4)	0.67
Multifocal LGE	0.8 (0.3-1.9)	0.56	0.9 (0.4-2.2)	0.79	0.4 (0.1-1.3)	0.14
Ring-like LGE	4.5 (2.5-8)	**< 0.001**	2 (1.1-3.5)	**0.02**	3.4 (1.8-6.2)	**< 0.001**
LVNC criteria	0.8 (0.3-1.7)	0.5	0.8 (0.4-1.9)	0.67	0.7 (0.3-1.9)	0.51
Mitral valve prolapse	0.5 (0.2-1)	**0.05**	1.5 (0.8-2.7)	0.2	0.5 (0.2-1.3)	0.18
EMB						
Inflammation	1.3 (0.6-2.6)	0.54	1.4 (0.6-3)	0.4	1.3 (0.6-3.2)	0.5
Fibrosis	0.5 (0.3-0.9)	**0.03**	0.8 (0.4-1.6)	0.54	0.7 (0.4-1.5)	0.4

The results of the univariable analysis for potential predictors of worsening LVEF or progression to DCM are listed.

Bold values indicate statistically significant *P* values ($P < 0.05$)

AVB, atrioventricular block; CI, confidence interval; CMPs, cardiomyopathies; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy; IVCD, intraventricular conduction delay; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVNC, left ventricular non compaction; NDLVC, nondilated left ventricular cardiomyopathy; NSVT, nonsustained ventricular tachycardia; OR, odds ratio; RV, right ventricular; RVEF, right ventricular ejection fraction; SCD, sudden cardiac death; TTN, titin; VHD, valvular heart disease; VUS, variants of uncertain significance.

* "High-risk" genes include *LMNA, FLNC, TMEM43, PLN, DSP*, and *RBM20*.

Table 3. Model performance in the entire NDLVC population

	Worsening LVEF		Evolution in DCM		Combined W + E	
Parameter	OR (CI 95%)	*P* value	OR (CI 95%)	*P* value	OR (CI 95%)	*P* value
Etiology GI	3.9 (1.6-9.3)	**0.003**	1.4 (0.6-3.2)	0.4	2.7 (1-7)	**0.05**
Negative genotype	0.3 (0.2-0.6)	**0.001**	0.3 (0.1-0.5)	**< 0.001**	0.2 (0.1-0.6)	**0.002**
Family history of CMPs and/or SCD	2.5 (1.1-5.9)	**0.04**	3 (1.3-6.9)	**0.01**	4.2 (1.5-11.5)	**0.005**
IVCD	3.1 (1.7-5.9)	**< 0.001**	2.1 (1.1-3.7)	**0.02**	3.3 (1.6-7.1)	**0.002**
Echo LVEF baseline < 45%	2 (1-3.9)	**0.04**	5.2 (2.8-9.9)	**< 0.001**	5.7 (2.6-12.4)	**< 0.001**
Ring-like LGE	2.4 (1.1-5.2)	**0.02**	1.2 (0.5-2.5)	0.7	1.7 (0.7-4.1)	0.2
NSVT	1.5 (0.8-2.8)	0.2	1.3 (0.9-2)	0.2	2.3 (1.1-4.7)	**0.03**
Model performance (AUC)	0.80 (CI, 95%: 0.75-0.86)		0.78 (CI, 95%: 0.73-0.84)		0.84 (CI, 95%: 0.79-0.89)	

Multivariable analysis for each endpoint.

Bold values indicate statistically significant *P* values ($P < 0.05$).

AUC, area under the curve; CI, confidence intervals; CMPs, cardiomyopathies; DCM, dilated cardiomyopathy; GI, genetic + inflammatory; IVCD, intraventricular conduction delays; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NDLVC, nondilated left ventricular cardiomyopathy; NSVT, nonsustained ventricular tachycardia; OR, odds ratio; SCD, sudden cardiac death.

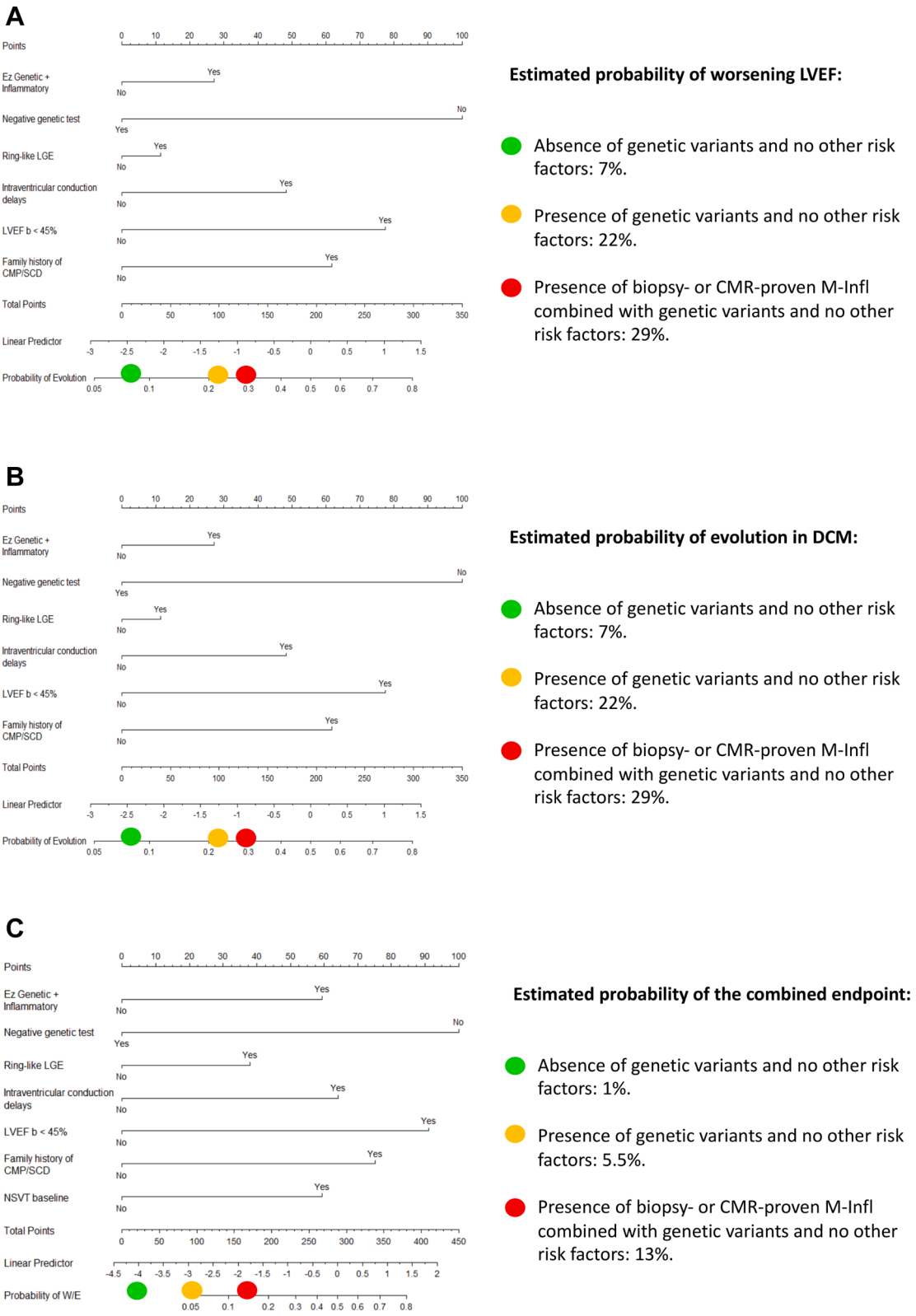


Figure 1. Nomograms for each endpoint in the overall population. Nomograms for predicting worsening LVEF (**A**), evolution in DCM phenotype (**B**) and combined worsening LVEF and evolution in DCM phenotype (**C**), in the study population. To use the nomogram, a vertical line needs to be delineated to the point row (**top**) to assign a point value for predictors. All values should then be added to obtain the total points (**bottom**) and subsequently convert them into an individual risk of different outcomes. LVEF refers to echocardiographic value. b, baseline; CMP, cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; Ez, etiology; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; M-Infl, myocardial inflammation; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death.

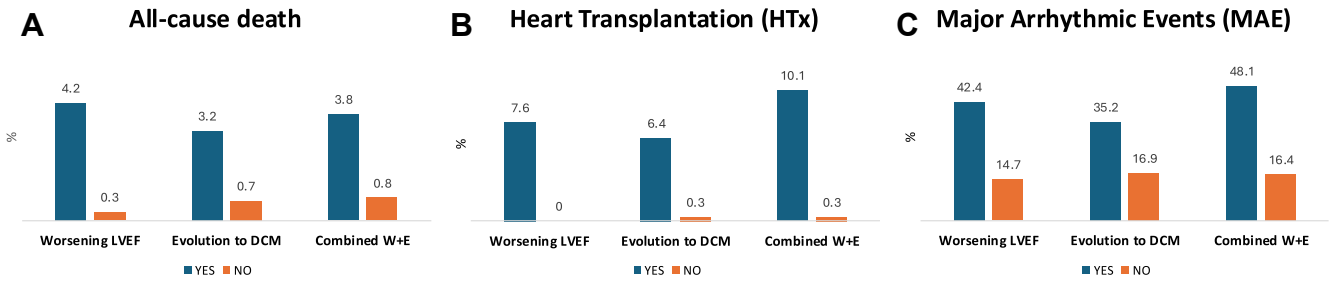


Figure 2. Major adverse clinical events. Figure shows the percentage of patients experiencing the event according to the presence or absence of worsening LVEF (**A**), evolution to DCM (**B**), or the combined W + E (**C**). Values are reported as percentages derived from the total number of patients in each subgroup. DCM, dilated cardiomyopathy; HTx, heart transplantation; LVEF, left ventricular ejection fraction; MAE, major arrhythmic event; NDLVC, nondilated left ventricular cardiomyopathy.

background significantly increased the risk. Consistent results were obtained in the subgroup with at least 24 months of follow-up (Supplemental Table S5).

Interestingly, in the subgroup of patients with baseline echocardiographic LVEF $\geq$ 50% (Supplemental Table S6), a multivariable model with negative genetic testing, GI etiology, a family history of CMPs or SCD, IVCD, LGE with a ring-like pattern, and NSVT at baseline Holter ECG monitoring, showed the highest performance in predicting worsening LVEF (AUC: 0.86; 95% CI, 0.8-0.92) and the

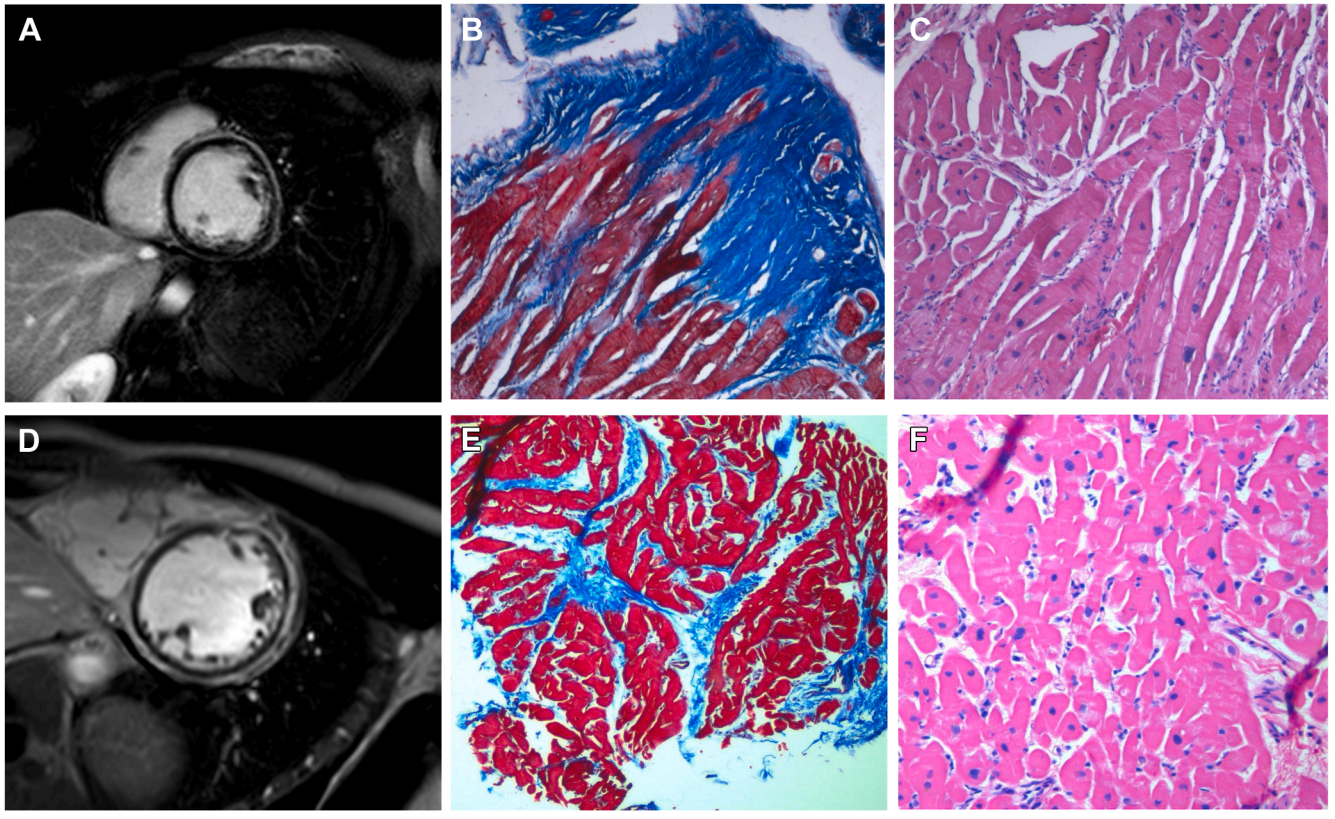
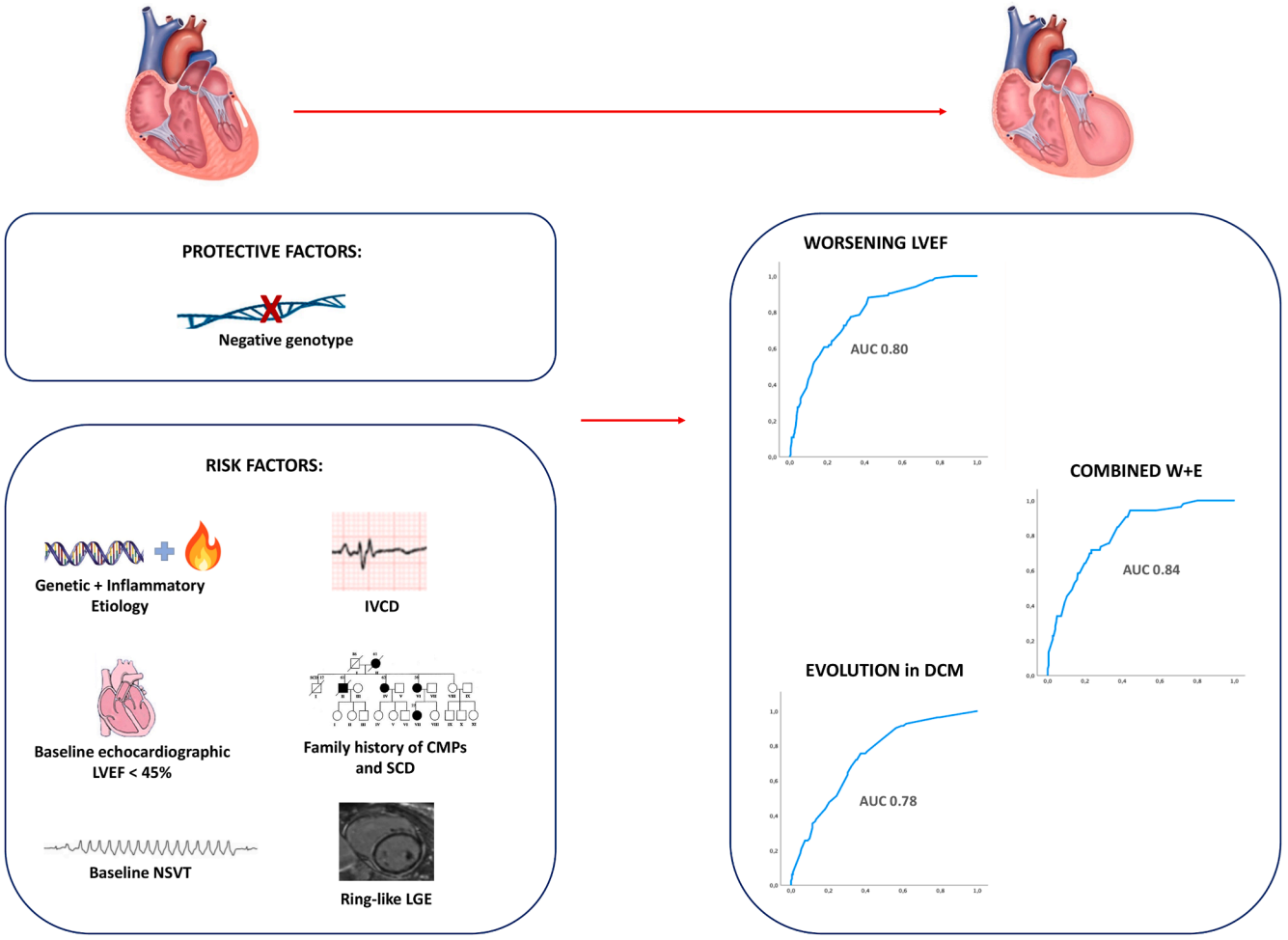


Figure 3. CMR and histologic findings in patient with worsening NDLVC. Upper panels: 25-year- old woman affected by NDLVC. On CMR (**A**) diffuse subepicardial ring-like LGE, on EMB (**B, C**) extensive myocardial fibrosis with cardiomyocytes loss. Patient underwent s-ICD implantation, experiencing an appropriate shock on VF during follow up. She progressively developed LV dilation and haemodynamic lability and is currently on heart transplant list. Lower panels: 35-year-old woman affected by NDLVC with mild LV dysfunction at onset. On CMR (**D**) circumferential ring-like LGE on EMB (**E, F**) intersitial fibrosis and mild edema. During follow-up, patient developed LV dilation and severe LV dysfunction, and an endocavitary ICD was placed. Genetic testing showed a pathogenic variant of DSP. CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; DSP, desmoplakin; EMB, endomyocardial biopsy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; M-Infl, myocardial inflammation; NDLVC, nondilated left ventricular cardiomyopathy; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; s-ICD, subcutaneous implantable cardioverter defibrillator; VF, ventricular fibrillation.



Central Illustration. Accuracy of multivariable model for the 3 endpoints. The accuracy of multivariable risk stratification models is shown. AUC, area under the curve; CMPs, cardiomyopathies; DCM, dilated cardiomyopathy; IVCD, intraventricular conduction delay; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death.

combined W + E endpoint (AUC: 0.9; 95% CI, 0.84-0.95). Moreover, in this subgroup, no patient with negative genetic testing experienced the combined W + E endpoint.

The analysis was used to develop nomograms for each endpoint in the overall study population (Fig. 1). Patients with negative genetic testing and no additional risk factors have the lowest likelihood of adverse remodelling. Conversely, those carrying pathogenic variants—particularly in high-risk genes and in the presence of M-Infl—represent the highest-risk group. Between these categories, the coexistence of multiple baseline features such as NSVT, LVEF < 45%, ring-like LGE, or positive family history increase the probability of adverse LV remodelling.

Discussion

The main findings of the study were that, in our cohort, approximately 38% of patients experienced adverse echocardiographic progression (worsening LVEF or evolution to a dilated phenotype). This represents a novel and clinically relevant observation in a population for which longitudinal data have been lacking. In the entire NDLVC population, major predictors of disease progression were a genetic and inflammatory (GI) etiology (proven by EMB), family history of CMPs or SCD, IVCD, echocardiographic LVEF < 45%, LGE with a ring-like pattern, and NSVT. On the opposite, a negative genetic testing emerged as the most protective factor across all endpoints in the whole population and in the subgroup with baseline echocardiographic LVEF ≥ 50%. These results highlight that a multimodal approach, combining deep phenotyping and genetic characterization, should be individualized and systematically pursued in patients with NDLVC, in line with the cardiomyopathy mindset proposed by the ESC Guidelines, to clarify which combinations of these factors are most strongly associated with the risk of progression of disease (Central Illustration).

Interestingly, common baseline variables, such as age, sex and NYHA class, were not associated with progression of disease across the 3 endopoints endopoints and were therefore not retained in the final multivariable models. This issue further highlights the need of a comprehensive phenotyping in clinical management of NDLVC.

To our knowledge, this is the first study to characterize the temporal evolution of NDLVC. This is of particular

relevance because of the heterogeneity of patients included in this disease, recently introduced in clinical practice, and still largely unexplored. In our cohort, approximately 38% of the population showed progression of disease, consistent with previous data on mildly dilated cardiomyopathy.[23] Furthermore, patients who experienced echocardiographic worsening truly represent a clinically progressing group, as they showed more adverse events, including all cause death, cardiac transplantation, and major arrhythmic events (Fig. 2). Therefore, the early identification of patients with NDLVC and subsequent negative evolution represents an important issue for addressing a personalized management.

The parameters associated with progression of disease in our study align with general knowledge about cardiomyopathies.[24,25] In support to recent literature in arrhythmogenic cardiomyopathy,[26] our cohort data showed that the protective effect of a negative genetic testing on progression of disease was a stronger predictor than the adverse impact of a high-risk genotype, especially in the subgroup with baseline LVEF $\geq$ 50%.

On the other side, our results suggest that a combined genetic and inflammatory etiology provides a better predictive value for adverse remodelling than a genetic etiology alone (Fig. 3). So far, the role of M-Infl in the development and progression of cardiomyopathies,[27] its relationship with genetically determined dilated or arrhythmogenic cardiomyopathies,[28] and—of a consequence—the effect of possible immunomodulatory strategies remain incompletely understood.[29] Despite needing confirmation and prospective clinical trials, the current results highlight—in the context of NDLVC—that the clinical judgement should systematically guide the search for M-Infl through a multimodal integrative approach to identify specific patients at high risk of progression of disease that can benefit from tight follow-up and possibly from targeted immunosuppression.

The multimodal approach to patients with NDLVC should systematically include CMR (with T2-weighted sequences) and genetic testing. Notably, commonly available clinical and instrumental factors, such as family history, ECG characteristics, and baseline arrhythmic profile at ECG Holter can provide an initial risk stratification and guide the clinical suspicion toward a genetically determined or inflammatory cardiomyopathy, requiring a deep phenotyping and a personalized management.

In this perspective, the aim is not to expose all patients to every advanced investigation but to identify those at higher risk of adverse remodelling who may benefit from early guideline-directed therapy, closer surveillance, and referral to specialized centres. FDG-PET[30] and particularly EMB should be reserved for selected patients with cardiomyopathies presenting features suggestive of inflammatory substrates, in which histologic evidence can provide actionable information to guide targeted immune-modulating therapies.

Limitations

This study has several limitations. First, its retrospective design. Second, it was conducted at 2 tertiary referral centres, which may have introduced selection bias. Third, esternal validation is lacking.

The inclusion of a broad spectrum of diseases, based on the phenotype-driven definition of NDLVC, introduced some heterogeneity. Notably, CMR data were unavailable for 12% of NDLVC cases. In addition, although all CMR examinations were centrally reviewed and considered as baseline, their timing varied across the study period, being performed within 3 months from diagnosis after 2015 and within 9 months before 2015. The detection of M-Infl varied based on histology or CMR assessment, but although T2-weighted CMR sequences might not fully correspond to M-Infl, the majority of cases had supportive histologic findings.

Importantly, although all patients received guideline-directed medical therapy, longitudinal treatment data were not available, preventing assessment of the potential influence of pharmacologic therapy on evolution of disease. Specifically designed prospective studies could provide greater insights into this aspect. Similarly, the lack of data on cardiac resynchronization therapy limited our ability to draw definitive conclusions, especially in patients with intraventricular conduction delays on ECG, but they represented only 1.4% of our population.

No patient was lost to follow-up, and major clinical outcomes (all cause death, transplantation, arrhythmic events) were retrospectively retrieved. However, the absence of standardized longitudinal echocardiographic assessments may have introduced potential bias and precluded time-to-event or competing risk analyses. Indeed, patients who died or underwent transplantation before the last echocardiogram could not be captured, leading to an inherent immortal time bias.

All these limitations make our study an hypothesis-generating one, and our results—although the first ones of their kind in the literature—provide preliminary insights that require confirmation in prospective, appropriately powered studies.

Conclusions

In this large multicentre cohort of patients with NDLVC, the integration of deep phenotyping—including family history of cardiomyopathy or sudden cardiac death, ECG conduction abnormalities, arrhythmic profile on Holter, ring-like LGE on CMR, and, in selected cases, histologic data—and genetics could predict adverse LV remodelling. These findings underscore the importance of multiparametric critical approach in such a heterogeneous disease to improve risk stratification and guide individualized management.

Despite these promising results, external validation in independent patient cohorts and prospective studies with extended follow-up are necessary to better understand the longitudinal progression in this newly identified heterogeneous group of cardiomyopathies.

Ethics statement

All participants provided written informed consent in compliance with the Declaration of Helsinki to be included in local research registries approved by their respective Ethics Committees and Institutional Review Boards. The study was conducted and reported in accordance with the

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The completed STROBE checklist is provided in Supplemental Table 1.

Patient Consent

The authors confirm that a patient consent form(s) has been obtained for this article.

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Disclosures

Dr Peretto has received speaker fees from Abbott. Dr Della Bella is a consultant for Abbott and Biosense and has received research grants from Abbott, Biosense, Biotronik, and Boston Scientific. The other authors have no conflicts of interest to disclose.

Data Availability

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

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2025.12.013