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ORIGINAL INVESTIGATIONS

Clinical Risk Prediction in Patients With Left Ventricular Myocardial Noncompaction

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ABSTRACT

BACKGROUND Left ventricular noncompaction (LVNC) is a heterogeneous entity with uncertain prognosis.

OBJECTIVES This study sought to develop and validate a prediction model of major adverse cardiovascular events (MACE) and to identify LVNC cases without events during long-term follow-up.

METHODS This is a retrospective longitudinal multicenter cohort study of consecutive patients fulfilling LVNC criteria by echocardiography or cardiovascular magnetic resonance. MACE were defined as heart failure (HF), ventricular arrhythmias (VAs), systemic embolisms, or all-cause mortality.

RESULTS A total of 585 patients were included (45 ± 20 years of age, 57% male). LV ejection fraction (LVEF) was 48% ± 17%, and 18% presented late gadolinium enhancement (LGE). After a median follow-up of 5.1 years, MACE occurred in 223 (38%) patients: HF in 110 (19%), VAs in 87 (15%), systemic embolisms in 18 (3%), and 34 (6%) died. LVEF was the main variable independently associated with MACE ($P < 0.05$). LGE was associated with HF and VAs in patients with LVEF >35% ($P < 0.05$). A prediction model of MACE was developed using Cox regression, composed by age, sex, electrocardiography, cardiovascular risk factors, LVEF, and family aggregation. C-index was 0.72 (95% confidence interval: 0.67-0.75) in the derivation cohort and 0.72 (95% confidence interval: 0.71-0.73) in an external validation cohort. Patients with no electrocardiogram abnormalities, LVEF ≥50%, no LGE, and negative family screening presented no MACE at follow-up.

CONCLUSIONS LVNC is associated with an increased risk of heart failure and ventricular arrhythmias. LVEF is the variable most strongly associated with MACE; however, LGE confers additional risk in patients without severe systolic dysfunction. A risk prediction model is developed and validated to guide management.
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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CMR = cardiovascular magnetic resonance

DCM = dilated cardiomyopathy

ECG = electrocardiogram

HF = heart failure

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

LVNC = left ventricular noncompaction

MACE = major adverse cardiovascular events

NCCM = noncompaction cardiomyopathy

SCD = sudden cardiac death

SE = systemic embolism

TTE = transthoracic echocardiography

VA = ventricular arrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

Left ventricular noncompaction (LVNC) is a poorly understood, heterogeneous entity characterized by prominent myocardial trabeculations (1). Although several definitions have been proposed, currently diagnosis is mainly based on morphologic findings by comparing the compacted and noncompacted myocardium layers (2-5) and not taking into account functional LV or clinical parameters, which has increased LVNC prevalence (6-8).

SEE PAGE 663

The pathogenesis of LVNC has been traditionally regarded as an arrest in myocardium compaction during embryogenesis due to genetic causes. Several genetic variants, including mainly sarcomeric genes, have been associated with the condition (1). These genotypes often overlap with other phenotypes such as dilated cardiomyopathy (DCM) or hypertrophic cardiomyopathy, and in terms of prognosis, some variants have been associated with both LV systolic dysfunction and adverse outcomes in LVNC (9,10).

However, growing evidence supports the idea that acquired and even reversible forms of LVNC can occur under different loading conditions, such as those during endurance sport or pregnancy. This challenges the concept of LVNC being a distinct cardiomyopathy and raises the question of whether it might simply be an anatomical phenotype (1,6,11). Therefore, it is important to distinguish high-risk LVNC forms that might develop a cardiomyopathy (noncompaction cardiomyopathy [NCCM]), and hence cardiovascular events, from those low-risk cases that might correspond to a morphologic trait (physiologic hypertrabeculation), which might not require strict clinical surveillance.

The prognosis of LVNC is remarkably heterogeneous, with heart failure (HF), ventricular arrhythmias (VAs) and systemic embolisms (SEs) being the most frequent cardiovascular complications (12). Recent studies have shown that LVNC has poorer prognosis compared with matched DCM control subjects (10). However, the degree of hypertrabeculation has not been associated with either LV remodeling or outcomes (7,13,14), with LV ejection fraction (LVEF) and late gadolinium enhancement (LGE) being the 2 main prognostic factors described so far (14,15). Furthermore, risk stratification in LVNC is particularly challenging, and specific recommendations are not available.

Therefore, we aimed to develop and validate a model for individualized prediction of cardiovascular events in patients with morphologic features of LVNC, to improve prognostic stratification and guide clinical management. In addition, an attempt was made to identify whether there is a subgroup of

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patients who correspond to physiologic hypertrabeculation forms, who are not at risk of developing events and, subsequently, who would have an excellent prognosis at follow-up.

METHODS

STUDY DESIGN AND POPULATION. We conducted an observational, retrospective, longitudinal cohort study of patients diagnosed with LVNC and followed at 12 Spanish referral inherited cardiac diseases units. From January 1, 2000, to December 31, 2018, all consecutive patients fulfilling Jenni criteria for LVNC by 2-dimensional transthoracic echocardiography (TTE) (3), and when available, both Petersen (4) and Jacquier (5) criteria by cardiovascular magnetic resonance (CMR) were recruited (CMR criteria prevailed over TTE in case of discrepancy). There were no exclusion criteria: all patients with available information on the occurrence and date of outcomes, regardless of the follow-up time, were considered for the analysis, except those with missing LVEF.

All patients underwent a comprehensive initial evaluation, which included medical and family history and pedigree construction. LVNC diagnosis was then confirmed, which was the moment of inclusion in the study. Patients were casually followed up on a regular yearly basis, irrespective of symptomatic status or clinical events, and follow-up was censored after last contact with the outpatient clinic. Data collection was completed on May 31, 2019, which was considered the end of study. Medical treatment was prescribed according to clinical guidelines (16,17). Periodic ambulatory Holter monitoring, exercise treadmill tests, and implantable cardiac device interrogations were performed. Family screening was recommended in all probands and was considered positive if at least 1 additional first-degree relative fulfilled imaging diagnostic criteria (by TTE and/or CMR when possible).

GENETICS. Genetic testing was indicated according to the criteria of each center and consisted of a next-generation sequencing panel of 213 genes related to inherited cardiovascular diseases (full explanation and list in the Supplemental Appendix and Supplemental Table 1). All genetic studies were analyzed at the same external center and were considered positive if a pathogenic or likely pathogenic variant was described according to the current American College of Medical Genetics and Genomics guidelines (18). Variants were classified according to the molecular function of the gene into sarcomere (*ACTC1*, *MYH7*, *MYBPC3*, *TTN*, *FHL1*, *FHOD3*, *LDB3*, *TNNC1*, *TNNI3*, *TNNT2*, *TPM1*), cytoskeleton (*ACTN2*, *DMD*, *FLNC*), desmosome (*DSP*, *JUP*), and others (*BAG3*, *HCN4*, *JPH2*, *MIB1*, *NKX2-5*, *Notch1*, *RBM20*, *TBX20*). A complex genotype was defined as the presence of pathogenic or likely pathogenic variants in more than 1 gene, as published elsewhere (9).

ADVERSE EVENTS. The clinical endpoints of the study were: 1) HF: a composite of HF hospitalization, need for cardiac resynchronization therapy implantation, heart transplantation, or LV assist device implantation; 2) VAs: aborted sudden cardiac death (SCD), ventricular fibrillation (VF), sustained or nonsustained ventricular tachycardia (VT), or appropriate implantable cardioverter-defibrillator (ICD) therapy; 3) SEs: embolic stroke or transient ischemic attack, embolic myocardial infarction, or peripheral artery embolism; and 4) all-cause mortality (cardiovascular mortality was also recorded). Major adverse cardiovascular events (MACE) were defined as a combination of the 4 primary endpoints. MACE were used to identify patients who did not develop events during follow-up and, subsequently, to determine variables associated with favorable prognosis.

VARIABLES. The electrocardiogram (ECG), TTE, and CMR tests performed closest to the date of diagnosis were used for the analysis. TTE and CMR were interpreted locally by specialists in cardiac imaging and genetic cardiomyopathies. LVEF was categorized according to HF guidelines (16,17) as preserved (LVEF ≥50%), mildly reduced (LVEF 35%-50%), and severely reduced (LVEF ≤35%). Age at diagnosis was divided into tertiles. An abnormal ECG was defined as

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TABLE 1 Left Ventricular Noncompaction Patient Characteristics According to the Occurrence of MACE

	All (N = 585)	MACE (n = 223)	No MACE (n = 362)	Crude HR (95% CI)	*P* Value
Clinical characteristics					
Age at diagnosis, y	45 ± 20	54 ± 17	40 ± 20	1.03 (1.03-1.04)	<0.001
≤35 y	191	31 (14)	160 (44)	1.00	
36-54 y	203	90 (40)	113 (31)	2.89 (1.91-4.35)	<0.001
≥55 y	191	102 (46)	89 (25)	4.48 (2.99-6.71)	<0.001
Male	334 (57)	136 (61)	198 (55)	1.26 (0.96-1.66)	0.086
Proband	437 (75)	201 (90)	236 (65)	4.00 (2.57-6.21)	<0.001
Baseline NYHA functional class III-IV	66 (11)	59 (27)	7 (2)	3.57 (2.65-4.82)	<0.001
Family history of CM[a]	107 (26)	49 (26)	58 (26)	0.90 (0.64-1.24)[b]	0.508
Family history of SCD[a]	65 (17)	33 (20)	32 (15)	1.00 (0.68-1.47)[b]	0.994
Positive family screening[a]	106 (42)	43 (42)	63 (42)	0.80 (0.56-1.14)[b]	0.219
Positive genotype[c]	192 (54)	69 (54)	123 (54)	0.87 (0.62-1.24)[d]	0.447
Noncompaction cardiomyopathy	423 (72)	202 (91)	221 (61)	2.64 (1.60-4.34)	<0.001
Cardiovascular risk factors					
Hypertension	139 (25)	83 (39)	56 (16)	2.58 (1.95-3.41)	<0.001
Dyslipidemia	142 (25)	89 (42)	53 (15)	2.37 (1.80-3.12)	<0.001
Diabetes mellitus	52 (9)	36 (17)	16 (5)	2.23 (1.56-3.20)	<0.001
Smoking	76 (19)	43 (28)	33 (14)	1.83 (1.28-2.61)	<0.001
BMI, kg/m^2	25.4 ± 4.9	26.8 ± 5.3	24.5 ± 4.5	1.06 (1.04-1.09)	<0.001
Cardiovascular risk factors	279 (48)	141 (63)	99 (27)	2.57 (1.95-3.38)	<0.001
Electrocardiogram					
Sinus rhythm	503 (91)	161 (80)	342 (98)	0.42 (0.30-0.60)	<0.001
QRS duration, ms	105 ± 29	118 ± 33	97 ± 22	1.02 (1.01-1.02)	<0.001
LBBB	81 (18)	45 (25)	36 (13)	1.87 (1.24-2.44)	0.001
Repolarization abnormalities	187 (35)	82 (44)	105 (31)	1.39 (1.04-1.86)	0.028
Abnormal ECG	271 (62)	136 (81)	135 (50)	2.31 (1.57-3.39)	<0.001
Echocardiography					
LVEF, %	48 ± 17	37 ± 15	55 ± 13	1.04 (1.04-1.05)	<0.001
LVEDD, mm	54 ± 10	59 ± 10	51 ± 8	1.05 (1.04-1.06)	<0.001
LVESD, mm	38 ± 11	46 ± 13	34 ± 8	1.06 (1.05-1.08)	<0.001
TAPSE, mm	21 ± 5	19 ± 5	23 ± 4	1.10 (1.05-1.14)	<0.001
PASP, mm Hg	34 ± 13	40 ± 14	29 ± 9	1.03 (1.02-1.04)	<0.001
LA diameter, mm	39 ± 9	43 ± 10	36 ± 7	1.04 (1.03-1.06)	<0.001
MR grade ≥3	27 (7)	22 (12)	5 (2)	1.94 (1.23-3.06)	0.005
Diastolic dysfunction grade ≥2	64 (22)	40 (35)	24 (13)	1.65 (1.10-2.46)	0.015

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the absence of sinus rhythm or presence of wide QRS or repolarization abnormalities, in agreement with (19). The variable "cardiovascular risk factors" was the composite of hypertension, diabetes mellitus, dyslipidemia, or smoking (body mass index was not significantly associated with MACE; therefore, obesity was not included in the composite variable). Patients with initial LV systolic dysfunction (LVEF <50%) or family aggregation were classified as NCCM. This stringent definition was designed as a highly specific criterion to identify patients with morphologic features of LVNC and overt cardiac affection.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD and as median (interquartile range). Categorical variables are expressed as the number of cases and proportions. Normality was evaluated in continuous variables using the Shapiro-Wilk test and compared among groups using Student's *t*-test and analysis of variance test. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. The effect of variables on outcomes was analyzed by univariate and multivariate Cox regression analyses. Medical treatment was not included in Cox regression analysis due to lack of information on time of prescription. Specifically, the effect of family aggregation on outcomes was analyzed only in probands and the effect of genotype on outcomes was analyzed only in patients who underwent genetic testing; specific variant carriers were compared with noncarriers.

Patients were followed-up from the moment of LVNC diagnosis until the last medical contact, when follow-up was censored (in case of no incident events). Candidate variables for the Cox regression

TABLE 1 Continued

	All (N = 585)	MACE (n = 223)	No MACE (n = 362)	Crude HR (95% CI)	*P* Value
Cardiovascular magnetic resonance					
LVEF, %	51 ± 16	40 ± 18	56 ± 11	1.05 (1.04-1.06)	<0.001
LVEF ≥50%	261	47 (34)	214 (75)	1.00	
LVEF 35%-50%	85	28 (20)	57 (20)	3.03 (2.07-4.46)	<0.001
LVEF ≤35%	78	64 (46)	14 (5)	5.20 (3.71-7.27)	<0.001
LVEDV, mL	167 ± 74	200 ± 96	152 ± 55	1.01 (1.01-1.01)	<0.001
LVESV, mL	87 ± 64	123 ± 86	71 ± 43	1.01 (1.01-1.01)	<0.001
RVEF, %	53.9 ± 12.3	48.7 ± 15.7	56.5 ± 9.1	1.04 (1.02-1.06)	<0.001
LGE	79 (18)	46 (30)	33 (12)	1.86 (1.31-2.63)	<0.001
Medical treatment[e]					
Beta-blockers	322 (55)	189 (85)	133 (37)		<0.001
ACE inhibitor/ARB	290 (50)	156 (70)	134 (38)		<0.001
Sacubitril-valsartan	30 (5)	27 (12)	3 (1)		<0.001
MRAs	165 (29)	120 (54)	45 (13)		<0.001
Ivabradine	45 (8)	31 (16)	14 (4)		<0.001
Diuretics	151 (26)	115 (52)	36 (10)		<0.001
OAC	156 (27)	110 (50)	46 (13)		<0.001

Values are mean ± SD, n, or n (%), unless otherwise indicated. For continuous variables, the HR corresponds to an increase in 1 U of the corresponding variable with the reported units in the table, except for LVEF, TAPSE, and RVEF, in which the which HR corresponds to a decrease in 1 U (eg, a 1-year increase in age at diagnosis confers an additional 3% risk of MACE [age is reported in years] and a 1-mm decrease in TAPSE confers an additional 10% risk of MACE [TAPSE is reported in mm]). [a]Values are n (% of probands). [b]Among probands. [c]Values are n (% of genetic tests). [d]Among patients who underwent genetic testing. [e]Time of treatment prescription was not available, so HR were not analyzed.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CM = cardiomyopathy; CI = confidence interval; ECG = electrocardiogram; HR = hazard ratio; LA = left atrial; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MACE = major adverse cardiovascular events; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; OAC = oral anticoagulation; PASP = pulmonary systolic artery pressure; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; TAPSE = tricuspid annular plane systolic excursion.

predictive model were selected based on the level of significance for the association with the outcome ($P < 0.2$) and clinical plausibility (sex, cardiovascular risk factors, and NCCM). The final model was defined using an Akaike information criterion stepwise strategy and missing data were handled using multiple imputation algorithms. Calibration and discrimination of the model were assessed with calibration plots and Harrell's C-statistic. In addition, nomograms were depicted to help risk calculation. For the external validation of the risk score, a previously published prospective multicenter Italian cohort of LVNC was used (14). In order to correct a possible bias due to premature censoring, an additional analysis was performed using inverse probability of censoring weighted estimation techniques (20) (full explanation in the Supplemental Appendix and Supplemental Tables 2-4).

The results are expressed as hazard ratio (HR) and 95% confidence interval (CI). A *P* value <0.05 was considered statistically significant. STATA version 15.1 for Mac (StataCorp) and RStudio version 1.4.1106 (RStudio) were used for the analysis.

Study protocols were approved by the hospital ethics committee on human research (validation number PR(AG)18/2020) and complied with the 1975 Declaration of Helsinki guidelines. All participants provided written informed consent.

RESULTS

DEMOGRAPHICS. Initially, 592 consecutive patients were evaluated but 7 (1.2%) were excluded due to incomplete data. Thus, 585 patients were included in the study, of whom 437 (75%) were probands. Demographic and clinical characteristics are described in Table 1: age at diagnosis was 45 ± 20 years, 334 (57%) were male, and median follow-up was 5.1 years (interquartile range: 2.3-8.1 years). LVEF by TTE was 48% ± 17% and 79 patients had myocardial fibrosis assessed by LGE (18% of those with CMR). Family screening was completed in 253 (58%) probands (most other relatives refused to undergo screening), being positive in 106 (42%). Genetic testing was performed in 236 (54%) probands and 118 (80%) relatives (n = 354 [61%] patients in total). Ninety-nine (42%) probands and 93 (79%) relatives harbored a pathogenic or likely pathogenic genetic variant (flowchart in Figure 1).

GENETICS. Pathogenic or likely pathogenic variants in probands included *MYH7* (19 cases, 19% of all positive genetic tests), *TTN* (n = 13, 13%), *MYBPC3*

and *ACTC1* (10 each, 10%), and *DSP*, *LDB3*, and *BAG3* (3 each, 3%) (full list in Supplemental Table 5). Overall, sarcomeric variants were found in 60 (61%) probands, and 21 (21%) harbored a complex genotype (**Figure 2**). Missense variants were described in 61% of cases and truncating variants in 18%. Clinical characteristics including age, sex, LVEF, and presence of LGE did not differ between patients with and without (likely) pathogenic variants (Supplemental Table 6). Similarly, the incidence of events was comparable between genotype-positive and genotype-negative individuals (Supplemental Table 7, see endpoints).

HEART FAILURE. HF occurred in 110 (19%) patients, with an incidence rate of 4.05 events per 100 person-years: 89 (15%) required hospitalization, 23 (3.9%) required cardiac resynchronization therapy implantation, and 14 (2.4%) required heart transplantation or LV assist device implantation (**Table 2**). The comparison of characteristics between patients with or without HF is shown in Supplemental Table 8. On multivariate analysis, LV systolic function (LVEF) by CMR (HR: 1.08; $P < 0.001$; 1% decrease in LVEF conferred an 8% increase in HF risk), right ventricular systolic function (tricuspid annular plane systolic excursion) by TTE (HR: 1.16; $P = 0.005$), systemic arterial hypertension (HR: 3.28; $P = 0.012$), and absence of sinus rhythm (HR: 2.64; $P = 0.043$) were the variables associated with HF (**Table 3**).

Compared with patients with an LVEF ≥50%, those with an LVEF 35% to 50% and ≤35% showed a higher risk of HF (**Figure 3A**). Myocardial fibrosis (LGE) was also significantly associated with HF in patients with an LVEF >35% (**Figure 3B**). In those with an LVEF ≤35%, LGE did not increase the predictive capacity of the model due to strong collinearity (mean LVEF was 39% in patients with LGE and 53% in patients without LGE; $P < 0.001$).

Subanalysis of the 354 patients who underwent genetic testing showed both pathogenic *TTN* variants and complex genotypes to be associated with lower LVEF and increased risk of HF (HR: 2.55 and HR: 2.08; $P = 0.05$ and $P = 0.04$, respectively). By contrast, *ACTC1* variants were associated with a lower HF incidence, while *MYH7* and *MYBPC3* were not associated with HF (Supplemental Table 7).

VENTRICULAR ARRHYTHMIAS. VAs occurred in 87 (15%) patients, with an incidence rate of 2.79 events per 100 person-years: 8 (1.4%) had aborted SCD or VF, 18 (3.1%) had sustained VT, 58 (9.9%) had nonsustained VT, and 15 (2.6%) had appropriate ICD therapies (13% of patients with ICD) (**Table 2**). The comparison of characteristics between patients with or without VAs is shown in Supplemental Table 8. On multivariate analysis, LV systolic function (LVEF) by CMR (HR: 1.03; $P = 0.033$) was the only variable associated with VAs (**Table 3**).

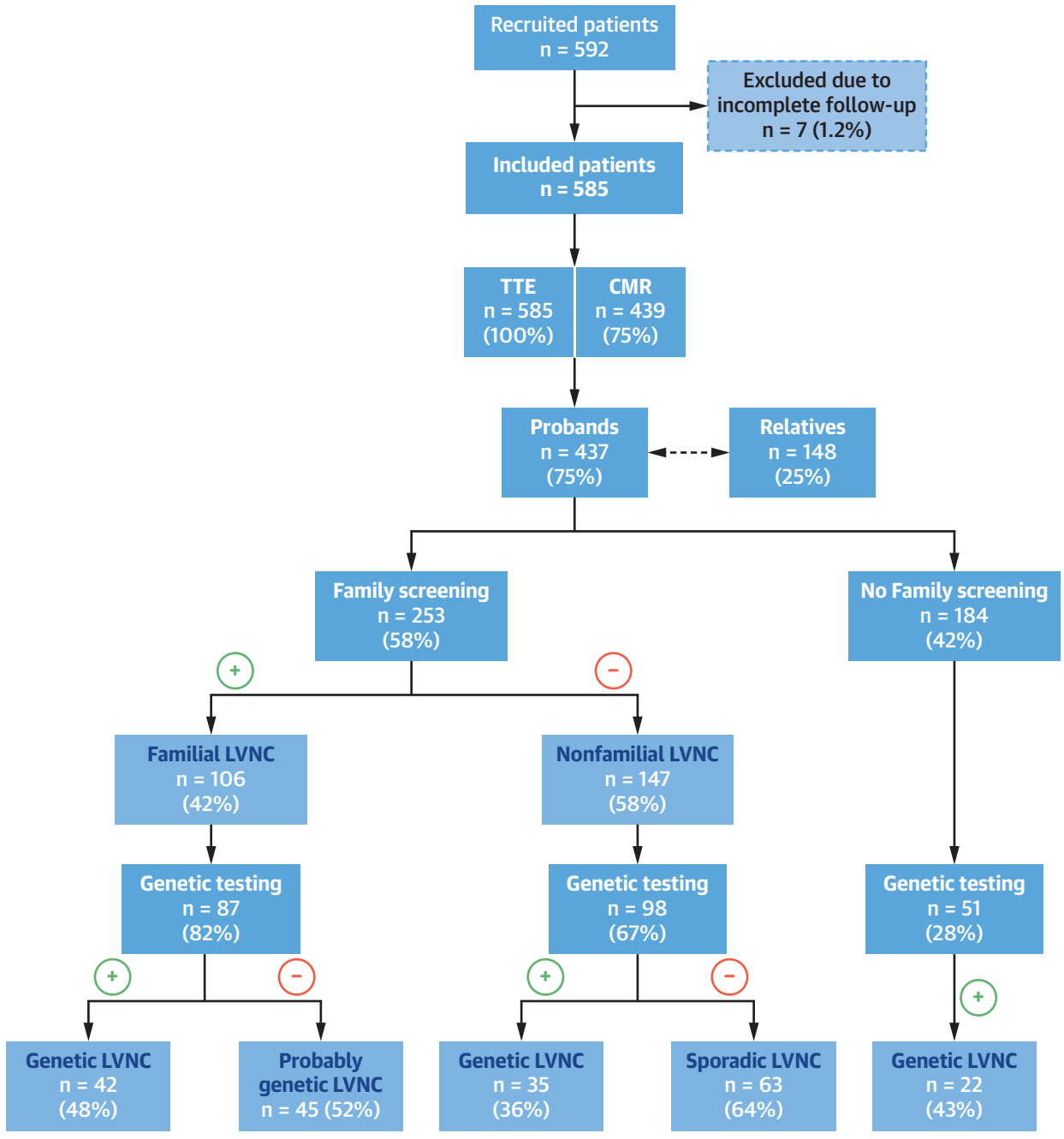
Compared with patients with an LVEF ≥50%, those with an LVEF ≤35% had an increased risk of VA (**Figure 3C**). However, 47 (54%) arrhythmic events (including 8 VF and 8 sustained VT) occurred in patients with an LVEF >35%; in this subset of patients, LGE was strongly associated with VAs (**Figure 3D**). After excluding nonsustained VT, LVEF by CMR was also associated with this harder endpoint in the multivariate analysis (HR: 1.04; $P = 0.035$).

Subanalysis of the genetically tested population revealed that *ACTC1* variants (HR: 2.08; $P = 0.04$), as well as desmosomal and cytoskeleton variants, were associated with VAs when adjusted for LVEF, while other sarcomeric variants were not (Supplemental Table 7).

SYSTEMIC EMBOLISMS. Eighteen (3.1%) patients presented a SE, with an incidence rate of 0.55 events per 100 person-years: 12 (2.1%) were embolic strokes, 5 (0.9%) were embolic transient ischemic attack, and 1 (0.2%) was peripheral embolism (**Table 2**). Clinical characteristics in patients with or without SEs are shown in Supplemental Table 8. On multivariate analysis, the variables associated with SEs were LV systolic function (LVEF) by TTE (HR: 1.04; $P = 0.049$) and anteroposterior left atrial diameter by TTE (HR: 1.06; $P = 0.014$) (LVEF by TTE was used for this endpoint in keeping with left atrial measurements by TTE) (**Table 3**). Thus, a patient with both an LVEF ≤30% and an left atrial diameter ≥45 mm had an over 3-fold increased risk of SEs (HR: 3.31; $P = 0.042$).

ALL-CAUSE MORTALITY. Thirty-four (5.8%) patients died during follow-up, with an incidence rate of 0.98 events per 100 person-years (**Table 2**) and a cumulative survival at 5 years of 96% (95% CI: 93%-98%). The comparison of characteristics between patients who died or survived during follow-up is shown in Supplemental Table 8. On multivariate analysis, age at diagnosis (HR: 1.07; $P < 0.001$) and male sex (HR: 3.84; $P = 0.008$) were the variables associated with all-cause death (**Table 3**); LVEF did not reach statistical significance (Supplemental Figure 1). Cardiovascular death occurred in 15 (2.6%) patients (44% of all-cause mortality), and LVEF was the only associated variable in the multivariate analysis (HR: 1.05; $P = 0.02$). Among patients who underwent genetic testing, *TTN* variants were associated with higher mortality (HR: 6.15; $P = 0.02$) (Supplemental Table 7).

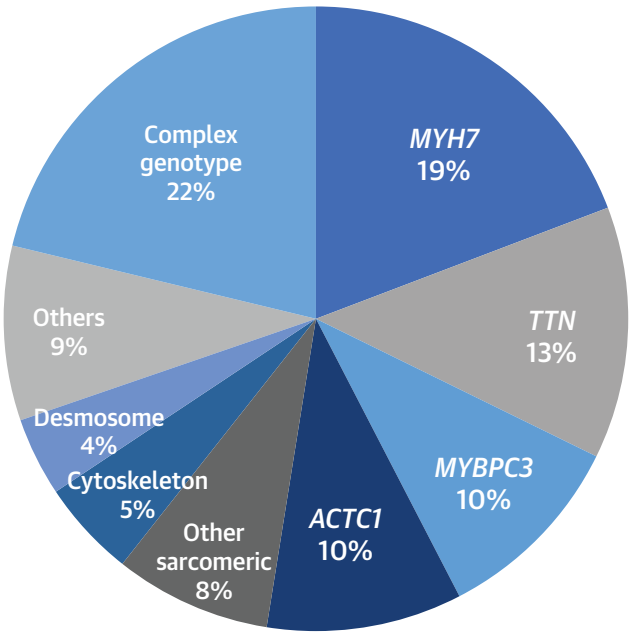
FIGURE 1 Study Flowchart



The diagram describes the protocol of the study. CMR = cardiovascular magnetic resonance; LVNC = left ventricular noncompaction; TTE = transthoracic echocardiography.

DEVELOPMENT AND VALIDATION OF A NEW PREDICTION MODEL. During follow-up, 223 (38%) patients presented at least 1 MACE, with an incidence rate of 8.92 per 100 person-years (Table 2). The comparison of characteristics between patients with or without MACE is shown in Table 1. On multivariate analysis, variables associated with MACE were LV systolic function (LVEF) by CMR, age at diagnosis, and

FIGURE 2 Genetics of Left Ventricular Noncompaction



Pathogenic or likely pathogenic variants in probands (n = 99). Complex genotype: *MYBPC3*, *MYH7*, and *TTN* (6 patients each); *DSP* (4); *TNNT2* (3); *KCNH2*, *LDB3*, *SCN5A*, and *TBX20* (2 each); *BAG3*, *CACNA1D*, *CASQ2*, *DSC2*, *FHL2*, *KCNE1*, *LMNA*, *MYL3*, *PRKAG2*, *RBM20*, *RYR2*, and *TNNI3* (1 each). See Methods for gene classification.

TABLE 2 Incidence of Clinical Endpoints in Left Ventricular Noncompaction

Endpoint	Sample	Incidence Rate (Events per 100 Person-Years) (95% CI)
HF	110 (19.0)	4.05 (3.36-4.88)
HF hospitalization	89 (15.0)	
CRT implantation	23 (3.9)	
Heart transplantation and/or left ventricular assist device implantation	14 (2.4)	
Ventricular arrhythmia	87 (15.0)	2.79 (2.26-3.44)
Aborted SCD/VF	8 (1.4)	
Sustained VT	18 (3.1)	
Nonsustained VT	58 (9.9)	
Appropriate ICD therapy	15 (2.6)	
Systemic embolism	18 (3.1)	0.55 (0.35-0.87)
Embolic stroke	12 (2.1)	
Embolic transient ischemic attack	5 (0.9)	
Peripheral artery embolism	1 (0.2)	
All-cause mortality	34 (5.8)	0.98 (0.70-1.37)
Cardiovascular mortality	15 (2.6)	
MACE	223 (38.0)	8.92 (7.83-10.20)

Values are n (%) unless otherwise indicated.

CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia; all other abbreviations as in Table 1.

abnormal ECG. Despite not achieving statistical significance, male sex, cardiovascular risk factors, and NCCM (LVEF <50% or family aggregation) were entered in the final model based on their clinical implications (Table 3, Figure 4).

A risk score model based on variables associated with MACE was designed to improve risk stratification in LVNC patients (Figure 5A). Thus, certain points were assigned to each variable and the sum total was associated with the probability of developing MACE during follow-up (Figure 5B) (see an example in Figure 5). The model was well calibrated with an adequate agreement between the observed and the predicted risk (calibration slope of 0.96; 95% CI: 0.66-1.20) and correct event risk estimation at 2 and 5 years (Supplemental Figure 2). Discrimination of the risk score was adequate, with an optimism-corrected C-index of 0.72 (95% CI: 0.67-0.75). Patients could be subsequently divided according to tertiles of score punctuation: compared with low-risk patients (<12 points), those at intermediate risk (12-20 points) and high risk (>20 points) showed a higher incidence of MACE (Figure 5C). An online calculator is available (21).

External validation was performed in a previously published cohort (14). There were certain differences between both cohorts, although baseline characteristics were mostly comparable (Supplemental Table 9). In the validation cohort, calibration slope was 1.04 (95% CI: 0.80-1.28), and the discrimination ability in this cohort was comparable to the derivation cohort (C-index of 0.72; 95% CI: 0.71-0.73). The model also allowed an adequate identification of the low and high risk strata patients, with the event rate of the intermediate-risk subgroup more similar to the low-risk subgroup (Supplemental Figure 3, Supplemental Table 10).

EVENT-FREE SURVIVAL AT FOLLOW-UP. Finally, following the previous model, variables associated with no MACE were used to construct a stepwise algorithm to identify patients free from events during follow-up (LVNC safety algorithm). LGE was included in the model based on its widely recognized prognostic implications. In this respect, a patient with a normal ECG, preserved systolic function (LVEF ≥50% by TTE), no myocardial fibrosis, and no family aggregation presented a 0% risk of cardiovascular events at 5.1 years of follow-up (based on observed risks in our cohort) (Figure 6).

DISCUSSION

In this observational, retrospective, longitudinal, multicenter, cohort study, 585 patients with

echocardiographic criteria of LVNC (confirmed by CMR in 75% of cases) were followed for a median of 5.1 years. MACE occurred in 38% of patients, with HF and VAs being the most prevalent. Age, male sex, LVEF, *TTN* variants, and complex genotype were found to be the main predictors. On the one hand, LGE was more frequent in patients with systolic dysfunction and was associated with poorer outcomes even when adjusted for LVEF. On the other hand, patients with normal ECG, preserved systolic function, no LGE, and negative familial screening presented no MACE during long-term follow-up (**Central Illustration**).

INCIDENCE OF EVENTS. Baseline patient characteristics in our cohort were comparable to other LVNC studies, including mean age (9,10,14), as well as LVEF (7,14), which was lower than 35% in one-quarter of the cohort. Thus, on the one hand, the incidence of MACE in our study was similar to that reported in a recent meta-analysis of 2,501 LVNC patients (12): 3.22 vs 3.53 HF hospitalizations per 100 person-years ($P = 0.461$) and 2.70 vs 2.17 VAs per 100 person-years ($P = 0.096$). This consistency is particularly significant given LVNC's well-known heterogeneity. On the other hand, the incidence of MACE was higher in our cohort compared with a meta-analysis of 4,554 DCM patients (22): 3.22 vs 2.37 HF hospitalizations per 100 person-years ($P = 0.014$) and 2.70 vs 2.14 VAs per 100 person-years ($P = 0.064$). Of note, one-half of our population had preserved LVEF at the first evaluation; thus, LVNC might have poorer outcomes compared with DCM when adjusted for LVEF, as previously suggested (10).

PROGNOSTIC ROLE OF LVEF AND LGE. LVEF proved to be the strongest predictor of cardiovascular events in our cohort, in line with previous studies showing LVEF <45% to be associated with poorer outcomes (12). LV systolic dysfunction by CMR has also shown incremental prognostic implications over clinical data (14). Considering the high incidence of HF, LVNC patients with reduced LVEF or high-risk features (LGE) might benefit from closer follow-up.

Additionally, LVEF was the strongest predictor of VAs, as reported elsewhere (12). Interestingly, one-half of VAs in our series (including 100% of VF and 44% of sustained VT) occurred in patients who did not fulfill criteria for prophylactic ICD implantation (16,17), implying that LVEF alone is not a precise predictor, as previously suggested (10). In this respect, LGE has been consistently associated with SCD in other cardiomyopathies such as DCM (23) even in the absence of severe LV systolic dysfunction (24).

TABLE 3 Variables Associated With Cardiovascular Events in Left Ventricular Noncompaction in Multivariate Analysis

Endpoint	Variable	Adjusted HR (95% CI)	*P* Value
Heart failure	LVEF (CMR)	1.08 (1.04-1.11)	<0.001
	TAPSE (TTE)	1.16 (1.05-1.28)	0.005
	Hypertension	3.28 (1.29-8.31)	0.012
	No sinus rhythm	2.64 (1.03-2.14)	0.043
	Age at diagnosis	1.00 (0.97-1.03)	0.963
	Male	0.71 (0.31-1.62)	0.420
	LGE	0.42 (0.17-1.03)	0.058
	LVEDV (CMR)	1.00 (0.99-1.01)	0.902
	LBBB	1.13 (0.47-2.75)	0.782
Ventricular arrhythmia	LVEF (CMR)	1.03 (1.00-1.06)	0.033
	Age at diagnosis	1.00 (0.97-1.03)	0.957
	Male	1.34 (0.59-3.03)	0.479
	LGE	1.58 (0.66-3.76)	0.301
	TAPSE (TTE)	1.00 (0.90-1.10)	0.937
	QRS, ms	1.00 (0.99-1.02)	0.783
Systemic embolism	LVEF (TTE)	1.04 (1.00-1.08)	0.049
	LA diameter	1.06 (1.01-1.11)	0.014
All-cause mortality	Age at diagnosis	1.07 (1.04-1.10)	<0.001
	Male	3.84 (1.42-10.34)	0.008
	LVEF (TTE)	0.99 (0.97-1.02)	0.516
	Hypertension	1.38 (0.62-3.09)	0.431
	Dyslipidemia	1.57 (0.74-3.33)	0.245
	Diabetes mellitus	1.48 (0.72-3.05)	0.290
MACE	LVEF (CMR)		
	LVEF ≥50%	1.00	
	LVEF 35%-50%	1.65 (1.16-2.37)	0.006
	LVEF ≤35%	2.60 (1.74-3.89)	<0.001
	Age at diagnosis		
	≤35 y	1.00	
	36-54 y	1.96 (1.26-3.05)	0.003
	≥55 y	2.71 (1.72-4.29)	<0.001
	Abnormal ECG[a]	1.49 (1.01-2.20)	0.047
	Cardiovascular risk factors	1.37 (0.99-1.89)	0.054
	Noncompaction cardiomyopathy[b]	1.54 (0.95-2.48)	0.079
	Male	1.29 (0.96-1.73)	0.089

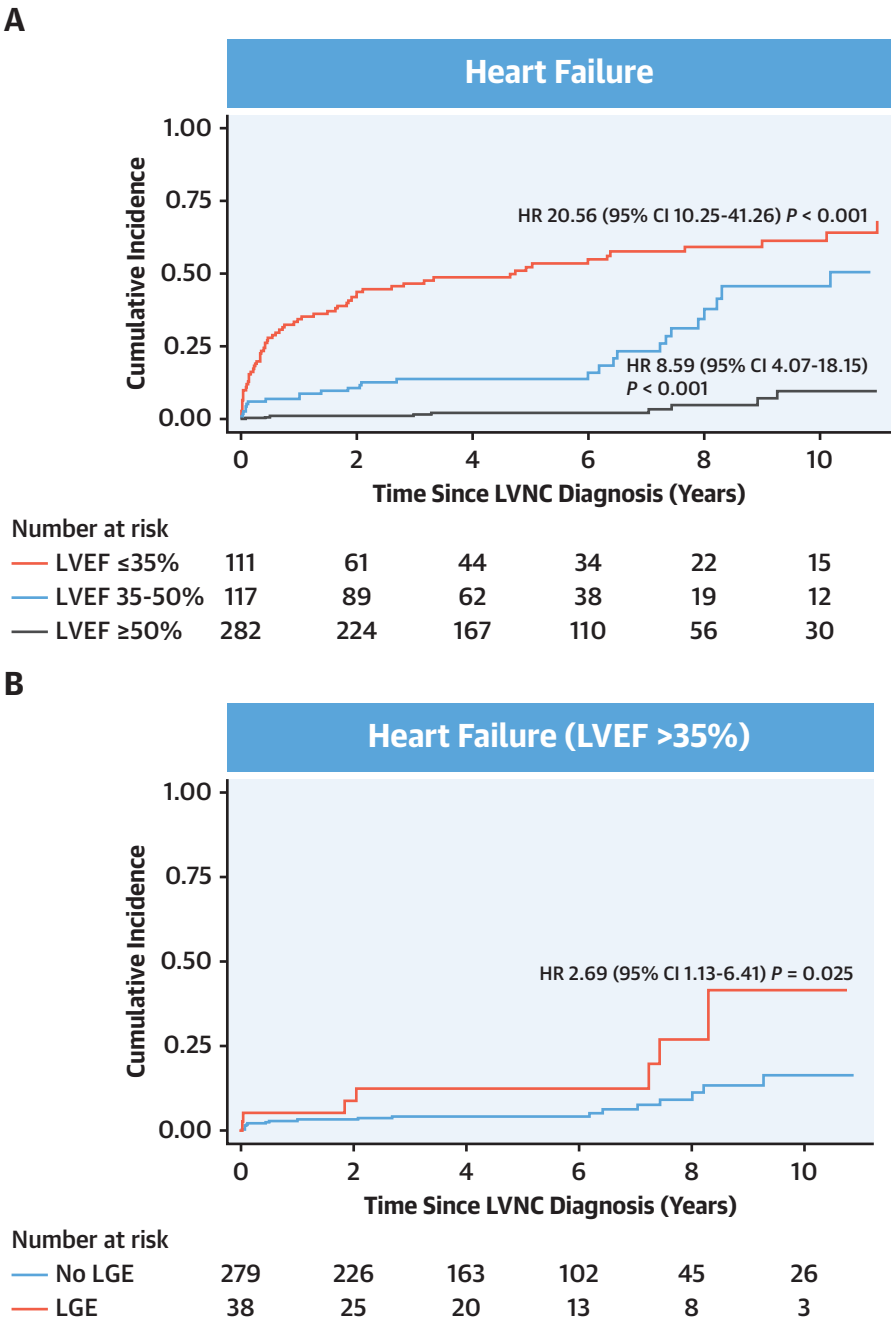
For continuous variables, the HR corresponds to an increase in 1 U of the corresponding variable with the reported units in the table, except for except for LVEF and TAPSE, in which the HR corresponds to a decrease in 1 U. See an example in Table 1. [a]Absence of sinus rhythm and/or presence of wide QRS and/or repolarization abnormalities. [b]Noncompaction cardiomyopathy = LVEF <50% and/or family aggregation.

CMR = cardiovascular magnetic resonance; TTE = transthoracic echocardiography; other abbreviations as in Table 1.

In LVNC patients, it has been associated with worse prognosis regardless of LV dilation (14) or LVEF (15). In our series, myocardial fibrosis did not become a variable associated with VAs due to strong collinearity with LVEF but was associated with a higher risk among patients with an LVEF >35%, as previously described in DCM (24).

Furthermore, LVEF was also associated with SEs and cardiovascular mortality. Interestingly, patients with reduced systolic function and dilated left atrium in our study showed a higher risk of SEs. Further

FIGURE 3 Cumulative Incidence of Heart Failure and Ventricular Arrhythmias



Kaplan-Meier curves for the cumulative incidence of **(A)** heart failure stratified by left ventricular ejection fraction (LVEF), **(B)** heart failure in LVEF >35% stratified by late gadolinium enhancement (LGE), **(C)** ventricular arrhythmias stratified by LVEF, and **(D)** ventricular arrhythmias in LVEF >35% stratified by LGE. CI = confidence interval; HR = hazard ratio; LVNC = left ventricular noncompaction.

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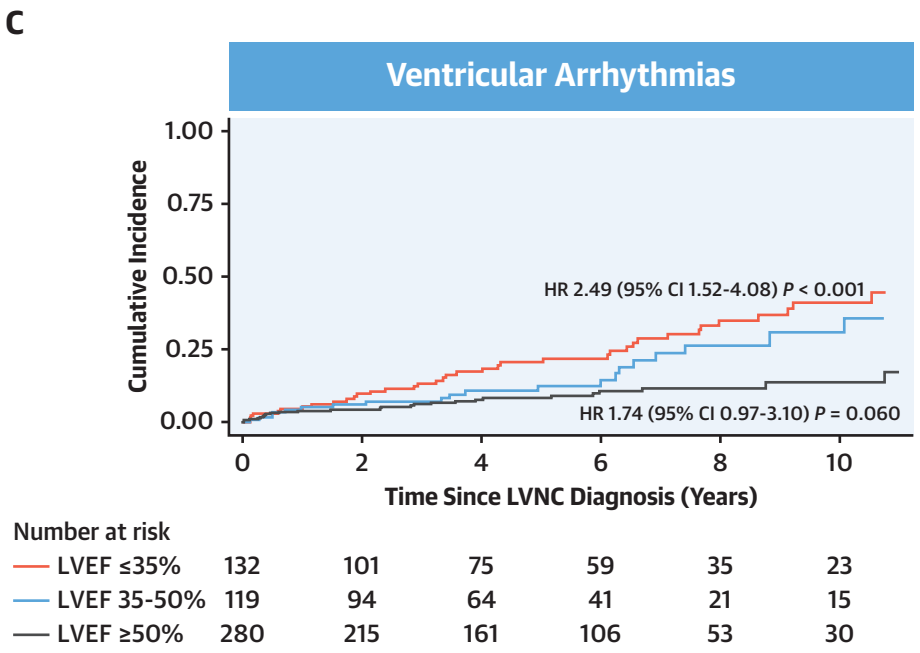
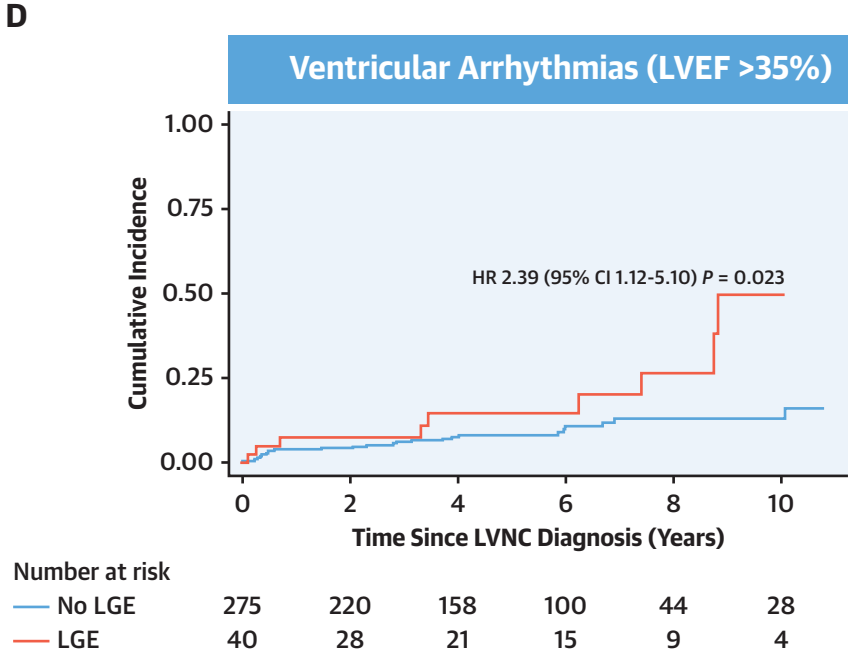
FIGURE 3 Continued

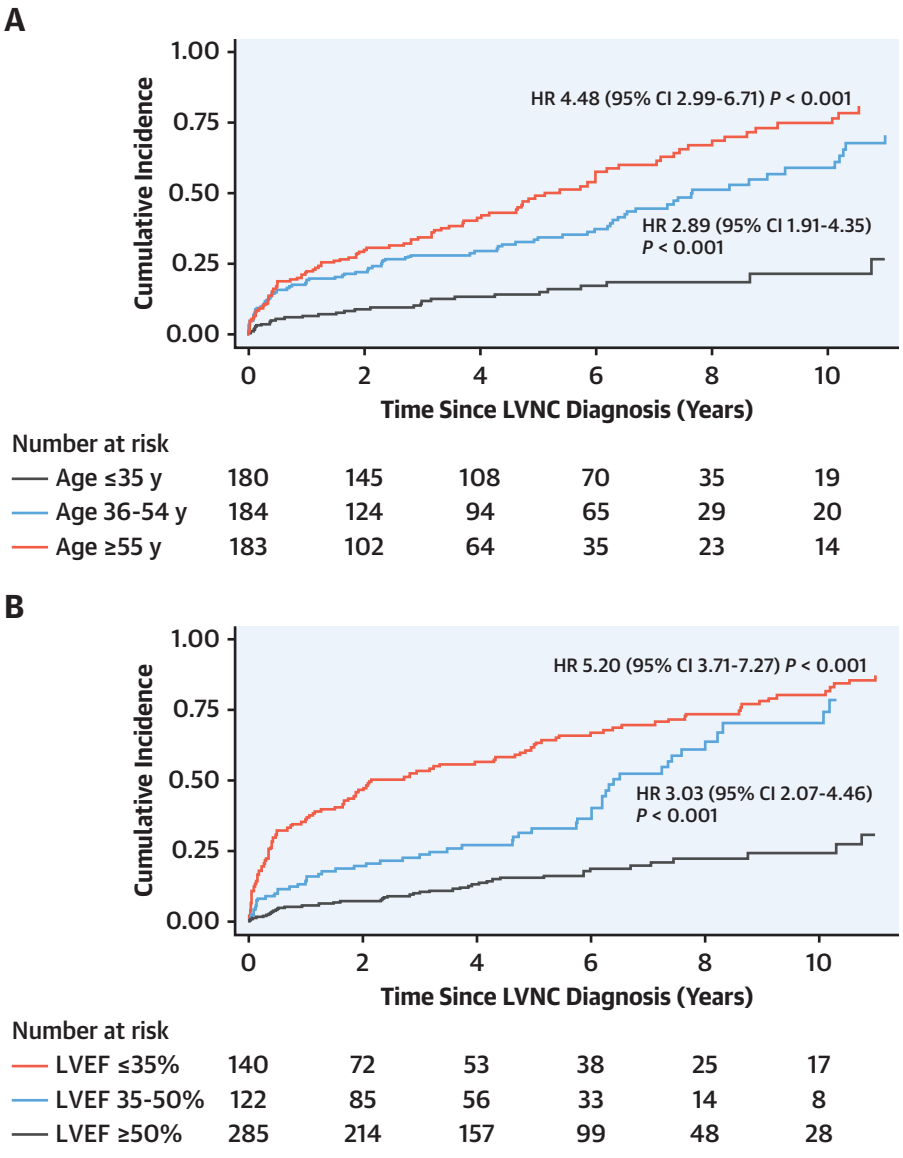




studies should confirm the thresholds to prescribe prophylactic oral anticoagulation in LVNC.

GENOTYPE-PHENOTYPE CORRELATIONS. Genotype has also been associated with outcomes in LVNC (9,10,25). In our study, the yield of genetic testing was slightly higher than other series (42% vs 32%-38%) (9,10). As expected (25), the majority of genetic variants involved sarcomeric genes. Similar to our findings, in LVNC patients, both *TTN* variants and complex genotypes conferred lower LVEF (9,26) and

FIGURE 4 Cumulative Incidence of Major Adverse Cardiovascular Events



Kaplan-Meier curves for the cumulative incidence of major adverse cardiovascular events stratified by the determinants of the risk prediction model: **(A)** age, **(B)** LVEF, **(C)** electrocardiogram (ECG), **(D)** cardiovascular risk factors (CVRF), **(E)** noncompaction cardiomyopathy (NCCM), and **(F)** sex. Abbreviations as in Figure 3.

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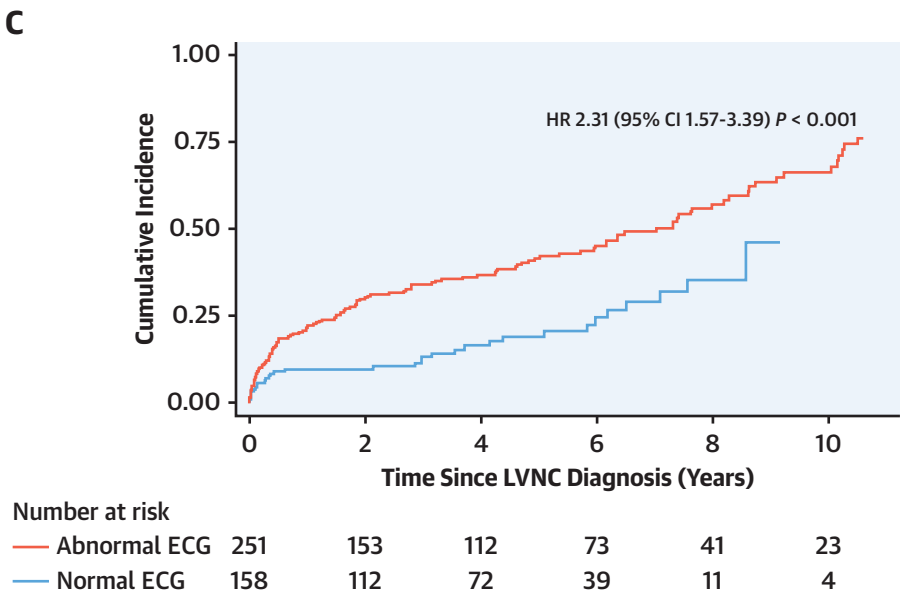
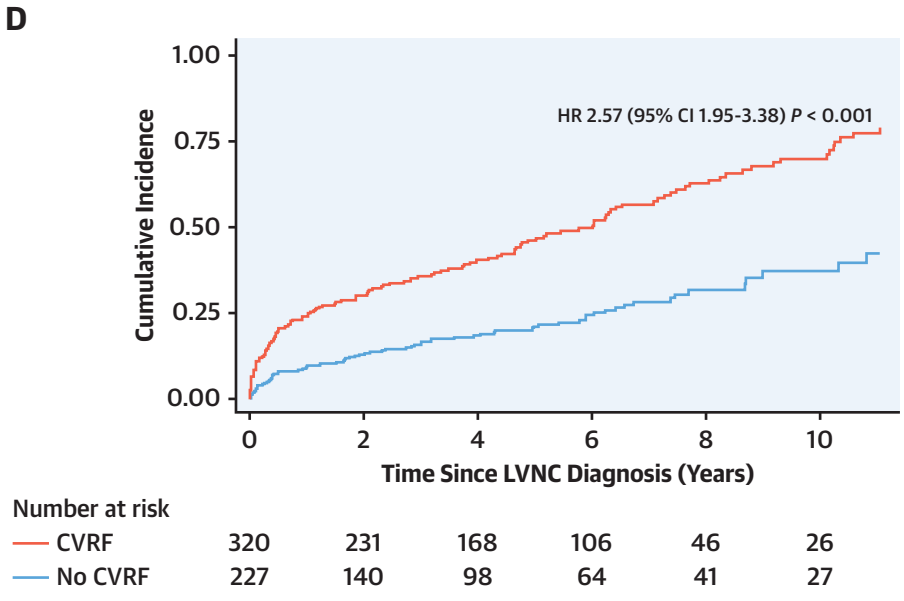
worse outcomes (10,25), and *ACTC1* variants were associated with VAs (27). *MYH7* variants were associated with neither HF nor other events, which, considering the large number of carriers in our cohort, is in line with previous studies showing a better prognosis in *MYH7* variants (9,25). With regard to *MYBPC3* variants, which have been previously associated with poor outcomes (9,25), they did not confer an increased risk of HF or other events in our cohort. This finding could be explained by the low number of carriers and events and by the fact that most of them presented preserved LVEF. Thus,

FIGURE 4 Continued

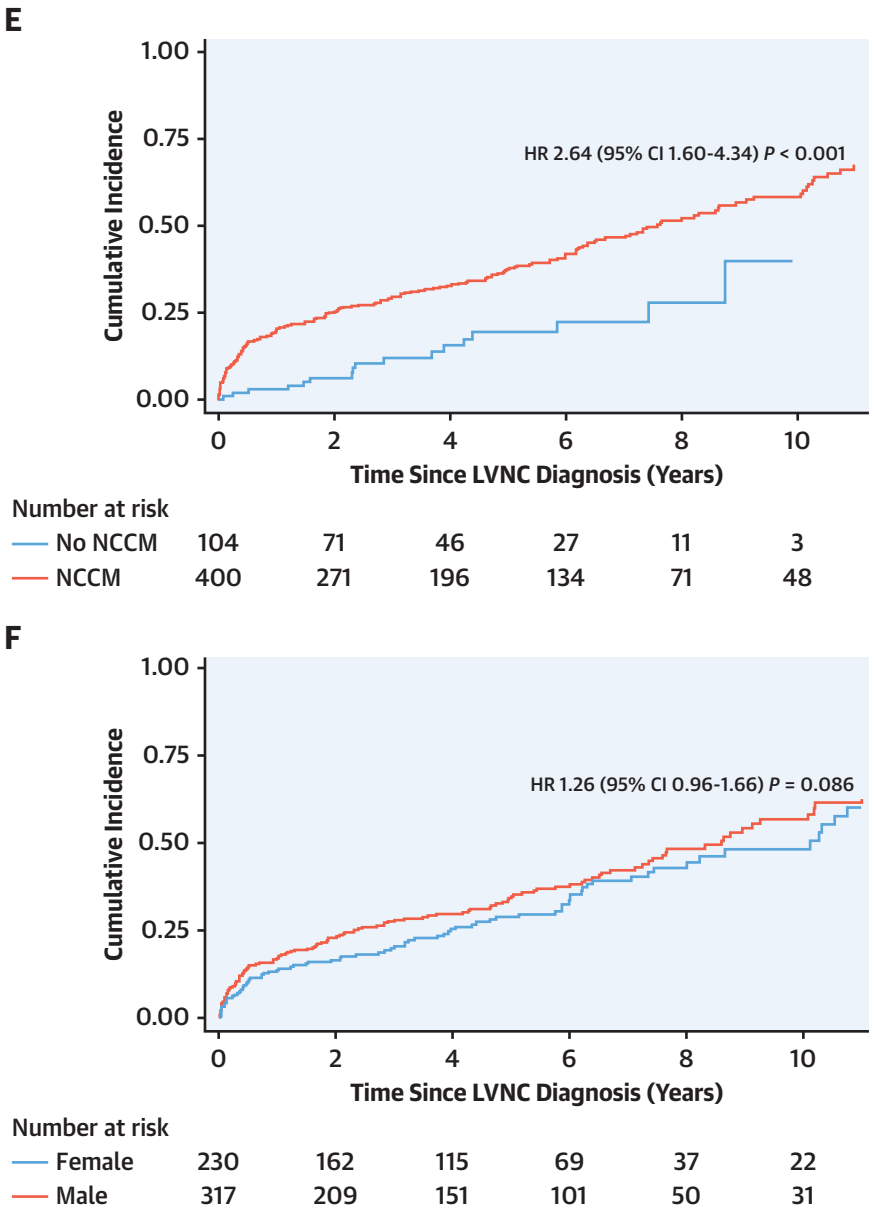




certain high-risk genotypes could be used in LVNC risk stratification (28) and tailor patient management, if confirmed in larger series. Nevertheless, as sporadic LVNC cases with negative genotype also occur (63 [14%] probands in our series), a concomitant acquired factor triggering myocardial hypertrabeculation might thus exist (11), which could also explain differential phenotypic expressions of the same genotype.

LVNC HOLISTIC DIAGNOSIS AND PROGNOSTIC STRATIFICATION. Ultimately, LVNC diagnosis should be based on a comprehensive evaluation at an expert cardiomyopathy unit considering not only the ratio of trabeculae, but also family history, symptoms, ECG parameters, imaging techniques (including functional LV variables and LGE), and genetics, among others (11,29-31). In this respect, we designed a stepwise algorithm to aid decision making in clinical

FIGURE 4 Continued



practice and specifically to identify low-risk LVNC forms (6,7,13). The model was deliberately simplified and contained readily available variables to facilitate its application following a logical and sequential diagnostic approach: ECG, TTE, CMR, and family screening. Furthermore, similarities with previously published LVNC algorithms (29,30) and the large scope of our series strengthen its clinical utility. Thus, on the one hand, patients with normal ECG, preserved LVEF, no LGE, and no family aggregation presented no events during long-term follow-up. They represent approximately 5% of our cohort and most likely correspond to physiologic hypertrabeculation cases with low pretest probability for LVNC, which might not require strict periodic follow-up and could benefit from a watchful wait-and-see strategy (13). In fact, these patients might simply fulfill imaging diagnostic criteria for

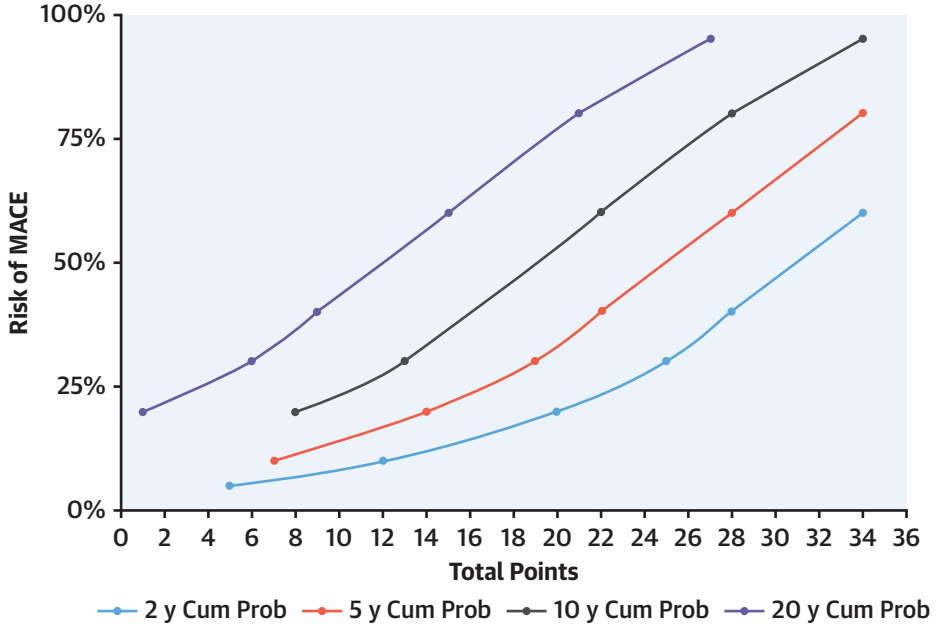
FIGURE 5 Risk Prediction Model of MACE in LVNC

A

Age (years)	Points
≤35	0
36-54	7
≥55	10
LVEF (%)	**Points**
≥50	0
35-50	5
≤35	10

Abnormal ECG	Points
N	0
Y	4
CV Risk Factors	**Points**
N	0
Y	3
NCCM	**Points**
N	0
Y	4
Gender	**Points**
Men	3
Women	0

B



(A) Risk score: variables associated with major adverse cardiovascular events (MACE) and corresponding punctuation. **(B)** Risk of developing MACE according to score punctuation at different follow-up times. **(C)** Kaplan-Meier curves for the cumulative incidence of MACE stratified by risk score group. Example: a male patient with LVNC (3 points), 40 years of age at diagnosis (7 points), with cardiovascular (CV) risk factors (3 points), normal ECG (0 points), initial LVEF of 60% (0 points), and no cardiomyopathy (preserved LVEF and no family aggregation = 0 points) has a score of 13 points, which confers a 10% 2-year and 17% 5-year risk of developing MACE. Abbreviations as in Figures 3 and 4.

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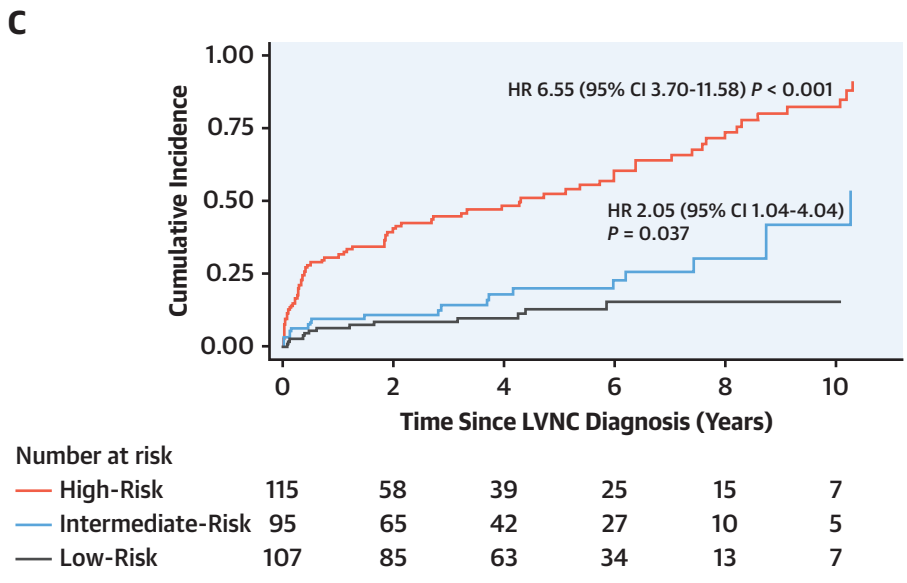
FIGURE 5 Continued

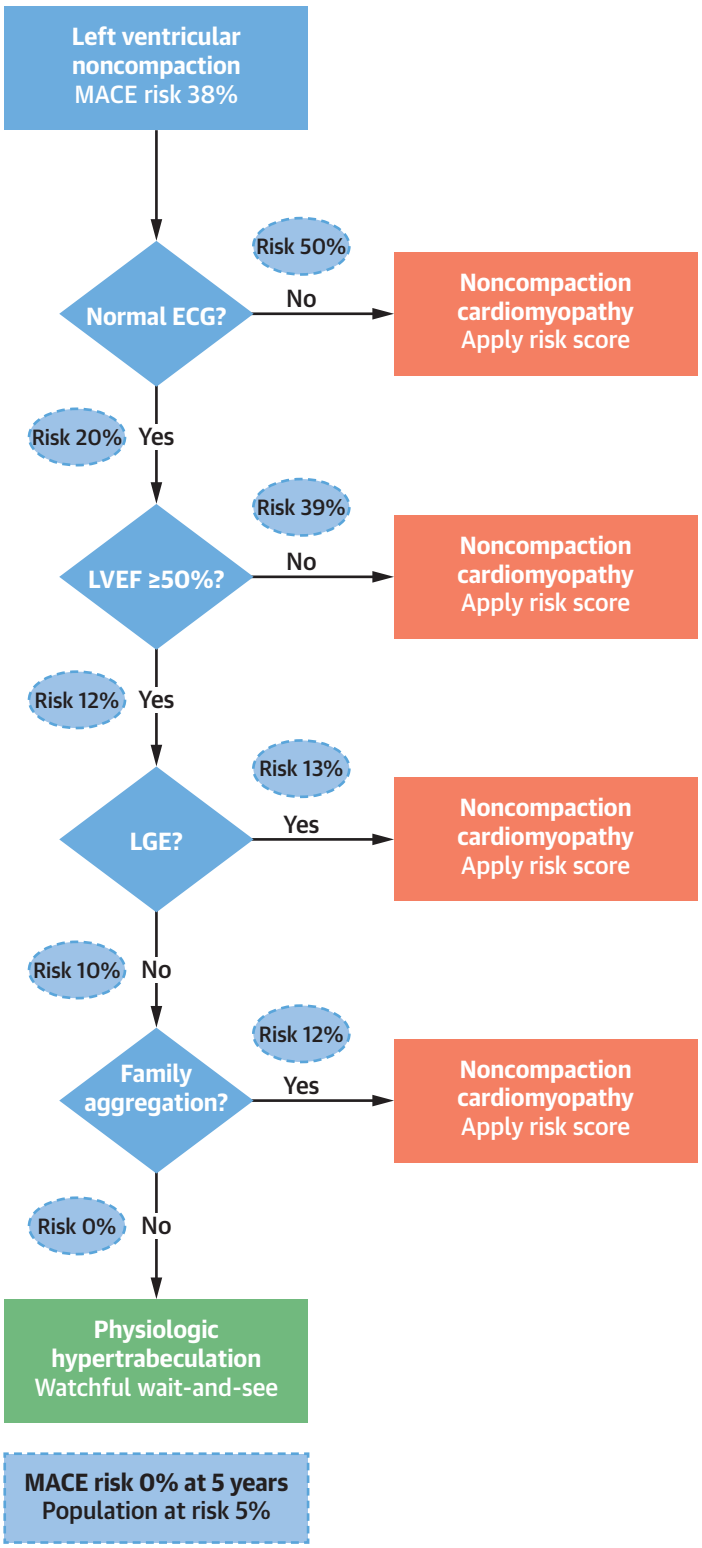


hypertrabeculation but might not have actual LVNC, which underlines the aforementioned limitations of imaging techniques in LVNC diagnosis.

On the other hand, patients with any abnormalities in the algorithm probably correspond to high-risk LVNC forms or NCCM. For these, we developed and validated a novel risk score for individualized prognostic stratification, an innovative and clinically oriented approach in LVNC, based on widely recognized prognostic variables such as ECG and LVEF, among others. This is an initial but promising tool in LVNC, which might allow for more personalized and precise patient management, ultimately improving outcomes. The model is in line with similar recently published risk scores for other cardiomyopathies, which all include nonsustained VT (32-34). Furthermore, its discriminative performance is remarkable and compares favorably with other well-validated prediction models such as the HCM Risk-SCD (C-index = 0.70) (32), and allows a correct event risk estimation of up to 5 years of follow-up, with significant survival differences between low-, intermediate-, and high-risk groups. The positive external validation further strengthens its applicability. Thus, its use should be encouraged to tailor patient management. In conclusion, our study demonstrates that a comprehensive evaluation is necessary in LVNC to correctly diagnose, risk-stratify, and guide patient follow-up.

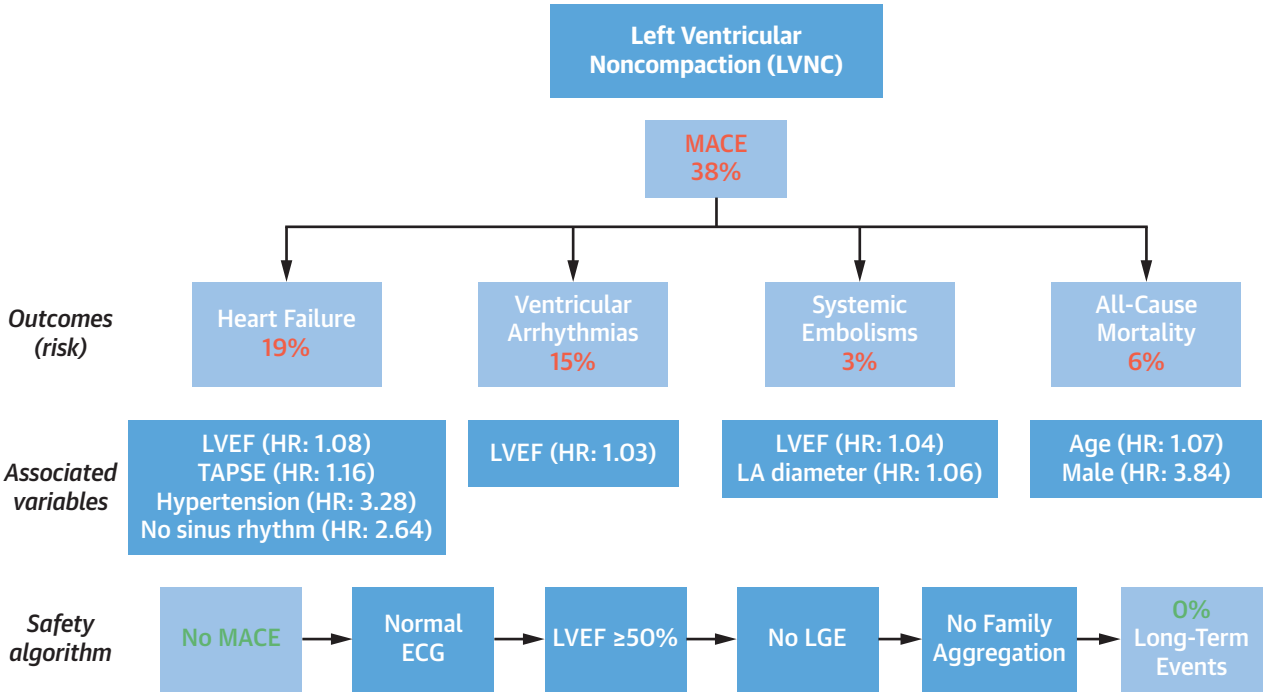
STUDY LIMITATIONS. Only patients followed at cardiomyopathy units were included, which might suppose a selection bias. However, this is likely consistent with most cardiomyopathy studies. Owing to the retrospective nature of the study, follow-up visits were not systematically scheduled and bias due to incomplete follow-up cannot be completely excluded. However, in order to correct this bias, an additional analysis was performed using inverse of probability-of-censoring estimation techniques (20). Similar results were observed with no clinically relevant changes and with comparable performance of the risk score, suggesting that the bias was nonsignificant. There was no core lab for imaging evaluation, and similar to previous LVNC studies (9,10), not all patients underwent a CMR. LGE was visually assessed and not quantified, and its strong collinearity with LVEF must have underscored its prognostic implications. It is noteworthy that interactions between LVEF and LGE have been previously described in LVNC (14,15). Right ventricular ejection fraction was not consistently reported in all CMR

FIGURE 6 **LVNC Safety Algorithm**



Stepwise approach to identify patients with morphologic features of LVNC but low-risk characteristics, who present an excellent long-term prognosis. Abbreviations as in Figures 3 and 4.

CENTRAL ILLUSTRATION **Outcomes of LVNC**



Casas, G. et al. J Am Coll Cardiol. 2021;78(7):643–662.

Left ventricular noncompaction (LVNC) carries an increased risk of major adverse cardiovascular events (MACE), mainly heart failure and ventricular arrhythmias. Variables independently associated with the individual components of the combined endpoint are described, with left ventricular ejection fraction (LVEF) being the most important. The LVNC safety algorithm is shown at the bottom of the figure: patients with morphologic criteria for LVNC, but with no other high-risk features, present no cardiovascular events at long-term follow-up. ECG = electrocardiogram; HR = hazard ratio; LA = left atrial; LGE = late gadolinium enhancement; TAPSE = tricuspid annular plane systolic excursion.

studies, so, alternatively, tricuspid annular plane systolic excursion by TTE was used. Information on biomarkers was not included in our study due to missing data from some of the centers and the fact that different biomarkers were used (B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide). In addition, time of medical treatment prescription was not available, so prognostic inferences could not be analyzed. Genetic testing was performed in 60% of the cohort, so the results might not be extrapolative. However, it would still be one of the largest genetic LVNC series, and the results are, without doubt, clinically meaningful. Finally, external validation of the prediction model was performed retrospectively on a smaller cohort with a shorter follow-up period, probably resulting in lower statistical power. In any case, in the validation cohort, the model identified reasonably well those patients at low and high risk of events, being suboptimal to discriminate the intermediate risk stratum. Although the global performance of the model in this external validation cohort was not unsatisfactory, a prospective external validation should be performed in the future.

CONCLUSIONS

LVNC carries a high risk of HF and VAs. LVEF is the most important prognostic factor, and myocardial fibrosis is associated with increased risk of events in patients without severe systolic dysfunction. Poor outcomes are described in *TTN* variants and

complex genotype carriers. A prediction model has been developed and externally validated to risk-stratify and guide management. Patients with normal ECG, preserved ejection fraction, no myocardial fibrosis, and no family aggregation present no cardiovascular events during long-term follow-up.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with LV myocardial noncompaction, the risk of MACE is related to older age at diagnosis, male sex, familial aggregation, cardiovascular risk factors, certain ECG abnormalities, reduced LVEF, and LGE on CMR.

TRANSLATIONAL OUTLOOK:

Further studies are needed to refine the diagnostic imaging criteria associated with prognosis and clarify genotype-phenotype correlations in patients with LV myocardial noncompaction.

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KEY WORDS genotype, late gadolinium enhancement, left ventricular ejection fraction, major adverse cardiovascular events, noncompaction cardiomyopathy, physiologic hypertrabeculation

APPENDIX For an expanded Methods and Results sections and supplemental tables and figures, please see the online version of this paper.