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VALORACIÓN DE CRITERIOS DIAGNÓSTICOS Y PREDICTORES DE EVENTOS EN NO COMPACTACIÓN DEL VENTRÍCULO IZQUIERDO

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TESIS DOCTORAL

VALORACIÓN DE CRITERIOS DIAGNÓSTICOS Y PREDICTORES DE EVENTOS EN NO COMPACTACIÓN DEL VENTRÍCULO IZQUIERDO

Tesis presentada para optar al grado de Doctor

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“Es difícil hacer predicciones,
especialmente sobre el futuro.”

Niels Bohr
Premio Nobel de Física

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ABREVIATURAS

A

AIC: Criterio de información de Akaike

AHA: Sociedad Americana del Corazón (*American Heart Association*)

AV: Arritmias ventriculares

C

C: Compactada

CIBER-CV: Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares

D

DAI: Desfibrilador automático implantable

DE: Desviación estándar

E

ECG: Electrocardiograma

ES: Embolias sistémicas

ESC: Sociedad Europea de Cardiología (*European Society of Cardiology*)

ETT: Ecocardiografía transtorácica

ETVI: Excesiva trabeculación del ventrículo izquierdo

F

FA: Fibrilación auricular

FEVI: Fracción de eyección del ventrículo izquierdo

FEVIp: Fracción de eyección del ventrículo izquierdo preservada

G

GCS: *Strain* circunferencial global

GLS: *Strain* longitudinal global

GLSr AI: *Strain* longitudinal reservorio de la aurícula izquierda

GRS: *Strain* radial global

H

HR: *Hazard ratio*

HUVH: Hospital Universitari Vall d'Hebron

I

IC: Insuficiencia cardíaca

IC95%: Intervalo de confianza del 95%

M

MACE: Eventos cardiovasculares adversos mayores (*major adverse cardiovascular events*)

MCD: Miocardiopatía dilatada

MCH: Miocardiopatía hipertrófica

MCNC: Miocardiopatía no compactada

MSC: Muerte súbita cardíaca

N

NC: No compactada

NCVI: No compactación del ventrículo izquierdo

NGS: *Next-generation sequencing*

O

OR: *Odds ratio*

R

RIC: Rango intercuartil

RMC: Resonancia magnética cardiovascular

RTG: Realce tardío de gadolinio

FIGURAS

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RESUMEN

La no compactación del ventrículo izquierdo (NCVI) es una entidad controvertida, caracterizada por la presencia de un miocardio hipertrabeculado, que puede considerarse una miocardiopatía o un rasgo fenotípico. El diagnóstico de la NCVI no está bien definido y su evolución es muy heterogénea. Por consiguiente, el objetivo principal de esta tesis doctoral fue el de intentar redefinir los criterios diagnósticos en NCVI y describir sus factores pronósticos. Diseñamos un estudio observacional, retrospectivo, longitudinal, de cohortes, en el que participaron 12 centros españoles de referencia. Se reclutaron de forma consecutiva todos los pacientes que cumplieran los criterios diagnósticos de NCVI desde 2000 a 2018.

En el primero estudio de la tesis, se analizaron las variables asociadas a un evento cardiovascular combinado (MACE), que incluyó insuficiencia cardíaca, arritmias ventriculares, embolismos sistémicos y/o mortalidad global. Se incluyeron 585 pacientes, con una edad de 45 ± 20 años y un 57% de hombres, con una fracción de eyección del ventrículo izquierdo (FEVI) de 48 ± 17% y un 18% de realce tardío de gadolinio (RTG). Durante un seguimiento mediano de 5,1 años, 223 (38%) pacientes presentaron MACE.

Las variables asociadas independientemente con el evento combinado fueron la edad, la FEVI y la presencia de alteraciones en el electrocardiograma (ECG); el sexo, los factores de riesgo cardiovascular y la miocardiopatía no compactada (agregación familiar y/o FEVI < 50%) fueron casi significativos estadísticamente. Se desarrolló un modelo predictivo de riesgo, basado en estas variables, que mostró una buena capacidad discriminativa (índice C de Harrell de 0,72) y una buena calibración; asimismo, el estudio de validación externa confirmó un rendimiento superponible. A su vez, los pacientes con hallazgos morfológicos de NCVI pero con un ECG normal, FEVI ≥ 50%, sin RTG ni agregación familiar, no presentaron ningún evento durante el seguimiento, sugiriendo que corresponden a casos de hipertrabeculación fisiológica.

Para el segundo estudio, se analizó el deterioro de la FEVI, definido como una caída absoluta de más de 10 puntos porcentuales de la FEVI, con una FEVI final < 50%. Se incluyeron 577 pacientes, con características basales idénticas al primer estudio y, durante un seguimiento ecocardiográfico mediano de 4,3 años, 34 (6%) de ellos presentaron un deterioro de la FEVI. El RTG y la fibrilación auricular (FA) basal fueron las variables asociadas independientemente al deterioro de la FEVI. Durante un seguimiento clínico posterior, 136 (24%) presentaron MACE. La FEVI basal y el deterioro de la FEVI, así como la FA y el QRS ancho, fueron los variables asociadas significativamente a MACE tras el ajuste multivariado. Los pacientes con FEVI inicial preservada pero con deterioro de la FEVI durante el seguimiento presentaron un riesgo intermedio de MACE.

En conclusión, la valoración exhaustiva de los pacientes con hallazgos morfológicos de NCVI permite predecir el riesgo de eventos cardiovasculares y establecer la probabilidad de miocardiopatía, por tanto tiene implicaciones tanto diagnósticas como pronósticas.

ABSTRACT

Left ventricular noncompaction (LVNC) is a controversial entity, characterized by the presence of a hypertrabeculated myocardium, which may be considered a cardiomyopathy or a phenotypic trait. The diagnosis of LVNC is not well defined, and its evolution is very heterogeneous. Therefore, the main objective of this doctoral thesis was to try to redefine the LVNC diagnostic criteria, and to describe its prognostic markers. We designed an observational, retrospective, longitudinal, cohort study, in which 12 reference Spanish centers participated. All consecutive patients who fulfilled the diagnostic criteria for LVNC from 2000 to 2018 were recruited.

In the first study of the thesis, the variables associated with a combined cardiovascular event (MACE) were analyzed, which included heart failure, ventricular arrhythmias, systemic embolisms and/or all-cause mortality. A total of 585 patients were included, aged 45 ± 20 years and 57% men, with a left ventricular ejection fraction (LVEF) of 48 ± 17% and 18% with late gadolinium enhancement (LGE). During a median follow-up of 5.1 years, 223 (38%) patients presented a MACE.

The variables independently associated with the combined event were age, LVEF, and the presence of electrocardiogram (ECG) abnormalities; sex, cardiovascular risk factors, and noncompaction cardiomyopathy (familial aggregation and/or LVEF < 50%) were almost statistically significant. A risk prediction model based on these variables was developed, showing a good discriminative capacity (Harrell's C-statistic of 0.72) and good calibration. An external validation confirmed a comparable performance. Besides, patients with morphological findings of LVNC but with a normal ECG, an LVEF ≥ 50%, no LGE and no familial aggregation, did not present any events during follow-up, suggesting that they correspond to physiological hypertrabeculation cases.

For the second study, LVEF decline was analyzed, defined as an absolute decrease of more than 10 percentage points in LVEF, with a final LVEF < 50%. A total of 577

patients were included in this study, with identical baseline characteristics, and during a median echocardiographic follow-up of 4.3 years, 34 (6%) of them presented a LVEF decline. LGE and baseline atrial fibrillation (AF) were independently associated with LVEF decline. During a subsequent clinical follow-up, 136 (24%) presented MACE. Baseline LVEF and LVEF decline, as well as AF and wide QRS, were the variables significantly associated with MACE after multivariate adjustment. Patients with initially preserved LVEF but with a subsequent LVEF decline, showed an intermediate risk of MACE.

In conclusion, a comprehensive assessment of patients with morphological findings of LVNC allows to predict the risk of cardiovascular events and to establish the probability of cardiomyopathy, therefore having both diagnostic and prognostic implications.

1

Introducción

1.1. DEFINICIÓN

La no compactación del ventrículo izquierdo (NCVI) es una entidad heterogénea caracterizada por la presencia de trabeculaciones miocárdicas prominentes y recesos intertrabeculares profundos (***Figura 1***)[1–3]. Inicialmente, se consideró que la NCVI correspondía a una miocardiopatía diferenciada: la miocardiopatía no compactada (MCNC). De hecho, fue catalogada como una miocardiopatía familiar no clasificada por la Sociedad Europea de Cardiología (ESC)[4] y como una miocardiopatía genética por la Sociedad Americana del Corazón (AHA)[5]. Sin embargo, la evidencia científica más reciente sugiere que la NCVI podría corresponder simplemente a un fenotipo morfológico ventricular, no necesariamente asociado con una miocardiopatía de base. En este sentido, tanto las guías de práctica clínica de la ESC sobre miocardiopatías[6], como un consenso de expertos reciente[1], sugieren que la NCVI no es una miocardiopatía per se sino un rasgo fenotípico. Por tanto, no existe todavía un consenso universal a día de hoy acerca de la definición y clasificación de esta entidad controvertida.

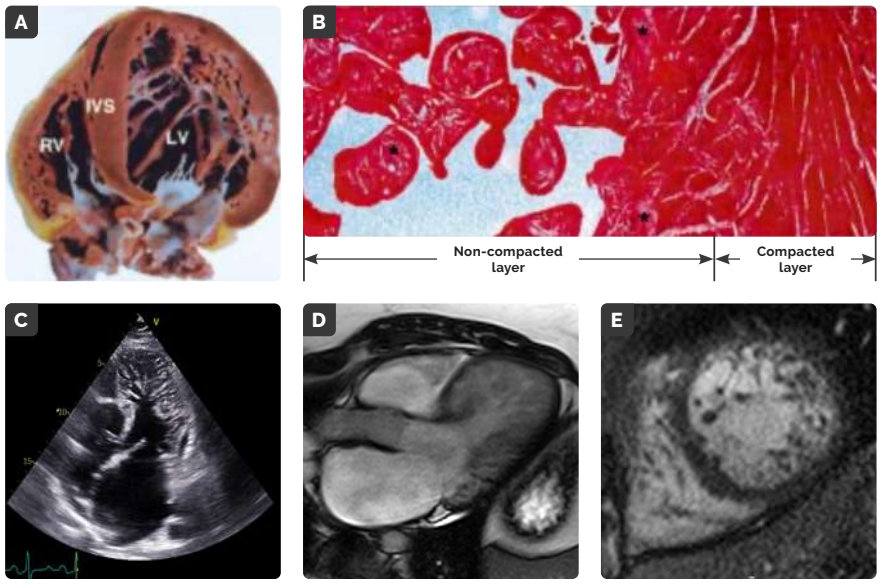


Figura 1: ***A – B***: Adaptado de Jenni *et al*[7]. Hallazgos. ***A)*** anatómicos e ***B)*** histológicos de un paciente con no compactación del ventrículo izquierdo. ***C – E***: Adaptado de Casas *et al*[8]. Hallazgos por ***C)*** ecocardiografía transtorácica (eje apical 4 cámaras) y por resonancia magnética cardiovascular ***D)*** eje apical 3 cámaras y ***E)*** eje corto basal, de pacientes con no compactación del ventrículo izquierdo.

1.2. FISIOPATOLOGÍA Y ETIOLOGÍA

Clásicamente, se había considerado que la NCVI era secundaria a un problema en la embriogénesis del miocardio. Según la teoría embrionaria, en etapas fetales iniciales el miocardio presenta un alto grado de trabeculación y durante el desarrollo fetal se va compactando progresivamente. De acuerdo con esta hipótesis, en la NCVI se produciría una detención en la compactación de la capa endocárdica del miocardio [9]. Sin embargo, estudios más recientes han refutado esta teoría, demostrando que no existe el fenómeno de compactación como tal, sino que hay un crecimiento paralelo e independiente de la capa trabeculada y compactada durante la formación embrionaria [10]. Por este motivo, en la actualidad se desaconseja el uso del término "no compactación", ya que conlleva connotaciones embriológicas erróneas, recomendándose la terminología "excesiva trabeculación" del ventrículo izquierdo (ETVI) o "hipertrabeculación" del ventrículo izquierdo [1,6]. Sin embargo, en esta tesis doctoral se seguirá utilizando indistintamente la nomenclatura NCVI debido a su importancia histórica y por congruencia con la literatura referenciada.

En paralelo a este cambio de paradigma sobre el origen de la entidad, múltiples estudios cuestionan el hecho que la NCVI sea una miocardiopatía como tal. De un lado, se ha descrito una alta prevalencia de hipertrabeculación en individuos sanos [11], especialmente utilizando criterios diagnósticos por resonancia magnética cardiovascular (RMC) según un gran metaanálisis [12]. Además, se ha observado que la excesiva trabeculación puede ser una respuesta fisiológica a ciertas condiciones de pre o poscarga cardíaca, y que puede ser adquirida e incluso reversible. En concreto, se ha descrito un alto porcentaje de NCVI en deportistas de alta intensidad, sin implicaciones pronósticas en cuanto a eventos cardiovasculares [13]. De hecho, el grado de hipertrabeculación se correlacionó con la carga deportiva en un gran estudio poblacional [14], lo que sugiere una adaptación fisiológica progresiva a la sobrecarga hemodinámica. En este mismo sentido, se ha descrito la aparición de *novo* de un fenotipo de NCVI en un alta proporción de mujeres embarazadas sin

antecedentes previos, que además retrograda en el postparto [15]. En definitiva, todo lo mencionado previamente sugiere que la NCVI podría corresponder a un rasgo morfológico fisiológico más que a una miocardiopatía como tal.

Sin embargo, también existe una base genética en la NCVI y se han descrito hasta 32 genes relacionados con la entidad [16], identificándose una causa genética en aproximadamente el 30% de casos [17]. Las variantes genéticas incluyen genes mayoritariamente sarcoméricos, pero también de membrana nuclear, citoesqueleto, desmosoma, mitocondriales, canales iónicos y vías de señalización como NOTCH (***Figura 2***) [3,16–18]. De hecho, un consenso de expertos sugiere realizar un estudio genético en NCVI en caso de sospecha clínica para confirmar el diagnóstico, con una recomendación clase IIb [19], mientras que las guías de la ESC sugieren el uso del estudio genético para el diagnóstico de las miocardiopatías en general con una recomendación clase I [6].

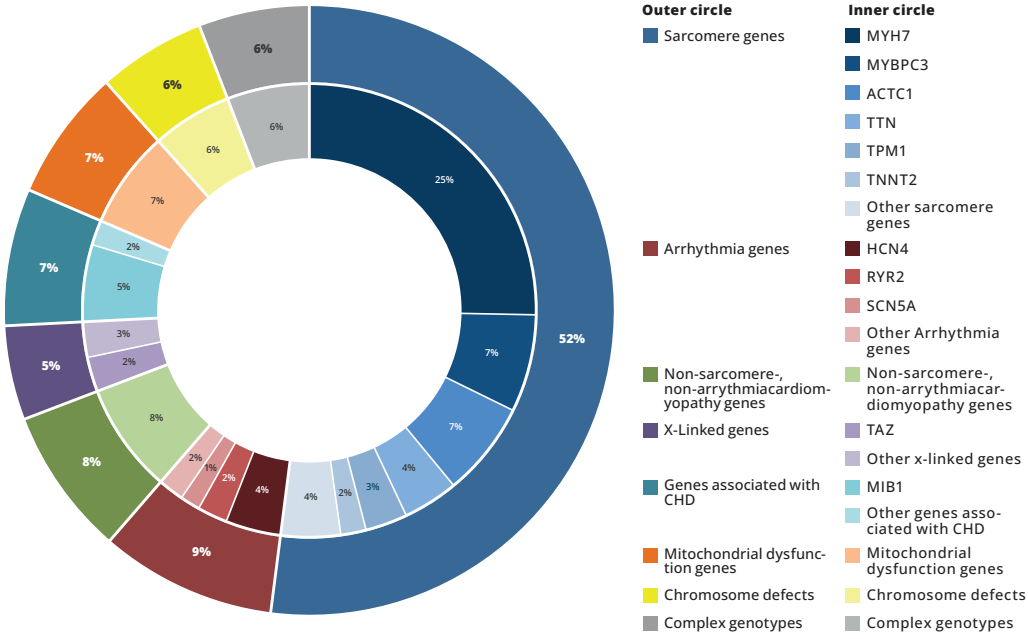


Figura 2: Origen genético de la no compactación del ventrículo izquierdo. Adaptado de van Waning *et al* [17].

Existe un solapamiento genético entre la NCVI y otras miocardiopatías como la miocardiopatía dilatada (MCD) y la miocardiopatía hipertrófica (MCH), especialmente en lo referente a genes sarcoméricos [17,20,21]. De hecho, algunos pacientes con fenotipo de MCD o MCH pueden presentar también hipertrabeculación, mientras que pacientes con NCVI pueden mostrar rasgos adicionales de MCD o MCH [22,23]. Incluso pueden coexistir diferentes fenotipos dentro de una familia con el mismo genotipo [24], lo que sugiere un componente modulador ambiental y/o epigenético de la expresividad fenotípica [25]. Este solapamiento pone de manifiesto la limitación que tiene el diagnóstico fenotípico en las miocardiopatías. De hecho, las guías de la ESC ya sugieren que la descripción fenotípica (miocardiopatía dilatada, hipertrófica, restrictiva, etc.) es solo el primer eslabón en el proceso diagnóstico de estas entidades, que idealmente siempre debería acabar con el diagnóstico etiológico basado en el genotipo [6].

En este mismo sentido, el estudio familiar es de especial importancia en la NCVI, ya que se ha descrito agregación familiar en aproximadamente el 40-50% de casos [24], lo que confirma el diagnóstico del caso índice y permite identificar familiares asintomáticos [26,27]. Los familiares de primer grado de un paciente con una variante genética patogénica o posiblemente patogénica deberían realizarse un estudio clínico y genético, con una recomendación clase I [6,19].

En definitiva, en la no compactación o excesiva trabeculación del ventrículo izquierdo parece existir un continuo entre el remodelado fisiológico y la miocardiopatía establecida [28], así como también parece haber un continuo en la expresividad fenotípica de las diferentes miocardiopatías [25].

1.3. DIAGNÓSTICO

El diagnóstico de la NCVI se realiza fundamentalmente por técnicas de imagen cardíaca, y en concreto por ecocardiografía transtorácica (ETT) y RMC. Existen múltiples criterios diagnósticos diferentes y todos ellos se basan en la comparación entre la capa compactada (C) y la capa no compactada (NC). Por ETT se han descrito, fundamentalmente, tres criterios diagnósticos principales: **1)** Chin: ratio C/NC ≤ 0,5 en telediástole en eje paraesternal corto [29]; **2)** Jenni: ratio NC/C ≥ 2 en telesístole en eje paraesternal corto (***Figura 3A***) [7]; y **3)** Stöllberger: ≥ 3 trabeculaciones protruyendo de la pared ventricular en eje apical (***Figura 3B-C***) y ratio NC/C ≥ 2 en telediástole en eje paraesternal corto [30].

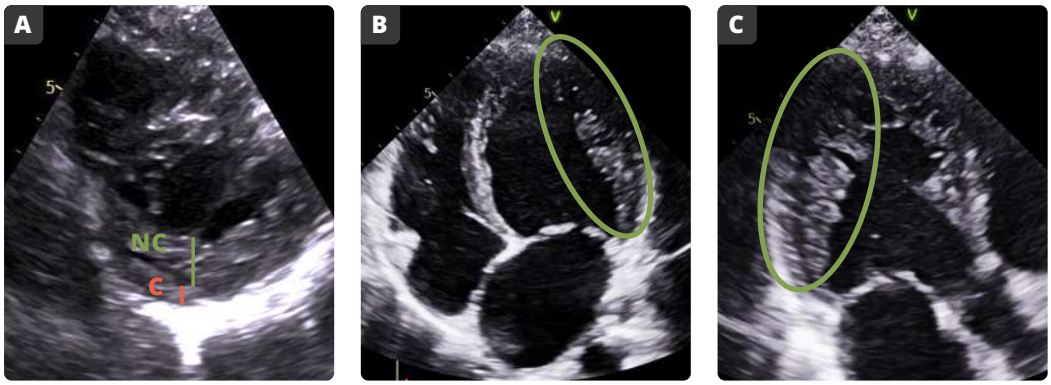


Figura 3: Criterios diagnósticos de no compactación del ventrículo izquierdo por ecocardiografía transtorácica. ***A)*** Jenni: ratio entra la capa no compactada (NC) y la capa compactada (C) [7]. ***B)*** y ***C)*** Stöllberger: trabeculaciones protruyentes en eje apical [30].

Por RMC se han descrito, fundamentalmente, cuatro criterios diagnósticos principales: **1)** Petersen: ratio NC/C > 2,3 en telediástole en eje longitudinal (***Figura 4A***) [31]; **2)** Jacquier: masa trabeculada > 20% de masa total en telediástole en un barrido de ejes cortos (***Figura 4B***) [32]; **3)** Stacey: ratio NC/C > 20% de la masa total en telesístole en eje corto apical [33]; y **4)** Captur: dimensión fractal apical máxima ≥ 1,30 en telediástole en un barrido de ejes cortos (***Figura 4C***) [34].

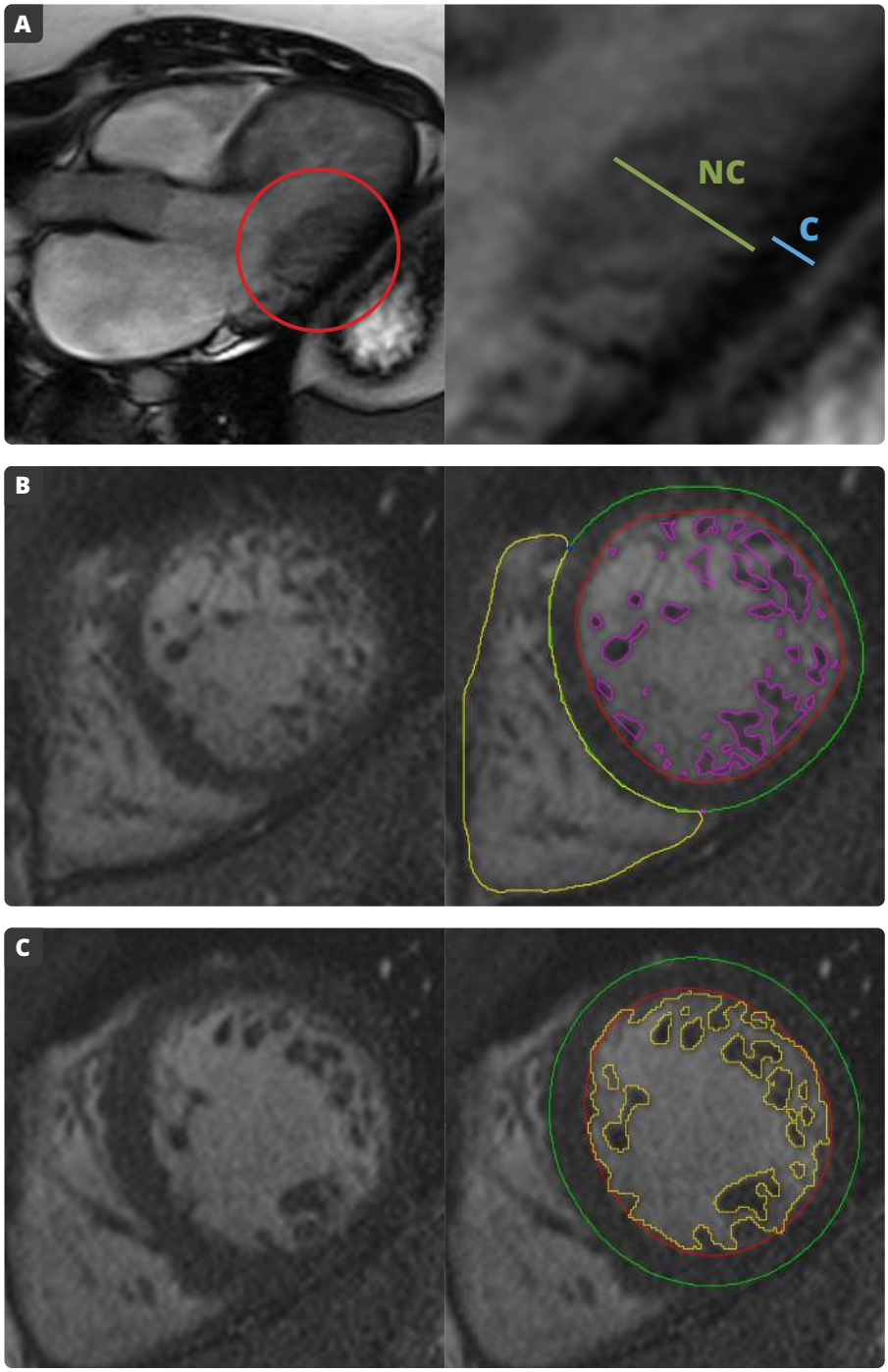


Figura 4: Criterios diagnósticos de no compactación del ventrículo izquierdo por resonancia magnética cardiovascular. ***A)*** Petersen: ratio entre la capa no compactada (NC) y la compactada (C) [31]. ***B)*** Jacquier: porcentaje de masa trabeculada [32]. ***C)*** Captur: dimensión fractal [34]. Adaptado de Casas *et al* [8].

Tabla 1: Resumen de los diferentes criterios diagnósticos en no compactación del ventrículo izquierdo. Adaptado de Casas *et al* [8].

Criteria	Chin	Jenni	Stöllberger	Petersen	Jacquier	Stacey	Grotthoff	Captur
Reference	29	7	30	31	32	33	64	34
Number of patients	8	7	62	7	16	122	12	30
Gold-standard diagnosis	Necropsy, 3 (38)	Anatomical examination, 7 (100)	> 3 trabeculations protruding from the LV wall and intertrabecular spaces	TTE or CMR evidence of a 2 -layered myocardium and 1 additional feature	Jenni criteria	Jenni and Petersen criteria	Jenni criteria and 1 additional feature	Jenni criteria and 1 additional feature
Age, y	9 [11-22]	39 ± 17	50 [18-75]	29 ± 13	48 ± 17	57 ± 17	35 ± 18	41 ± 13
Females	3 (38)	2 (29)	13 (21)	2 (29)	6 (38)	50 (41)	9 (75)	14 (47)
Left ventricular systolic function	FS range 10%-33%	LVEF 29% ± 6%	FS < 30% in 43 (69) patients	LVEF 53% ± 17%	Not reported	LVEF 44% ± 16%	LVEF 51% ± 16%	LVEF 52% ± 17%
Cardiovascular events	5 (63)	7 (100) death and/or heart transplant	45 (73) heart failure	3 (43)	Not reported	36 (30) heart failure	6 (50) ventricular tachycardia	20 (67)
Imaging technique	TTE	TTE	TTE	CMR (1.5 T)	CMR (1.5 T)	CMR (1.5 T)	CMR (1.5 T)	CMR (1.5 T)
View	Short-axis	Short-axis	Apical views	Longitudinal-axis	Short-axis stack	Short-axis	Short-axis stack	Short-axis stack
Cardiac cycle phase	End-diastole	End-systole	End-diastole	End-diastole	End-diastole	End-systole	End-diastole	End-diastole
Trabeculation measurement	Distance between the epicardial surface and trough of a trabecular recess (X) and the distance between the epicardial surface and peak of the trabeculation (Y)	Measurement of the wall thickness of the NC and C myocardial layers	Presence of more than 3 trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in 1 image plane and measurement of the wall thickness of the NC and C myocardial layers	Measurement of the wall thickness of the NC and C myocardial layers	Semiautomatic outlining of endocardial and epicardial contours, including papillary muscles	Measurement of the wall thickness of the NC and C myocardial layers	Manual tracing of epicardial borders in 4-chamber and vertical long-axis views, propagation algorithm in short- axis and manual tracing of trabeculations	Segmentation of the endocardial border and box-counting method for fractal analysis
Cutoff point	X/Y ≤ 0,5	NC/C ≥ 2	NC/C ≥ 2	NC/C ≥ 2,3	Trabeculated mass > 20% of the total LV mass	NC/C ≥ 2	Trabeculated mass > 15 g/m^2 or > 25% of the total LV mass or NC/C ≥ 3	Maximal apical fractal dimension ≥ 1,30
Interobserver variability	Significant at apical segments, insignificant at mid and basal segments	Not reported	Not reported	Not reported	Intraclass correlation coefficient 0,95 (95%CI, 0,89-0,97)	Spearman correlation 0,82 and 0,78 for the compacted and noncompacted layers, respectively	Not reported	Intraclass correlation coefficient 0,96 (95%CI, 0,93-0,97)
Figure		3A	3B-C	4A	4B	4B	4B	4C

***95%CI**, 95% confidence interval; **C**, compacted; **CMR**, cardiovascular magnetic resonance; **FS**, fractional shortening; **LVEF**, left ventricular ejection fraction; **NC**, noncompacted; **TTE**, transthoracic echocardiography.Unless otherwise indicated, the data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].*

Todos estos criterios se basan exclusivamente en parámetros morfológicos y no son diagnósticos por sí mismos de miocardiopatía, ya que no consideran variables funcionales como la dilatación o hipertrofia ventricular, la función sistólica o fracción de eyección del ventrículo izquierdo (FEVI), o variables de caracterización tisular por RMC como la fibrosis miocárdica valorada por realce tardío de gadolinio (RTG) (***Figura 5***) o por T1 *mapping* (***Figura 6***). Esto conlleva una baja especificidad para diagnosticar miocardiopatía, y un consiguiente sobrediagnóstico de la entidad, con prevalencias mucho más altas de lo esperable, especialmente cuando se utilizan los criterios de RMC [12].

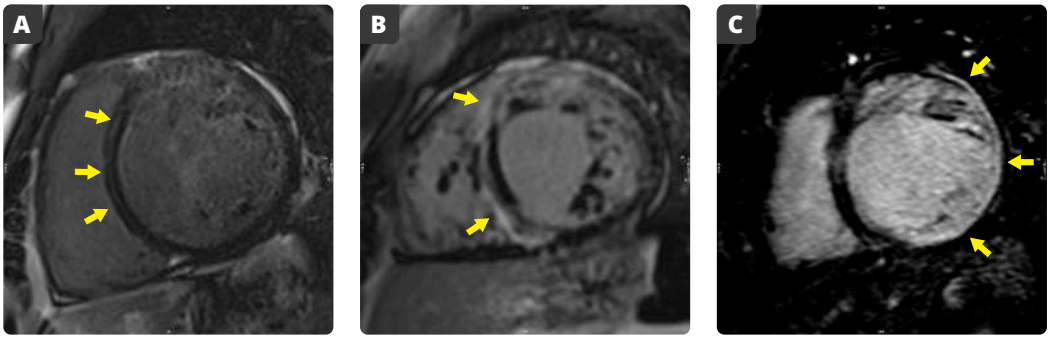


Figura 5: Patrones de realce tardío de gadolinio valorados por resonancia magnética cardiovascular en pacientes con no compactación del ventrículo izquierdo.
A) Patrón lineal intramiocárdico septal tenue. ***B)*** Patrón subepicárdico septal extenso y heterogéneo. ***C)*** Patrón transmural lateral.

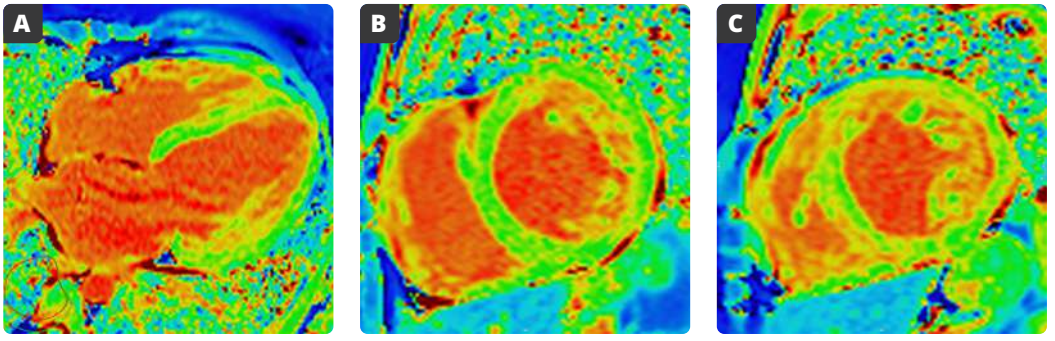


Figura 6: Mapa T1 nativo por resonancia magnética cardiovascular de un paciente con no compactación del ventrículo izquierdo que muestra una elevación difusa del valor miocárdico de T1 nativo, sugiriendo fibrosis intersticial difusa (valor T1 global: 1120 ms; valor referencia para este escáner: 950 – 1050 ms).
A) Eje apical 4 cámaras. ***B)*** Eje corto basal. ***C)*** Eje corto medio.

Como se ha comentado previamente, tanto la genética como el estudio familiar pueden ayudar en el diagnóstico: la identificación de una variante genética patogénica / posiblemente patogénica y/o la presencia de hipertrabeculación en un familiar, nos indicarán que los hallazgos morfológicos de NCVI descritos en el caso índice corresponden a una miocardiopatía y no a un rasgo fenotípico aislado [26]. En este mismo sentido, se debe valorar también la presencia de síntomas, alteraciones en el electrocardiograma (ECG) [35], antecedentes familiares [27], presencia de arritmias ventriculares (AV) en el holter o inducción de AV en la ergometría [36], así como parámetros avanzados de imagen cardíaca, como la deformación miocárdica o *strain* [37,38], o las secuencias de T1 *mapping* por RMC (***Figura 6***) [39]. De esta manera, un individuo que presente hipertrabeculación de forma aislada, sin dilatación, hipertrofia ni disfunción ventricular, ni tampoco fibrosis miocárdica, antecedentes familiares, o alteraciones en el resto de exploraciones complementarias comentadas, probablemente constituya un caso de fenotipo ventricular fisiológico.

En definitiva, la valoración integral de un paciente con NCVI, más allá de la ratio entre la capa compactada y la no compactada, nos ayudará en el diagnóstico diferencial entre una hipertrabeculación fisiológica (rasgo morfológico aislado) y una hipertrabeculación patológica (miocardiopatía). Esta diferenciación es especialmente relevante en los deportistas que, como se ha comentado previamente, presentan una elevada prevalencia de hipertrabeculación [13]. En este sentido, se han sugerido diversos algoritmos que intentan integrar todos los parámetros previamente comentados para ayudar en la toma de decisiones en la práctica clínica (***Figura 7***) [28,40,41]. Sin embargo, no existe un consenso universal al respecto ni unos criterios diagnósticos estandarizados o *gold standard*.

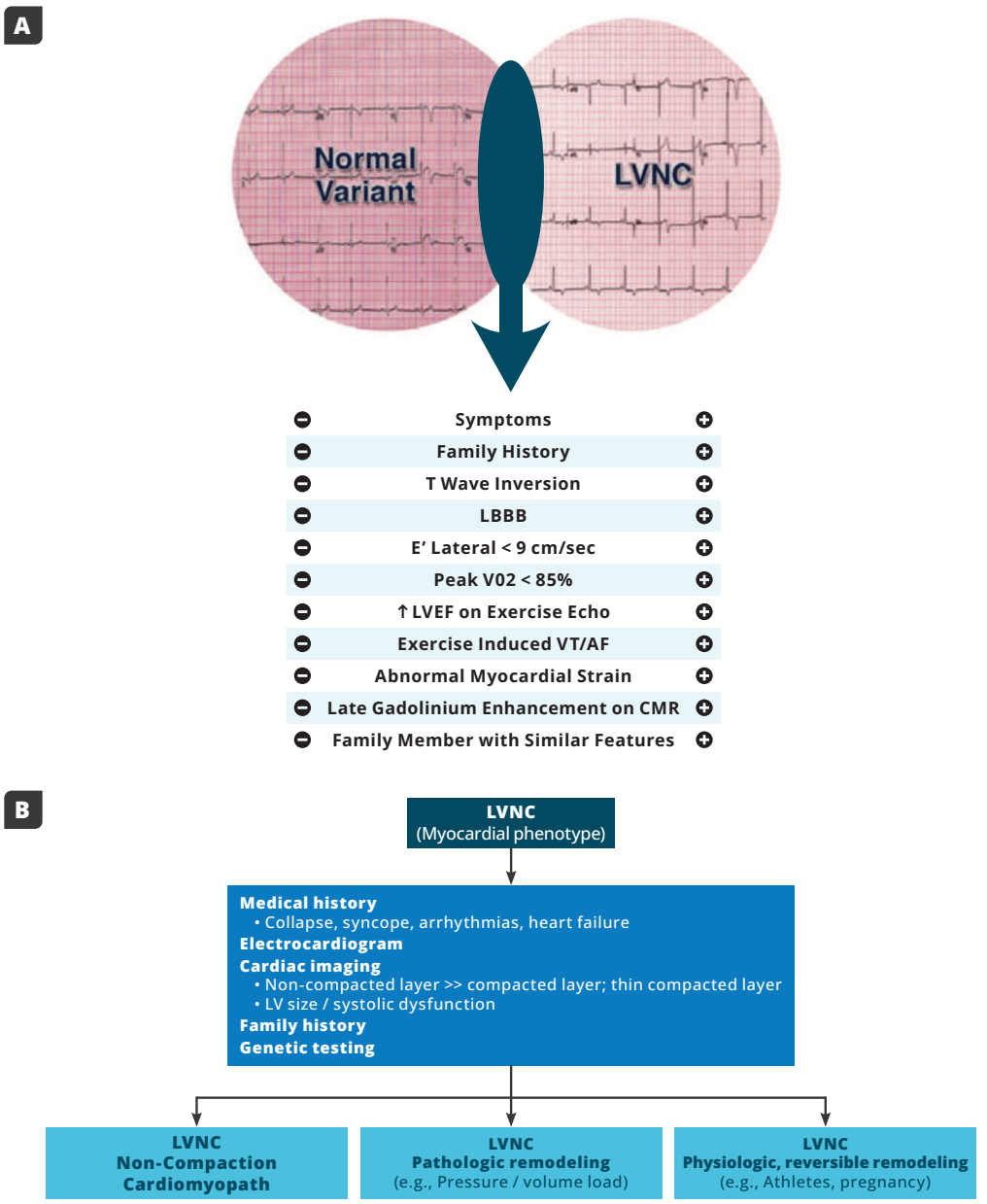


Figura 7: ***A)*** Adaptado de Gati *et al* [40]. ***B)*** Adaptado de Oechslin *et al* [28]. Algoritmos para diferenciar una hipertrabeculación fisiológica o rasgo morfológico aislado de una hipertrabeculación patológica o miocardiopatía establecida en ***A)*** deportistas y en ***B)*** la población general.

1.4. PRONÓSTICO

Las principales complicaciones cardiovasculares de los pacientes con NCVI son la insuficiencia cardíaca (IC), las arritmias ventriculares (AV), las embolias sistémicas (ES) y la mortalidad cardiovascular. Sin embargo, el pronóstico de la NCVI es muy heterogéneo, con resultados llamativamente discordantes según las diferentes series. Esta inconsistencia se podría deber, al menos parcialmente, a la falta de consenso sobre la definición de la entidad y a la variabilidad entre los diferentes criterios diagnósticos.

Los primeros estudios publicados sobre la historia natural de la enfermedad describieron un mal pronóstico, con un alto riesgo de complicaciones cardiovasculares graves, incluyendo muerte, AV o trasplante cardíaco[22,29]. Estos dos artículos se basaban en series de pocos pacientes, utilizaban técnicas de imagen de menor resolución que las actuales y los hallazgos se podrían justificar en parte por el sesgo de publicación habitual cuando se describe una entidad por primera vez. Sin embargo, estudios más recientes que incluyeron un mayor número de pacientes mostraron hallazgos similares: la supervivencia en NCVI fue inferior a la población general[42], el pronóstico de pacientes con NCVI de causa genética fue peor que el de controles apareados con MCD[43] y la tasa de eventos cardiovasculares ajustada por la FEVI fue más alta en NCVI que en MCD en un estudio prospectivo multicéntrico[44]. Estos resultados también se confirmaron en un metaanálisis reciente, que describió una mayor incidencia de ingresos por IC en NCVI comparado con MCD, con proporciones similares de AV y ES[45].

En el otro extremo encontramos estudios que muestran un pronóstico más benigno de esta entidad, hasta el punto de sugerir que no se trata de una enfermedad como tal sino de un rasgo morfológico aislado. Un estudio retrospectivo antiguo y con pocos pacientes mostró un mejor pronóstico de lo que se había descrito inicialmente, con una baja tasa de eventos graves[36]. Estudios más recientes basados en RMC han demostrado igualmente una buen pronóstico en esta entidad:

la presencia y el grado de hipertrabeculación no se asoció con cambios a largo plazo en los volúmenes ventriculares ni en la FEVI en un gran estudio poblacional[46], mientras que el hecho de cumplir criterios diagnósticos de NCVI no se correlacionó con eventos cardiovasculares en pacientes sometidos a RMC[47,48], ni a un peor pronóstico en pacientes con MCD[49].

En lo que respecta a los factores pronósticos, se han publicado múltiples estudios al respecto, siendo la FEVI y el RTG dos de los predictores de eventos más consistentes y potentes, en consonancia con otras miocardiopatías. En un estudio prospectivo multicéntrico basado en RMC, la FEVI resultó ser un predictor independiente de eventos cardiovasculares, con un efecto predictivo adicional a las variables clínicas[50]. En otro gran estudio retrospectivo unicéntrico, la FEVI se asoció de forma independiente con la mortalidad por cualquier causa[42], mientras que en otro estudio retrospectivo multicéntrico, la FEVI fue un predictor pronóstico independiente en portadores de variantes patogénicas[51]. Estos hallazgos se confirmaron en el metaanálisis citado anteriormente, que demostró un riesgo aumentado de muerte cardiovascular en pacientes con FEVI < 45%[45]. En cambio, una FEVI > 45% se asoció a un pronóstico benigno con una tasa muy baja de eventos en un estudio prospectivo multicéntrico[44].

Por otra parte, el RTG (***Figura 5***) demostró tener una asociación independiente con el riesgo de eventos cardiovasculares en un estudio prospectivo multicéntrico, destacando el valor predictivo incremental añadido a las variables clínicas y funcionales del ventrículo izquierdo (dilatación y/o disfunción sistólica)[50]. Estos hallazgos fueron corroborados en un metaanálisis de RMC en NCVI: el RTG se asoció con un combinado de eventos cardiovasculares, con la muerte cardíaca y con un combinado de eventos cardíacos duros[52]. Cabe destacar que el riesgo atribuido al RTG fue independiente de la FEVI y en especial que aquellos pacientes con FEVI preservada y sin RTG no presentaron ningún evento cardíaco duro durante el seguimiento[52].

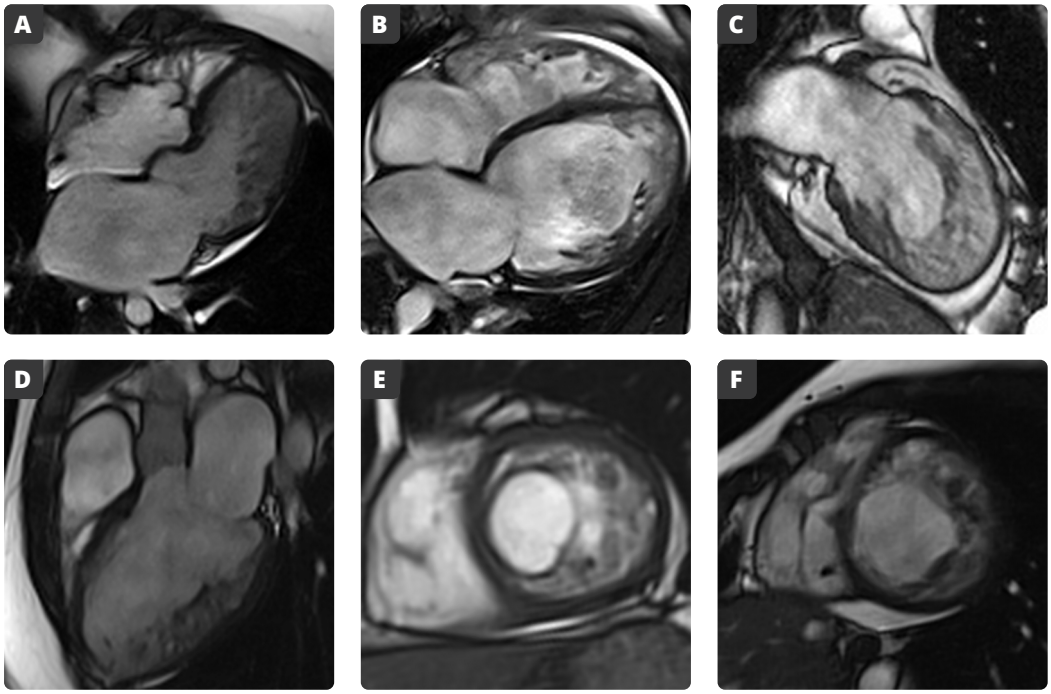


Figura 8: Pacientes con no compactación del ventrículo izquierdo con diferentes grados de hipertrabeculación valorada por resonancia magnética cardiovascular. ***A)*** y ***B)***: eje apical 4 cámaras. ***C)***: eje apical 2 cámaras. ***D)***: eje apical 3 cámaras. ***E)*** y ***F)***: eje corto.

Existe más controversia acerca del papel pronóstico de la hipertrabeculación *per se* (***Figura 8***). Como se ha comentado previamente, algunos estudios han demostrado una ausencia de asociación entre el grado de hipertrabeculación y el pronóstico [46,48]. En cambio, un gran estudio poblacional demostró que el grado de hipertrabeculación medido por tomografía computarizada cardíaca se asoció con un riesgo creciente de eventos cardiovasculares incluyendo muerte, insuficiencia cardíaca, infarto de miocardio y/o ictus [53]. Tampoco hay consenso respecto a la implicación pronóstica de la extensión de la hipertrabeculación: un estudio basado en RMC mostró que no se correlacionaba con eventos cardiovasculares (mortalidad global y combinado de insuficiencia cardíaca, ictus o fibrilación auricular) [48], mientras que la presencia de hipertrabeculación extendiéndose desde segmentos basales hasta apicales se asoció de forma independiente con la mortalidad en un estudio retrospectivo

unicéntrico[42]. El adelgazamiento miocárdico, otro hallazgo morfológico habitual en la NCVI, también se ha correlacionado con el doble de riesgo ajustado de eventos cardiovasculares (mortalidad global, insuficiencia cardíaca, taquicardia ventricular, ictus, implante de un dispositivo de asistencia ventricular y/o trasplante cardíaco) en un gran estudio retrospectivo unicéntrico[54].

Adicionalmente, también se han descrito múltiples correlaciones genotipo-fenotipo en la NCVI. Las variantes genéticas se asocian con un mayor grado de hipertrabeculación[55], con una mayor prevalencia de disfunción ventricular[51,55] y con una mayor incidencia de complicaciones cardiovasculares, especialmente los genes de alto riesgo: *LMNA* y *RBM20* (muerte cardiovascular, muerte súbita cardíaca, taquicardia ventricular sostenida y/o trasplante cardíaco)[43], *MYBPC3* y *TTN* (muerte cardíaca, taquicardia ventricular sostenida, fibrilación ventricular, descarga apropiada, implante de un dispositivo de asistencia ventricular, ictus, insuficiencia cardíaca y/o trasplante cardíaco)[17], entre otros[56]. En cambio, los genes *MYH7* y *ACTC1* se asocian con un curso más benigno, con una menor incidencia del evento cardiovascular combinado comentado en la referencia previa[17,51]. Finalmente, algunos trabajos han estudiado la relación entre los biomarcadores y el pronóstico y, en concreto, dos series han demostrado el papel del NTproBNP para predecir eventos cardiovasculares (mortalidad global, insuficiencia cardíaca, taquicardia ventricular, ictus, implante de un dispositivo de asistencia ventricular y/o trasplante cardíaco), independientemente de la FEVI o de los volúmenes ventriculares[54,57].

2

Hipótesis

2.1. HIPÓTESIS PRINCIPAL

En la no compactación del ventrículo izquierdo, la historia clínica personal y familiar, el electrocardiograma, las pruebas de imagen cardíaca y la genética son esenciales para determinar la probabilidad de tener una miocardiopatía, para identificar a individuos sanos y para estratificar el riesgo cardiovascular; por tanto, tienen una utilidad tanto diagnóstica como pronóstica.

2.2. HIPÓTESIS SECUNDARIA

La fracción de eyección del ventrículo izquierdo es uno de las principales variables asociadas a eventos cardiovasculares en la no compactación del ventrículo izquierdo, y su evolución a lo largo del tiempo tiene un impacto pronóstico independiente.

2.3. JUSTIFICACIÓN DEL TRABAJO

Existen muchas limitaciones en el conocimiento de la NCVI. Por un lado, no disponemos de un consenso para el diagnóstico de la entidad, ni existen algoritmos diagnósticos validados que incorporen el análisis integral de los pacientes más allá de los rasgos morfológicos de hipertrabeculación. Esto conlleva muchos diagnósticos erróneos, con la consiguiente carga psicológica para individuos sanos y un sobrecoste innecesario para los sistemas de salud. Además, no se han estudiado los cambios dinámicos en la FEVI, por lo que el hecho de presentar una FEVI conservada inicialmente (que podría sugerir un rasgo morfológico aislado), no descarta la posibilidad de presentar un deterioro de la misma durante el seguimiento, lo cual sería más compatible con una miocardiopatía. Por otro lado, no está bien establecido el pronóstico de esta entidad, ni tampoco se han estudiado en profundidad los factores predictores de eventos cardiovasculares, siendo complicado a día de hoy explicar a los pacientes cual va a ser la historia natural de su patología.

A nivel práctico, esto se traduce en la falta de documentos de consenso o guías de práctica clínica específicos, con la consiguiente variabilidad en el manejo de los

pacientes y, consecuentemente, en una evolución potencialmente desfavorable. Por lo tanto, es necesario un estudio completo y profundo de la entidad, que permita mejorar el conocimiento que tenemos al respecto y que nos ayude en el diagnóstico diferencial y en la estratificación pronóstica. El objetivo ideal sería el de ofrecer a nuestros pacientes una asistencia de mejor calidad, más individualizada y más basada en la evidencia científica, lo cual podría mejorar, hipotéticamente, su pronóstico a largo plazo.

3

Objetivos

3.1. OBJETIVO PRINCIPAL

- Desarrollar un modelo predictivo de riesgo de eventos cardiovasculares en individuos con no compactación del ventrículo izquierdo.

3.2 OBJETIVOS SECUNDARIOS

- Diseñar un algoritmo que permita establecer la probabilidad de tener una miocardiopatía en individuos con no compactación del ventrículo izquierdo, y, especialmente, identificar los casos de bajo riesgo (sin una miocardiopatía asociada).
- Describir las variables asociadas al deterioro de la fracción de eyección del ventrículo izquierdo a lo largo del seguimiento y su consiguiente impacto pronóstico.

4

Metodología

4.1. METODOLOGÍA DEL PRIMER ESTUDIO: PREDICCIÓN DE EVENTOS CARDIOVASCULARES EN LA NO COMPACTACIÓN DEL VENTRÍCULO IZQUIERDO

4.1.1. Diseño y población

Diseñamos un estudio multicéntrico, observacional, retrospectivo, longitudinal y de cohortes sobre NCVI. En el estudio participaron 12 centros de referencia españoles a través de la red de investigación Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBER-CV; Madrid, España) (listado completo en la ***Tabla 2***). Desde el 1 de enero de 2000 hasta el 31 de diciembre de 2018, se reclutaron todos los pacientes consecutivos diagnosticados de NCVI de acuerdo a los criterios de Jenni [7] por ETT, y a los criterios de Petersen [31] y Jacquier [32] por RMC (en caso de estar disponible). No se definieron criterios de exclusión: todos los pacientes con diagnóstico principal de NCVI fueron incluidos en el estudio. Los casos sin información disponible sobre la ocurrencia y la fecha de eventos cardiovasculares o sobre la FEVI basal no fueron considerados para el análisis.

Tabla 2: Listado completo de los 12 centros que participaron en el estudio.

Centro	Nº pacientes incluidos (primer estudio)	Nº pacientes incluidos (segundo estudio)
Hospital Universitari Vall d'Hebron	211	208
Complexo Hospitalario Universitario de A Coruña	133	133
Hospital Universitario Puerta de Hierro	51	50
Hospital Universitario y Politécnico La Fe de Valencia	40	39
Hospital Universitario Virgen de la Arrixaca	34	31
Hospital Universitario de Salamanca	30	30
Hospital Universitario Virgen de las Nieves	22	22
Hospital Universitario Son Llatzer	21	21
Hospital Universitari Germans Trias i Pujol	18	18
Hospital Universitario Virgen de la Victoria	12	12
Hospital Universitario 12 de Octubre	10	10
Hospital Universitari Dr Josep Trueta	3	3
TOTAL	**585**	**577**

Todos los pacientes recibieron una visita inicial exhaustiva en un centro de referencia para cardiopatías familiares. Esta valoración incluyó la anamnesis completa, la elaboración de un árbol familiar, la exploración física, y la realización de un ECG y

una ETT. En esta visita se confirmó el diagnóstico de NCVI por un cardiólogo experto y fue considerada el momento de inclusión en el estudio.

A todos los casos índices (o probandos) se les recomendó la realización de un estudio familiar fenotípico (*screening*), que se consideró positivo si al menos un familiar de primer grado cumplía los criterios diagnósticos de NCVI por ETT y/o RMC (si posible). El estudio genético se indicó según los protocolos locales de cada centro y consistió en un panel *next-generation sequencing* (NGS) de 213 genes relacionados con enfermedades cardíacas hereditarias (listado completo en la ***Tabla Suplementaria 1***). Todos los estudios genéticos fueron analizados en el mismo centro externo (Health in Code; A Coruña, España) y fueron considerados positivos en caso de describirse una variante patogénica o posiblemente patogénica de acuerdo a las recomendaciones actuales [58]. Las variantes se clasificaron según su función molecular en sarcómero (*ACTC1*, *MYH7*, *MYBPC3*, *TTN*, *FHL1*, *FHOD3*, *LDB3*, *TNNC1*, *TNNI3*, *TNNT2*, *TPM1*), citoesqueleto (*ACTN2*, *DMD*, *FLNC*), desmosoma (*DSP*, *JUP*), y otras (*BAG3*, *HCN4*, *JPH2*, *MIB1*, *NKX2-5*, *Notch1*, *RBM20*, *TBX20*). Un genotipo complejo se definió como la presencia de variantes patogénicas o posiblemente patogénicas en más de un gen, según lo publicado previamente [51]. En caso de documentarse un genotipo positivo en un probando, se recomendó el estudio genético familiar en cascada.

Los pacientes recibieron un seguimiento clínico periódico y estructurado según los protocolos de cada centro, con visitas normalmente anuales, y con la realización periódica de ECG, ETT, holter de monitorización, ergometrías convencionales y analíticas. El tratamiento médico y la indicación de dispositivos fueron prescritos según las guías de práctica clínica [59–62].

4.1.2. Variables analizadas

Todos los datos fueron recogidos de los registros médicos electrónicos de forma pseudoanonimizada. Se incluyeron variables basales demográficas, antecedentes

médicos personales e historia familiar cardiológica, datos sobre agregación familiar, genotipo y tratamiento médico. El ECG, la ETT y la RMC más cercanos a la fecha del diagnóstico de NCVI fueron usados para el análisis. La ETT y la RMC fueron adquiridas e interpretadas localmente por especialistas en imagen cardíaca y miocardiopatías; la indicación de realizar una RMC siguió los protocolos locales.

La FEVI se categorizó según las guías de práctica clínica[59,60] en: preservada (FEVIp; FEVI ≥ 50%), ligeramente reducida (FEVI 35 – 50%) y severamente reducida (FEVI ≤ 35%). Un ECG anormal se definió como la ausencia de ritmo sinusal (o presencia de fibrilación auricular, FA), y/o la presencia de un complejo QRS ancho (≥ 120 ms) y/o de alteraciones de la repolarización, de acuerdo con criterios publicados[63]. La variable "factores de riesgo cardiovascular" se definió como el combinado de hipertensión arterial, diabetes mellitus, dislipemia y/o tabaquismo. Los pacientes con agregación familiar y/o disfunción sistólica basal (FEVI < 50%) se clasificaron como afectos de una miocardiopatía no compactada (MCNC). Se utilizó esta definición estricta de MCNC como un criterio específico para identificar pacientes con hallazgos morfológicos de NCVI y afectación cardíaca evidente, pudiéndose diferenciar de aquellos casos con hipertrabeculación probablemente fisiológica.

4.1.3. Eventos

Los eventos clínicos del estudio fueron: **1) Insuficiencia cardíaca (IC)**, un combinado de ingreso por IC, necesidad de trasplante cardíaco, implante de un dispositivo de asistencia ventricular izquierda y/o de una terapia de resincronización cardíaca; **2) Arritmias ventriculares (AV)**, un combinado de muerte súbita cardíaca (MSC), fibrilación ventricular, taquicardia ventricular sostenida y/o no sostenida y/o descarga apropiada de un desfibrilador automático implantable (DAI); **3) Embolismos sistémicos (ES)**, ictus o accidente isquémico transitorio embólico, infarto de miocardio embólico y/o embolia arterial periférica; y **4) Mortalidad global**. Aunque también se registró la mortalidad cardiovascular, se consideró como evento primario la mortalidad global de acuerdo a publicaciones previas[54].

Finalmente, se definió un combinado de eventos cardiovasculares adversos mayores (*major adverse cardiovascular events*; **MACE**) que incluyó cualquiera de los cuatros eventos clínicos primarios. Este evento amplio se diseñó con la idea de identificar aquellos individuos que no desarrollaron ninguna complicación cardiovascular durante el seguimiento, lo que permitiría excluir de forma razonable la presencia de una miocardiopatía asociada al fenotipo de no compactación.

4.1.4. Análisis estadístico

Las variables continuas se expresan como media ± desviación estándar (DE) y como mediana y rango intercuartil (RIC). Las variables categóricas se expresan como número de casos y proporciones. La normalidad se evaluó en las variables continúas utilizando la prueba de Shapiro-Wilk y se comparó entre grupos utilizando la prueba t de Student y la prueba ANOVA. Las variables categóricas se compararon utilizando la prueba de chi-cuadrado o la prueba exacta de Fisher, según corresponda.

Para el análisis de supervivencia, el inicio del seguimiento se consideró la primera visita en la unidad de referencia de cardiopatías familiares y el seguimiento fue censurado en el momento de ocurrencia de algún MACE o después de la última visita en caso de no presentar ningún evento. La recogida de datos se completó el 31 de mayo de 2019, considerándose el final del estudio. El efecto de las variables en los eventos clínicos se analizó mediante análisis de regresión de Cox univariado y multivariado. El tratamiento médico no se incluyó en el análisis de regresión de Cox debido a la falta de información sobre el momento de la prescripción. Específicamente, el efecto de la agregación familiar en los eventos clínicos se analizó solo en los probandos y el efecto del genotipo se analizó solo en los pacientes que se sometieron a pruebas genéticas; los portadores de variantes específicas se compararon con los no portadores.

Las variables candidatas para el modelo predictivo de regresión de Cox se seleccionaron en función del nivel de significación de la asociación con el resultado

(p < 0,2) y la plausibilidad clínica (género y agregación familiar / MCNC). El modelo final se definió utilizando el criterio de información de Akaike (AIC) por pasos y los datos faltantes se manejaron utilizando algoritmos de imputación múltiple. La calibración y discriminación del modelo se evaluaron con gráficos de calibración y el estadístico C de Harrell. Además, se describieron nomogramas para ayudar al cálculo del riesgo. Para la validación externa del modelo de riesgo, se utilizó una cohorte italiana prospectiva multicéntrica previamente publicada [50].

Los resultados se expresan como *hazard ratio* (HR) e intervalo de confianza del 95% (IC95%). Un valor p < 0,05 se consideró estadísticamente significativo. Para el análisis se utilizó STATA versión 15,1 para Mac (Stata Corporation, College Station, Texas, EE. UU.) y R Studio.

Los protocolos del estudio fueron aprobados por el comité de ética del Hospital Universitari Vall d'Hebron (HUVH; Barcelona, España) (número de validación PR(AG)18/2020) y cumplieron con las directrices de la Declaración de Helsinki de 1975. Todos los participantes dieron su consentimiento informado por escrito.

4.2. METODOLOGÍA DEL SEGUNDO ESTUDIO: DETERIORO DE LA FRACCIÓN DE EYECCIÓN DEL VENTRÍCULO IZQUIERDO Y SU RELACIÓN CON EVENTOS CARDIOVASCULARES EN LA NO COMPACTACIÓN DEL VENTRÍCULO IZQUIERDO

4.2.1. Diseño y población

El diseño del segundo estudio fue superponible al primero (multicéntrico, observacional, de cohortes) y la población incluida fue idéntica. Como única particularidad, los pacientes que no disponían de FEVI al final del seguimiento no fueron considerados para el análisis, ya que el objetivo final era determinar la prevalencia, factores asociades e implicaciones pronósticas de los cambios evolutivos de la FEVI. El protocolo de seguimiento fue el mismo.

Adicionalmente, para este estudio se realizó un análisis centralizado (*core laboratory*) en el HUVH de las RMC de los individuos considerados de bajo riesgo en la literatura: FEVIp (≥ 50%) y sin RTG. Este subestudio se planteó con el objetivo de intentar mejorar el diagnóstico diferencial entre una miocardiopatía subclínica y una hipertrabeculación fisiológica (ver explicación completa en el siguiente apartado).

4.2.2. Variables analizadas

Todos los datos fueron recogidos de los registros médicos electrónicos de forma pseudoanonimizada. Las variables basales recogidas fueron las mismas que las del primer estudio. Para este trabajo también se recogió información sobre las ETT de seguimiento periódicas (normalmente anuales), y especialmente sobre la última ETT disponible. Estos datos fueron adquiridos e interpretados localmente por expertos en imagen cardíaca.

Para el subestudio de RMC, se consideraron únicamente los individuos de bajo riesgo. Se enviaron las imágenes pseudoanonimizadas y se analizaron de forma centralizada en el HUVH por un único operador, ciego a la incidencia de eventos adversos en el momento del análisis. Se utilizaron los softwares dedicados de RMC cvi42 (Circle Cardiovascular Imaging; Calgary, Canada) y Medis (Medical Imaging Systems, Leiden, The Netherlands). En la ***Tabla 3*** se describen todas las variables analizadas; en resumen se obtuvieron las variables morfo-funcionales básicas, parámetros de cuantificación de la trabeculación biventricular (***Figura 4*** y ***9***) y variables de deformación miocárdica (***Figura 10***). Específicamente, para el análisis de supervivencia posterior, el *strain* longitudinal reservorio de la aurícula izquierda se dividió en cuartiles.

Tabla 3: Resumen de las variables de resonancia magnética cardiovascular analizadas en el subestudio de individuos de bajo riesgo.

Variable	Definición	Figura	Referencia	Software
Ventrículo izquierdo				
FEVI (%)	Fracción de eyección del ventrículo izquierdo			cvi42
iVTDVI (ml/m²)	Volumen telediastólico del ventrículo izquierdo indexado por superficie corporal			cvi42
iVTSVI (ml/m²)	Volumen telesistólico del ventrículo izquierdo indexado por superficie corporal			cvi42
Masa ventricular indexada (gr/m²)	Masa ventricular total indexada por superficie corporal			cvi42
Ratio NC/C	Ratio entre la capa no compactada y la capa compactada (eje longitudinal)	4A	31	cvi42
% masa ventricular trabeculada (%)	Porcentaje de masa trabeculada respecto a la masa total	4B	32	cvi42
Masa ventricular trabeculada indexada (gr/m²)	Masa trabeculada indexada por superficie corporal	4B	64	cvi42
DF apical máxima	Dimensión fractal máxima de los segmentos apicales	4C	34	cvi42
DF global media	Dimensión fractal media de todo el ventrículo izquierdo	4C	34	cvi42
GLS VI (%)	*Strain* longitudinal global del ventrículo izquierdo	10A-B		cvi42
GCS VI, % (DE)	*Strain* circunferencial global del ventrículo izquierdo	10A-B		cvi42
GRS VI (%)	*Strain* radial global del ventrículo izquierdo	10A-B		cvi42
Ventrículo derecho				
FEVD (%)	Fracción de eyección del ventrículo derecho			cvi42
iVTDVD (ml/m²)	Volumen telediastólico del ventrículo derecho indexado por superficie corporal			cvi42
iVTSVD (ml/m²)	Volumen telesistólico del ventrículo derecho indexado por superficie corporal			cvi42
NC/C ratio 4 cámaras	Ratio entre la capa no compactada y la capa compactada (eje 4 cámaras)	9A	65	cvi42
NC/C ratio eje corto	Ratio entre la capa no compactada y la capa compactada (eje corto)	9B	65	cvi42
GLS VD (%)	*Strain* longitudinal global del ventrículo derecho	10C-D		Medis
Aurícula izquierda				
Volumen auricular biplano indexado, (mL/m²)	Volumen auricular biplano (4 y 2 cámaras) indexado por superficie corporal			cvi42
FEAI (%)	Fracción de eyección de la aurícula izquierda			cvi42
GLSr AI, % (DE)	Strain longitudinal reservorio de la aurícula izquierda	10E-F		Medis
GCS AI (%)	Strain circunferencial global de la aurícula izquierda			Medis

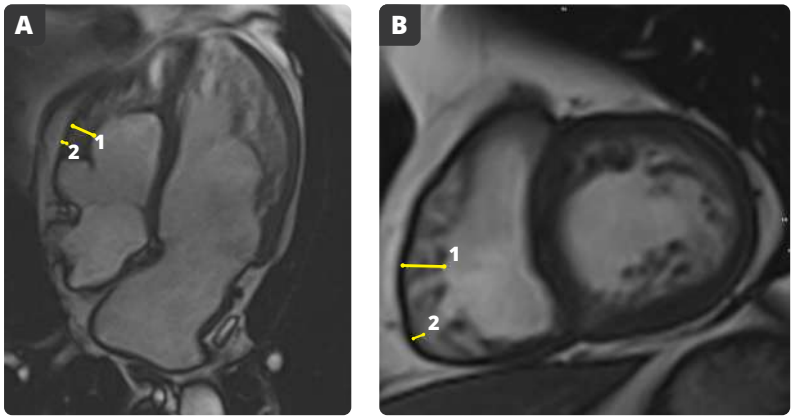


Figura 9: Valoración del grado de hipertrabeculación del ventrículo derecho por resonancia magnética cardiovascular en un ***A)*** plano apical 4 cámaras y ***B)*** eje corto

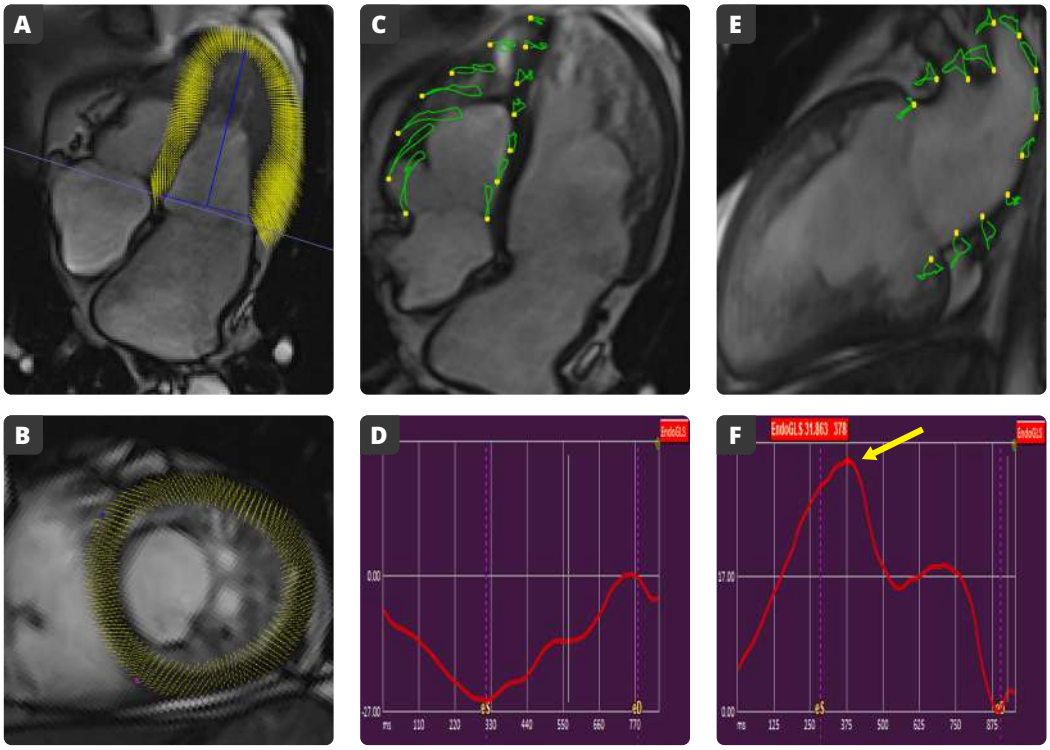


Figura 10: Valoración de los parámetros de deformación miocárdica o *strain*. Contornos del ventrículo izquierdo en ***A)*** eje apical 4 cámaras y ***B)*** eje corto. ***C)*** Contornos del ventrículo derecho. ***D)*** Curva de *strain* longitudinal global del ventrículo derecho. ***E)*** Contornos de la aurícula izquierda. ***F)*** Curva de *strain* longitudinal global de la aurícula izquierda; la flecha amarilla señala el *strain* reservorio.

4.2.3. Eventos

El estudio incluyó dos eventos primarios: **1) Deterioro de la FEVI**, definido como una caída absoluta de más de 10 puntos porcentuales de la FEVI respecto a la FEVI inicial, con una FEVI final inferior al 50% (ambas mediciones por ETT), de acuerdo con los criterios del ensayo clínico TRED-HF[66]; y **2) MACE**: combinado de insuficiencia cardíaca, arritmias ventriculares, embolismos sistémicos y mortalidad global (según los criterios definidos en el primer estudio). Para el subestudio de RMC, se definió un evento combinado de deterioro de la FEVI y/o MACE.

4.2.4. Análisis estadístico

La estadística descriptiva fue superponible a la del primer estudio. Para el análisis de supervivencia se siguió una estrategia de análisis diferente. En concreto, para el deterioro de la FEVI, la fecha del último seguimiento se definió como la fecha del primer ETT que cumplía los criterios del evento primario. Los pacientes que no presentaron cambios significativos de la FEVI durante el seguimiento fueron censurados a fecha del último ETT disponible. Para los MACE, el seguimiento se inició después del primer ETT que evidenció un deterioro de la FEVI, o después del primer ETT disponible en caso de no presentar dicha disminución de la FEVI. Para los pacientes que no presentaron MACE, se censuró el seguimiento en la última visita médica con la unidad de referencia. El estudio se cerró el 30 de junio de 2023.

La asociación de las variables con los eventos se analizó mediante regresión de Cox univariada y multivariada. Adicionalmente, se realizó un análisis mediante la técnica de eliminación hacia atrás (*backward stepwise regression*) (valor p para inclusión 0,05, valor de p para exclusión 0,10), para seleccionar las variables candidatas y evitar el sobreajuste. Las variables con > 25% de datos no disponibles no se utilizaron para el análisis multivariado.

Los resultados se expresan como HR e IC95%. Un valor $p < 0,05$ se consideró estadísticamente significativo. Para el análisis se utilizó STATA versión 15,1 para Mac (Stata Corporation, College Station, Texas, EE. UU.).

Los protocolos del estudio fueron aprobados por el comité de ética del HUVH (número de validación PR(AG)18/2020) y cumplieron con las directrices de la Declaración de Helsinki de 1975. Todos los participantes dieron su consentimiento informado por escrito.

5

Resultados

5.1. RESULTADOS DEL PRIMER ESTUDIO: PREDICCIÓN DE EVENTOS CARDIOVASCULARES EN LA NO COMPACTACIÓN DEL VENTRÍCULO IZQUIERDO

5.1.1. Características basales y genética

Inicialmente se reclutaron 592 pacientes, pero 7 (1,2%) se excluyeron por ausencia de datos clínicos y/o ecocardiográficos. Por tanto, finalmente se incluyeron 585 pacientes en el estudio (***Figura 11***; ***Tabla 2***). De estos, 437 (75%) eran casos índices. En la ***Tabla 4*** se muestran las características demográficas y clínicas basales: la edad media fue de 45 ± 20 años y 334 (57%) eran hombres. La FEVI fue del 48 ± 17% y 79 pacientes presentaban fibrosis miocárdica valorada por RTG (18% de aquellos con RMC disponible), siendo la FEVI inferior en los pacientes con fibrosis comparado con aquellos sin RTG (39 ± 16% Vs 53 ± 14%; p < 0,001).

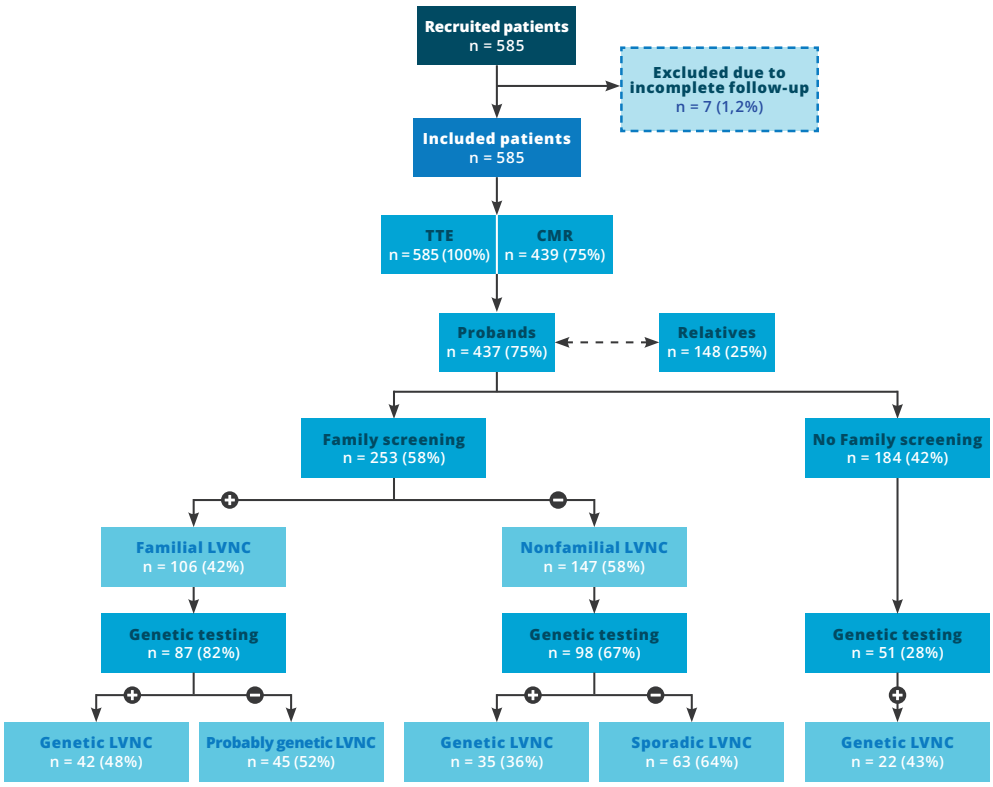


Figura 11: Diagrama de flujo del primer estudio. Adaptado de Casas *et al* [67].

***LVNC**: left ventricular noncompaction. Otras abreviaciones como en **Tabla 1**.*

Tabla 4: Características basales de los pacientes con no compactación del ventrículo izquierdo de acuerdo a la ocurrencia de eventos cardiovasculares adversos mayores. Adaptado de Casas *et al* [67].

	Cohorte global (n = 585)	MACE (n = 223)	No MACE (n = 362)	HR crudo (IC 95%)	p Valor
Características clínicas					
Edad al diagnóstico, años (DE)	45 (20)	54 (17)	40 (20)	1,03 (1,03-1,04)	<0,001
≤ 35 años, n (%)	191	31 (14)	160 (44)	1	
36 – 54 años, n (%)	203	90 (40)	113 (31)	2,89 (1,91-4,35)	<0,001
≥ 55 años, n (%)	191	102 (46)	89 (25)	4,48 (2,99-6,71)	<0,001
Sexo masculino, n (%)	334 (57)	136 (61)	198 (55)	1,26 (0,96-1,66)	0,086
Probando, n (%)	437 (75)	201 (90)	236 (65)	4,00 (2,57-6,21)	<0,001
CF NYHA III-IV basal, n (%)	66 (11)	59 (27)	7 (2)	3,57 (2,65-4,82)	<0,001
Historia familiar de MC, n (% de probandos)	107 (26)	49 (26)	58 (26)	0,90* (0,64-1,24)	0,508
Historia familiar de MSC, n (% de probandos)	65 (17)	33 (20)	32 (15)	1,00* (0,68-1,47)	0,994
Screening familiar positivo, n (% de probandos)	106 (42)	43 (42)	63 (42)	0,80* (0,56-1,14)	0,219
Genotipo positivo, n (% de probandos con estudio genético)	192 (54)	69 (54)	123 (54)	0,87† (0,62-1,24)	0,447
Miocardiopatía no compactada, n (%)	423 (72)	202 (91)	221 (61)	2,64 (1,60-4,34)	<0,001
Factores de riesgo cardiovascular					
Hipertensión arterial, n (%)	139 (25)	83 (39)	56 (16)	2,58 (1,95-3,41)	<0,001
Dislipidemia, n (%)	142 (25)	89 (42)	53 (15)	2,37 (1,80-3,12)	<0,001
Diabetes mellitus, n (%)	52 (9)	36 (17)	16 (5)	2,23 (1,56-3,20)	<0,001
Tabaquismo, n (%)	76 (19)	43 (28)	33 (14)	1,83 (1,28-2,61)	<0,001
IMC, kg/m^2 (DE)	25,4 (4,9)	26,8 (5,3)	24,5 (4,5)	1,06 (1,04-1,09)	<0,001
Factores de riesgo cardiovascular, n (%)	279 (48)	141 (63)	99 (27)	2,57 (1,95-3,38)	<0,001
Electrocardiograma					
Ritmo sinusal, n (%)	503 (91)	161 (80)	342 (98)	0,42 (0,30-0,60)	<0,001
QRS, ms (DE)	105 (29)	118 (33)	97 (22)	1,02 (1,01-1,02)	<0,001
BRIHH, n (%)	81 (18)	45 (25)	36 (13)	1,87 (1,24-2,44)	0,001
Alteraciones de la repolarización, n (%)	187 (35)	82 (44)	105 (31)	1,39 (1,04-1,86)	0,028
ECG anormal, n (%)	271 (62)	136 (81)	135 (50)	2,31 (1,57-3,39)	<0,001
Ecocardiografía					
FEVI, % (DE)	48 (17)	37 (15)	55 (13)	1,04 (1,04-1,05)	<0,001
DTDVI, mm (DE)	54 (10)	59 (10)	51 (8)	1,05 (1,04-1,06)	<0,001
DTSVI, mm (DE)	38 (11)	46 (13)	34 (8)	1,06 (1,05-1,08)	<0,001
TAPSE, mm (DE)	21 (5)	19 (5)	23 (4)	1,10 (1,05-1,14)	<0,001
PAPS, mmHg (DE)	34 (13)	40 (14)	29 (9)	1,03 (1,02-1,04)	<0,001
Diámetro AI, mm (DE)	39 (9)	43 (10)	36 (7)	1,04 (1,03-1,06)	<0,001
IM grado ≥ 3, n (%)	27 (7)	22 (12)	5 (2)	1,94 (1,23-3,06)	0,005
Disfunción diastólica grado ≥ 2, n (%)	64 (22)	40 (35)	24 (13)	1,65 (1,10-2,46)	0,015
Resonancia magnética cardiovascular					
FEVI, % (DE)	51 (16)	40 (18)	56 (11)	1,05 (1,04-1,06)	<0,001
FEVI ≥ 50%, n (%)	261	47 (34)	214 (75)	1	
FEVI 35 – 50%, n (%)	85	28 (20)	57 (20)	3,03 (2,07-4,46)	<0,001
FEVI ≤ 35%, n (%)	78	64 (46)	14 (5)	5,20 (3,71-7,27)	<0,001
VTDVI, ml (DE)	167 (74)	200 (96)	152 (55)	1,01 (1,01-1,01)	<0,001
VTSVI, ml (DE)	87 (64)	123 (86)	71 (43)	1,01 (1,01-1,01)	<0,001
FEVD, % (DE)	53,9 (12,3)	48,7 (15,7)	56,5 (9,1)	1,04 (1,02-1,06)	<0,001
RTG, n (%)	79 (18)	46 (30)	33 (12)	1,86 (1,31-2,63)	<0,001
Tratamiento médico ‡					
Beta-bloqueantes, n (%)	322 (55)	189 (85)	133 (37)		<0,001
IECA / ARAII, n (%)	290 (50)	156 (70)	134 (38)		<0,001
Sacubitril-valsartan, n (%)	30 (5)	27 (12)	3 (1)		<0,001
ARM, n (%)	165 (29)	120 (54)	45 (13)		<0,001
Ivabradina, n (%)	45 (8)	31 (16)	14 (4)		<0,001
Diuréticos, n (%)	151 (26)	115 (52)	36 (10)		<0,001
Anticoagulación oral, n (%)	156 (27)	110 (50)	46 (13)		<0,001

Para las variables continuas, el hazard ratio corresponde a un aumento de una unidad de la variable correspondiente con las unidades informadas en la tabla, excepto para FEVI, TAPSE y FEVD, que corresponde a una disminución de una unidad. Por ejemplo: un aumento de 1 año en la edad en el momento del diagnóstico confiere un riesgo adicional de 3% de MACE (la edad se informa en años), y una disminución de 1 mm en TAPSE confiere un riesgo adicional de 10% de MACE (TAPSE se informa en mm).

***AI**: aurícula izquierda. **ARAII**: antagonistas de los receptores de la angiotensina II. **ARM**: antagonistas de los receptores mineralocorticoides. **BRIHH**: bloqueo de rama izquierda del haz de hiss. **CF NYHA**: clase funcional de la New York Heart Association. **DE**: desviación estándar. **DTDVI**: diámetro telediastólico del ventrículo izquierdo. **DTSVI**: diámetro telesistólico del ventrículo izquierdo. **ECG**: electrocardiograma. **FEVD**: fracción de eyección del ventrículo derecho. **FEVI**: fracción de eyección del ventrículo izquierdo. **HR**: Hazard ratio. **IC**: intervalo de confianza. **IECA**: inhibidores de la enzima convertidora de la angiotensina. **IM**: insuficiencia mitral. **IMC**: índice de masa corporal. **MACE**: eventos cardiovasculares adversos mayores. **MC**: miocardiopatía. **MSC**: muerte súbita cardíaca. **PAPS**: presión de la arteria pulmonar sistólica. **RTG**: realce tardío de gadolinio. **TAPSE**: excursión sistólica del anillo tricúspide. **VTDVI**: volumen telediastólico del ventrículo izquierdo. **VTSVI**: volumen telesistólico del ventrículo izquierdo.*

***Entre probandos. †Entre pacientes que se sometieron a estudio genético.**
**‡El momento de prescripción del tratamiento no estaba disponible, por lo que no se analizaron los HR.*

El screening familiar se completó en 253 (58%) probandos, siendo positivo en 106 (42%). La mayoría del resto de casos y/o familiares rechazaron el estudio, o no se pudo realizar por razones logísticas u otros motivos. Se procedió con el estudio genético en 236 (54%) casos índices, y en 99 de ellos (42%) se describió una variante genética patogénica o posiblemente patogénica. Para los familiares, el rendimiento del estudio genético fue superior: 79% de positivos en los 118 casos estudiados. En total, 354 pacientes (61% de la cohorte) fueron estudiados genéticamente, con un 54% de casos mostrando un genotipo positivo. Conviene destacar que el estudio genético se indicó siguiendo los protocolos locales de cada centro y según la sospecha de miocardiopatía, intentando priorizar los casos con más probabilidad pretest y evitando su uso indiscriminado en cualquier individuo con hallazgos morfológicos de NCVI.

Específicamente, las variantes (posiblemente) patogénicas descritas en las probandos incluyeron *MYH7* (19 casos, 19% de todos los estudios genéticos positivos), *TTN* (13, 13%), *MYBPC3* y *ACTC1* (10 cada uno, 10%), así como *DSP*, *LDB3* y *BAG3* (3 cada uno, 3%) (listado completo en la ***Tabla Suplementaria 2***). En total, se describieron variantes sarcoméricas en 60 (61%) de los casos índices y 21 (21%) mostraron un genotipo complejo (***Figura 12***). Las variantes encontradas fueron sinsentido y truncamientos en 61% y 18% de los casos respectivamente.

Las características clínicas, incluyendo edad, sexo, FEVI y RTG, fueron comparables entre la población con genotipo positivo y negativo (***Tabla Suplementaria 3***). Tampoco hubo diferencias en la incidencia de MACE entre los dos grupos (***Tabla 5***).

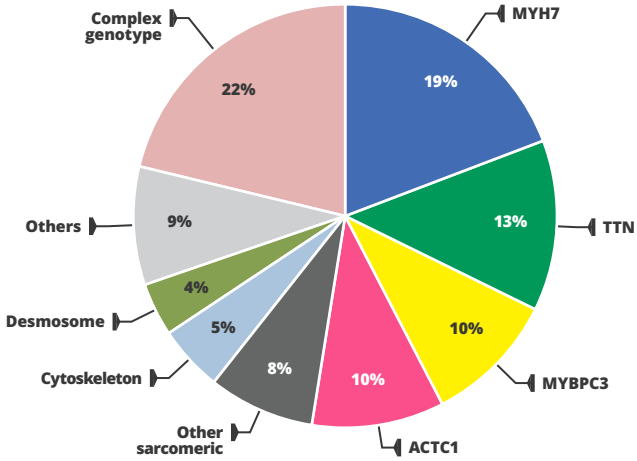


Figura 12: Genotipo de los probandos. Adaptado de Casas *et al* [67].

Tabla 5: Incidencia de eventos cardiovasculares de acuerdo a las variantes genéticas más frecuentemente descritas. Adaptado de Casas *et al* [67].

	Todos los pacientes con estudio genético (n = 354)	Genotipo positivo (n = 192)			*ACTC1* (n = 50)			*MYH7* (n = 42)		
	n (%)	n (%)	HR	p	n (%)	HR	p	n (%)	HR	p
Insuficiencia cardíaca	65 (18)	32 (17)	0,78	0,33	5 (10)	0,33	0,02	5 (12)	0,79	0,61
Arritmias ventriculares	63 (18)	37 (19)	1,14	0,62	12 (24)	0,98	0,96	7 (17)	1,28	0,55
Embolismos sistémicos	8 (2)	3 (2)	0,52	0,37	0 (0)	-	1	1 (2)	1,22	0,85
Mortalidad global	11 (3)	8 (4)	2,00	0,31	3 (6)	1,18	0,81	0 (0)	-	1
MACE	128 (36)	69 (36)	0,87	0,45	17 (34)	0,55	0,02	10 (24)	0,91	0,77
FEVI (ETT), % (media, DE)	50 (17)	50 (18)	-	0,42	62 (14)	-	0,01	47 (17)	-	0,18
RTG	39 (15)	23 (16)	-	0,45	3 (9)	-	0,34	5 (16)	-	0,79

	MYBPC3 (n = 18)			*TTN* (n = 17)			Genotipo complejo (n = 25)		
	n (%)	HR	p	n (%)	HR	p	n (%)	HR	p
Insuficiencia cardíaca	2 (11)	0,64	0,53	5 (29)	2,55	0,05	10 (40)	2,08	0,04
Arritmias ventriculares	3 (17)	0,92	0,89	3 (18)	1,22	0,73	4 (16)	0,66	0,43
Embolismos sistémicos	0 (0)	-	1	1 (6)	3,58	0,24	1 (4)	1,98	0,52
Mortalidad global	0 (0)	-	1	2 (12)	6,15	0,02	1 (4)	0,93	0,95
MACE	6 (33)	0,84	0,69	8 (47)	2,05	0,05	13 (52)	1,20	0,54
FEVI (ETT), % (media, DE)	50 (16)	-	0,90	42 (16)	-	0,04	43 (20)	-	0,04
RTG	6 (50)	-	0,01	1 (7)	-	0,37	4 (20)	.	0,47

***ETT**: ecocardiografía transtorácica. Otras abreviaciones como en **Tabla 4**.*

5.1.2. Insuficiencia cardíaca, arritmias ventriculares, embolismos sistémicos y mortalidad global

Durante un seguimiento mediano de 5,1 (2,3 - 8,1) años, se documentaron los siguientes eventos: 110 (19%) episodios de insuficiencia cardíaca, 87 (15%) arritmias ventriculares, 18 (3%) embolismos sistémicos y 34 (6%) muertes. En total, 223 (38%) pacientes presentaron al menos un MACE, con una tasa de incidencia de 8,92 (IC95% 7,83 – 10,20) eventos por 100 personas-año (listado completo de eventos en la ***Tabla 6***).

Tabla 6: Incidencia de eventos cardiovasculares en no compactación del ventrículo izquierdo. Adaptado de Casas *et al* [67].

Evento	n (%)	Tasa de incidencia, eventos por 100 personas-años (IC 95%)
Insuficiencia cardíaca	**110 (19)**	4,05 (3,36-4,88)
Ingreso por IC	89 (15)	
Implante de TRC	23 (3,9)	
Trasplante cardíaco y/o implante de un DAVI	14 (2,4)	
Arritmias ventriculares	**87 (15)**	2,79 (2,26-3,44)
TV no sostenida	58 (9,9)	
TV sostenida	18 (3,1)	
Descarga apropiada del DAI	15 (2,6)	
MSC / fibrilación ventricular	8 (1,4)	
Embolismos sistémicos	**18 (3,1)**	0,55 (0,35-0,87)
Ictus embólico	12 (2,1)	
AIT embólico	5 (0,9)	
Embolismo arterial periférico	1 (0,2)	
Mortalidad global	**34 (5,8)**	0,98 (0,70-1,37)
Mortalidad cardiovascular	15 (2,6)	
MACE	**223 (38)**	8,92 (7,83-10,20)

***AIT**: accidente isquémico transitorio. **DAI**: desfibrilador automático implantable. **DAVI**: dispositivo de asistencia de ventrículo izquierdo. **IC**: insuficiencia cardiaca. **TRC**: terapia de resincronización cardíaca. **TV**: taquicardia ventricular. Otras abreviaturas como en **Tabla 4**.*

Las características de los pacientes con y sin IC se muestran en la ***Tabla 7***. En el análisis multivariado, la función sistólica del ventrículo izquierdo (FEVI por RMC) (***Figura 13A***), la función sistólica del ventrículo derecho (TAPSE por ETT), la hipertensión arterial y la ausencia de ritmo sinusal se asociaron de forma independiente al evento combinado (***Tabla 8***). El RTG perdió la significación debido a la fuerte colinealidad con la FEVI; sin embargo, en los pacientes con FEVI > 35% se asoció a un riesgo aumentado de IC (***Figura 13B***). En el subgrupo de pacientes con estudio genético, las variantes en *TTN* y el genotipo complejo se asociaron a una mayor incidencia de IC,

mientras que las variantes en *ACTC1* se correlacionaron con un riesgo menor; *MYH7* y *MYBPC3* no se asociaron (***Tabla 5***).

Tabla 7: Características basales de los pacientes con no compactación del ventrículo izquierdo de acuerdo a la ocurrencia de insuficiencia cardíaca y arritmias ventriculares. Adaptado de Casas *et al* [67].

	Todos (n = 585)	Insuficiencia cardíaca (n = 110)				Arritmias ventriculares (n = 87)			
		Sí	No	HR Crudo (IC 95%)	p	Sí	No	HR Crudo (IC 95%)	p
Características clínicas									
Edad al diagnóstico, años (DE)	45 (20)	55 (16)	43 (20)	1,04 (1,02-1,05)	0,000	50 (15)	45 (20)	1,02 (1,01-1,03)	0,001
Sexo masculino, n (%)	334 (57)	67 (61)	267 (56)	1,33 (0,90-1,97)	0,149	60 (69)	274 (55)	1,69 (1,07-2,66)	0,025
Factores de riesgo cardiovascular									
Hipertensión arterial, n (%)	139 (25)	43 (41)	96 (21)	2,83 (1,90-4,21)	0,000	24 (29)	115 (24)	1,28 (0,79-2,06)	0,314
Dislipidemia, n (%)	142 (25)	48 (46)	94 (21)	2,74 (1,86-4,03)	0,000	28 (34)	114 (24)	1,40 (0,88-2,21)	0,154
Diabetes mellitus, n (%)	52 (9)	21 (20)	31 (7)	2,02 (1,40-2,92)	0,000	9 (11)	43 (9)	1,13 (0,65-1,97)	0,658
Electrocardiograma									
Ritmo sinusal, n (%)	503 (91)	73 (73)	430 (96)	0,31 (0,20-0,48)	0,000	68 (85)	435 (93)	0,78 (0,42-1,46)	0,437
QRS, ms (DE)	105 (29)	126 (32)	100 (25)	1,02 (1,02-1,03)	0,000	119 (32)	103 (27)	1,01 (1,00-1,02)	0,001
BRIHH, n (%)	81 (18)	30 (32)	51 (15)	2,54 (1,64-3,92)	0,000	19 (30)	62 (16)	1,99 (1,17-3,41)	0,012
Alteraciones de la repolarización, n (%)	187 (35)	45 (52)	142 (32)	1,96 (1,28-2,98)	0,002	34 (48)	153 (33)	1,52 (0,95-2,42)	0,079
Ecocardiografía									
FEVI, % (DE)	48 (17)	32 (13)	52 (15)	0,93 (0,91-0,94)	0,000	39 (16)	50 (16)	0,97 (0,96-0,98)	0,000
DTDVI, mm (DE)	54 (10)	62 (10)	52 (9)	1,07 (1,05-1,09)	0,000	58 (10)	53 (10)	1,03 (1,01-1,05)	0,001
DTSVI, mm (DE)	38 (11)	50 (13)	36 (10)	1,09 (1,07-1,10)	0,000	44 (13)	37 (11)	1,04 (1,02-1,06)	0,000
TAPSE, mm (DE)	21 (5)	19 (5)	22 (5)	0,92 (0,88-0,96)	0,001	20 (5)	21 (5)	0,96 (0,91-1,02)	0,190
PAPS, mmHg (DE)	34 (13)	42 (14)	31 (11)	1,04 (1,02-1,05)	0,000	35 (11)	34 (13)	1,00 (0,98-1,02)	0,964
Diámetro AI, mm (DE)	39 (9)	45 (9)	37 (8)	1,06 (1,04-1,07)	0,000	42 (9)	38 (9)	1,03 (1,01-1,05)	0,014
Resonancia magnética cardiovascular									
FEVI, % (DE)	51 (16)	34 (16)	54 (14)	0,91 (0,90-0,93)	0,000	44 (18)	52 (15)	0,97 (0,96-0,99)	0,000
VTDVI, ml (DE)	167 (74)	213 (96)	159 (66)	1,01 (1,01-1,01)	0,000	209 (100)	161 (68)	1,01 (1,00-1,01)	0,000
VTSVI, ml (DE)	87 (64)	140 (80)	78 (57)	1,02 (1,01-1,02)	0,000	120 (90)	83 (60)	1,01 (1,00-1,01)	0,000
FEVD, % (DE)	54 (12)	43 (15)	56 (11)	0,91 (0,89-0,94)	0,000	54 (15)	54 (12)	1,00 (0,96-1,04)	0,977
RTG, n (%)	79 (18)	25 (34)	54 (15)	2,33 (1,42-3,82)	0,001	19 (32)	60 (16)	1,98 (1,14-3,44)	0,015

*Abreviaciones como en **Tabla 4***

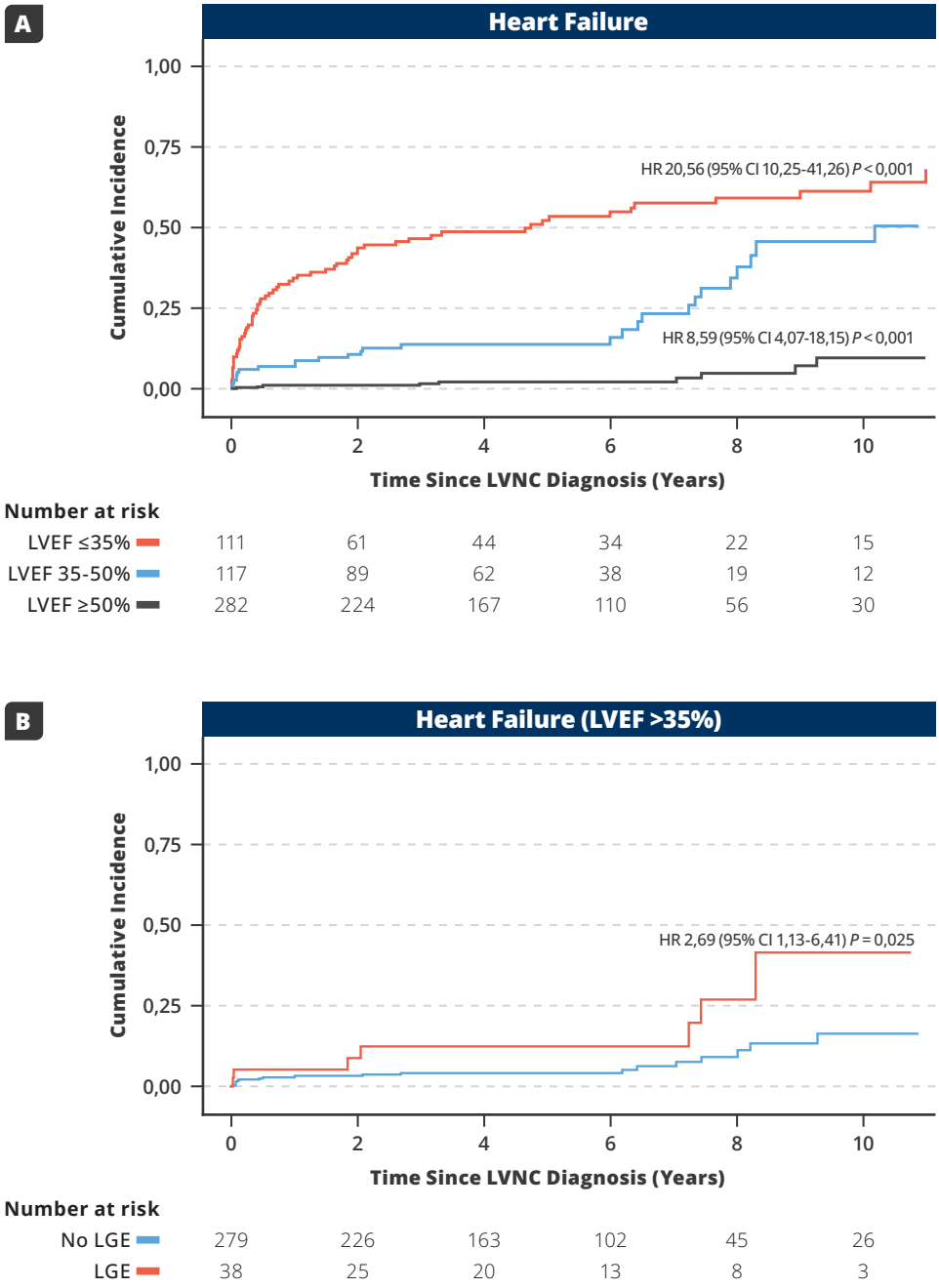


Figura 13: Curvas de Kaplan Meier de incidencia acumulada de insuficiencia cardíaca, estratificadas ***A)*** por la fracción de eyección del ventrículo izquierdo y ***B)*** por la presencia de realce tardío de gadolinio en FEVI > 35%. Adaptado de Casas *et al* [67].

***LGE**: late gadolinium enhancement. Otras abreviaturas como en **Tabla 1** y **Figura 11**.*

Tabla 8: Análisis multivariado de eventos cardiovasculares en no compactación del ventrículo izquierdo. Adaptado de Casas *et al* [67].

Evento	HR ajustado (IC 95%)	p Valor
Insuficiencia cardíaca		
FEVI (RMC) (%)	1,08 (1,04-1,11)	<0,001
TAPSE (ETT) (mm)	1,16 (1,05-1,28)	0,005
Hipertensión arterial	3,28 (1,29-8,31)	0,012
No ritmo sinusal	2,64 (1,03-2,14)	0,043
Edad (años)	1,00 (0,97-1,03)	0,963
Sexo masculino	0,71 (0,31-1,62)	0,420
RTG	0,42 (0,17-1,03)	0,058
VTDVI (RMC) (ml)	1,00 (0,99-1,01)	0,902
BRIHH	1,13 (0,47-2,75)	0,782
Arritmias ventriculares		
FEVI (RMC) (%)	1,03 (1,00-1,06)	0,033
Edad (años)	1,00 (0,97-1,03)	0,957
Sexo masculino	1,34 (0,59-3,03)	0,479
RTG	1,58 (0,66-3,76)	0,301
TAPSE (ETT) (mm)	1,00 (0,90-1,10)	0,937
QRS (ms)	1,00 (0,99-1,02)	0,783
Embolismos sistémicos		
FEVI (ETT) (%)	1,04 (1,00-1,08)	0,049
Diámetro AI (ETT) (mm)	1,06 (1,01-1,11)	0,014
Mortalidad global		
Edad (años)	1,07 (1,04-1,10)	<0,001
Sexo masculino	3,84 (1,42-10,34)	0,008
FEVI (ETT) (%)	0,99 (0,97-1,02)	0,516
Hipertensión arterial	1,38 (0,62-3,09)	0,431
Dislipidemia	1,57 (0,74-3,33)	0,245
Diabetes mellitus	1,48 (0,72-3,05)	0,290
MACE		
FEVI (RMC)		
FEVI ≥ 50%	1	
FEVI 35 – 50%	1,65 (1,16-2,37)	0,006
FEVI ≤ 35%	2,60 (1,74-3,89)	<0,001
Edad		
≤ 35 años	1	
36 – 54 años	1,96 (1,26-3,05)	0,003
≥ 55 años	2,71 (1,72-4,29)	<0,001
ECG anormal	1,49 (1,01-2,20)	0,047
Factores de riesgo cardiovascular	1,37 (0,99-1,89)	0,054
Miocardiopatía no compactada	1,54 (0,95-2,48)	0,079
Sexo masculino	1,29 (0,96-1,73)	0,089

***ECG anormal**: ausencia de ritmo sinusal y/o presencia de QRS ancho y/o alteraciones de la repolarización. Miocardiopatía no compactada: agregación familiar y/o FEVI < 50%. **RMC**: resonancia magnética cardiovascular. Otras abreviaturas como en la **Tabla 4** y **5**.*

Las características de los pacientes con y sin AV se muestran en la ***Tabla 7***. En el análisis multivariado, la función sistólica del ventrículo izquierdo (FEVI por RMC) fue la única variable asociada al evento combinado (***Tabla 8***). Comparado con los pacientes con FEVI ≥ 50%, aquellos con FEVI ≤ 35% presentaron un riesgo aumentado de AV (***Figura 14A***). Sin embargo, 47 (54%) eventos arrítmicos (incluyendo 8

casos de fibrilación ventricular y 8 de taquicardia ventricular sostenida) ocurrieron en pacientes con FEVI > 35%; en este subgrupo de pacientes el RTG se asoció de forma potente a una mayor incidencia de AV (***Figura 14B***). En el subgrupo de pacientes con estudio genético, las variantes de *ACTC1* así como las del desmosoma y citoesqueleto se asociaron a las AV después de ajustar por la FEVI (***Tabla 5***).

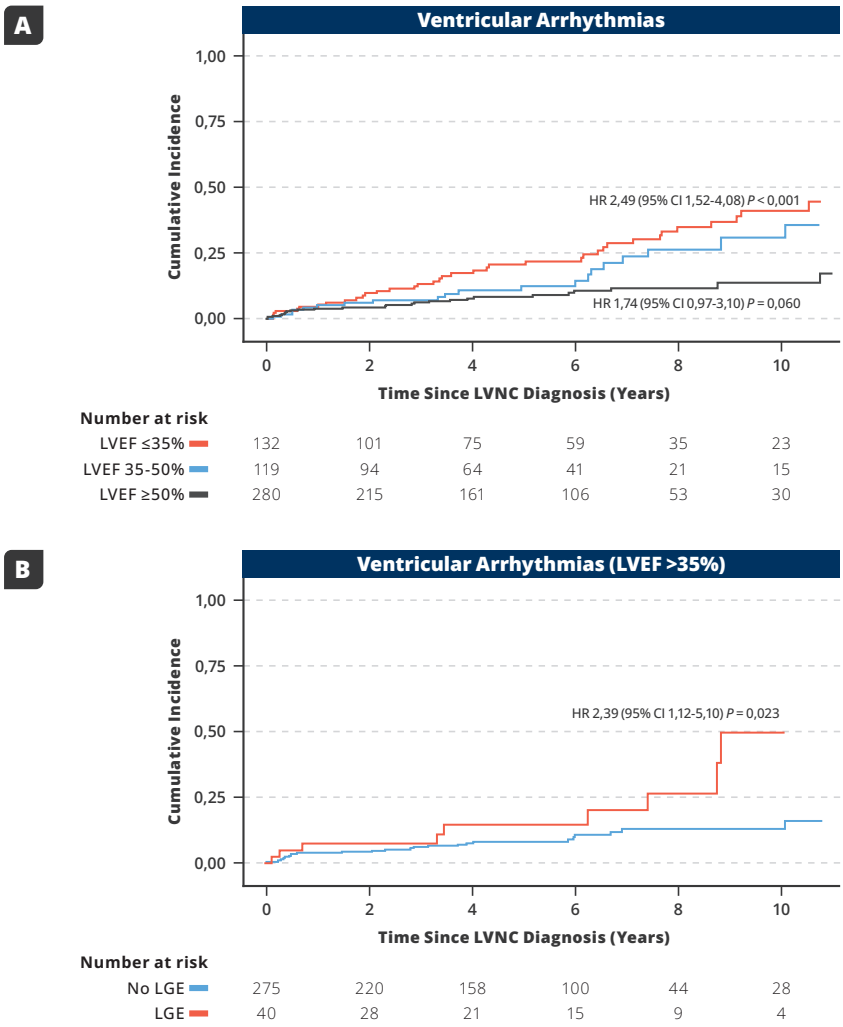


Figura 14: Curvas de Kaplan Meier de incidencia acumulada de arritmias ventriculares, estratificadas ***A)*** por la fracción de eyección del ventrículo izquierdo y ***B)*** por la presencia de realce tardío de gadolinio en FEVI > 35%. Adaptado de Casas *et al* [67].

*Abreviaciones como en **Tabla 1**, **Figura 11** y **13**.*

En lo que respecta a las ES, las características basales según la ocurrencia del evento se muestran en el Anexo (***Tabla Suplementaria 4***). En el análisis multivariado, las variables que se asociaron fueron la función sistólica del ventrículo izquierdo (FEVI) y el diámetro anteroposterior de la aurícula izquierda (ambas mediciones por ETT) (***Tabla 8***). Las características de los pacientes que fallecieron se muestran en el Anexo (***Tabla Suplementaria 4***); la supervivencia global a 5 años fue del 96% (***Figura 15***). En el análisis multivariado, la edad y el sexo masculino fueron las variables que se asociaron con la mortalidad global (***Tabla 8***), mientras que la FEVI fue el único predictor de mortalidad cardiovascular (HR 1,05, IC95% 1,03 – 1,07, p = 0,02). Las variantes en *TTN* se asociaron a una mayor mortalidad entre los pacientes con estudio genético (***Tabla 5***).

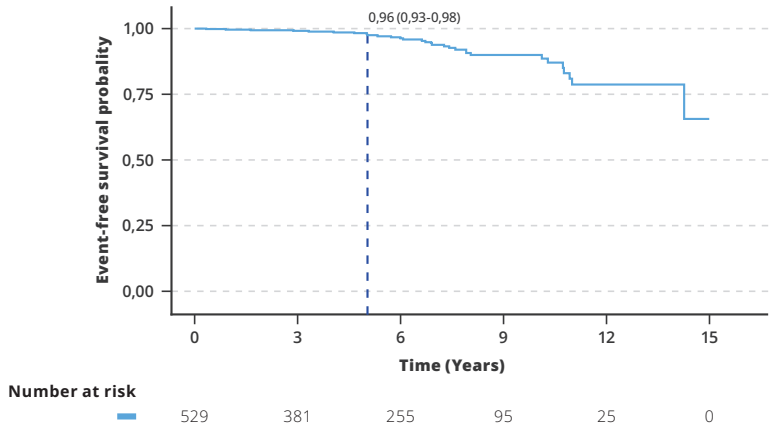


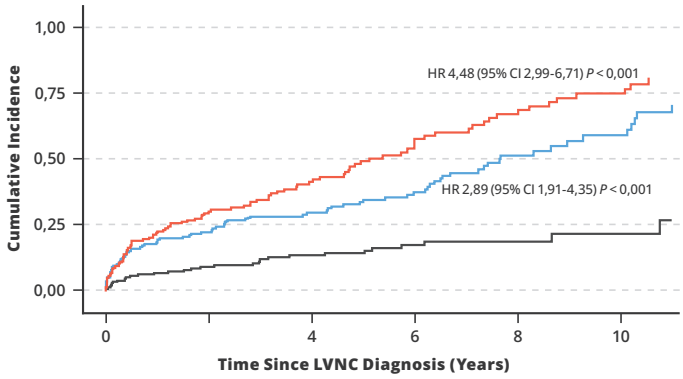
Figura 15: Curva de Kaplan Meier de supervivencia libre de mortalidad por cualquier causa

5.1.3. Desarrollo y validación de un modelo predictivo de riesgo para MACE

En el seguimiento, 223 (38%) pacientes presentaron al menos un MACE; en la ***Tabla 4*** se muestran sus características basales. Cabe destacar que los pacientes con MACE tenían una edad más avanzada, una mayor carga de factores de riesgo cardiovascular, una mayor prevalencia de alteraciones electrocardiográficas y una mayor afectación estructural tanto por ETT como por RMC (dimensiones y función sistólica biventricular y RTG entre otros).

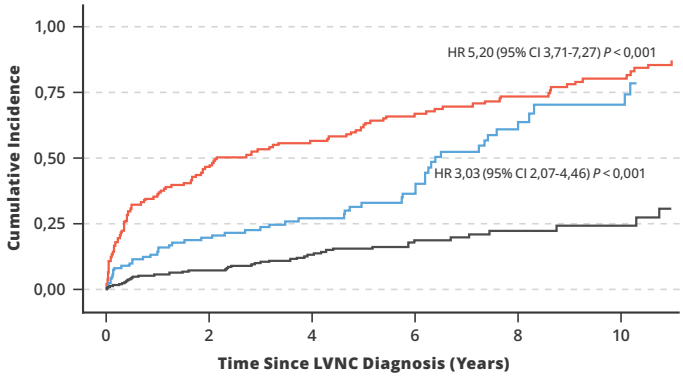
En el análisis multivariado, la función sistólica del ventrículo izquierdo (FEVI por RMC), la edad y la presencia de un ECG anormal (ausencia de ritmo sinusal, QRS ancho y/o alteraciones de la repolarización) se asociaron de forma independiente al riesgo de MACE. La FEVI y la edad se estratificaron para facilitar la aplicabilidad clínica del modelo predictivo: la FEVI según las guías de práctica clínica (ver métodos) y la edad por terciles. A pesar de que no alcanzaron la significación estadística, el sexo masculino, la presencia de factores de riesgo cardiovascular y la MCNC (agregación familiar y/o FEVI < 50%) se incluyeron en el modelo final de acuerdo a sus implicaciones clínicas (***Tabla 8***, ***Figura 16***).

A



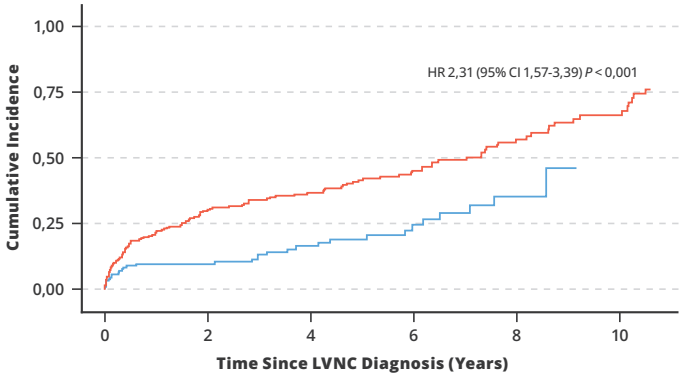
Number at risk						
Age ≤35 y	180	145	108	70	35	19
Age 36-54 y	184	124	94	65	29	20
Age ≥55 y	183	102	64	35	23	14

B



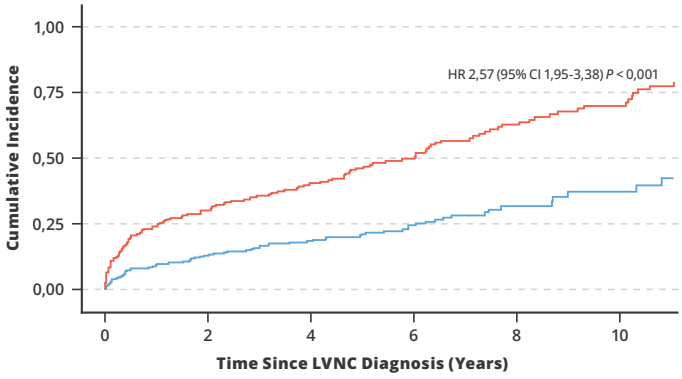
Number at risk						
LVEF ≤35%	140	72	53	38	25	17
LVEF 35-50%	122	85	56	33	14	8
LVEF ≥50%	285	214	157	99	48	28

C



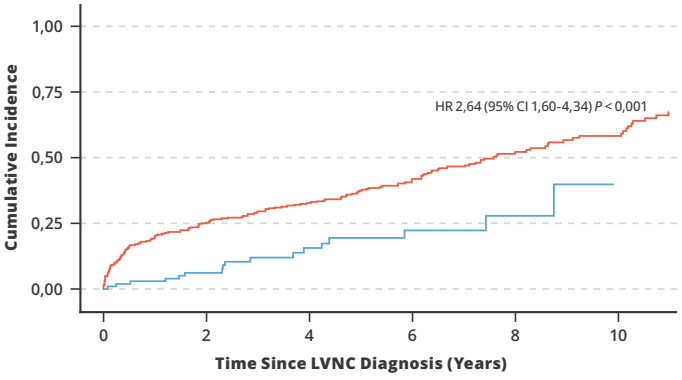
Number at risk						
Abnormal ECG	251	153	112	73	41	23
Normal ECG	158	112	72	39	11	4

D



Number at risk						
CVRF	320	231	168	106	46	26
No CVRF	227	140	98	64	41	27

E



Number at risk						
No NCCM	104	71	46	27	11	3
NCCM	400	271	196	134	71	48

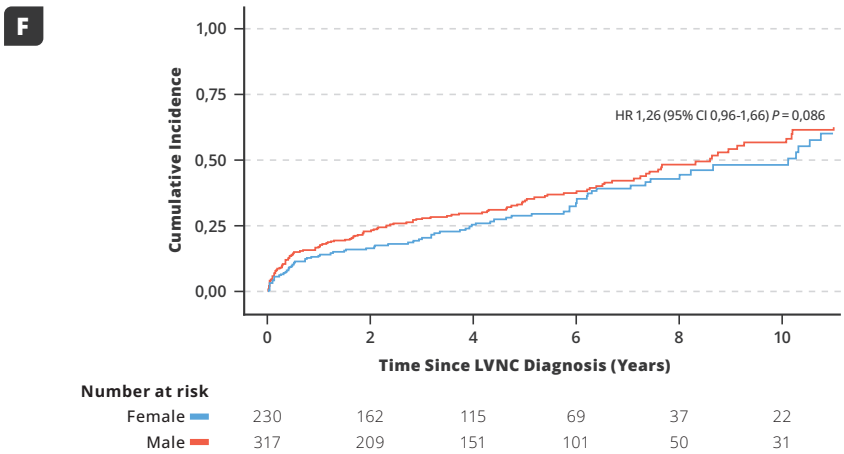


Figura 16: Curvas de Kaplan Meier de incidencia acumulada de MACE, estratificadas ***A)*** por la edad, ***B)*** por la fracción de eyección del ventrículo izquierdo, ***C)*** por la presencia de un ECG anormal, ***D)*** por factores de riesgo cardiovascular, ***E)*** por miocardiopatía no compactada y ***F)*** por el sexo. Adaptado de Casas *et al* [67].

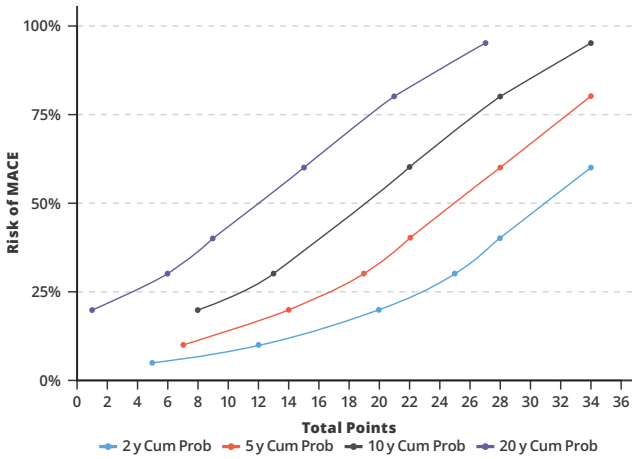
***CVRF**: cardiovascular risk factors; **NCCM**: noncompaction cardiomyopathy.*
*Otras abreviaciones como en **Tabla 1** y **Figura 11**.*

A partir de las variables mencionadas en el análisis por regresión de Cox, se desarrolló un modelo predictivo de riesgo con el objetivo de mejorar la estratificación pronóstica en la NCVI. Se asignó una puntuación a cada variable de acuerdo a sus coeficientes de asociación (***Figura 17A***) (también disponible online; https://www.lvnc-riskscore.com), de manera que la puntuación total se correlacionó con el riesgo de MACE a lo largo del seguimiento (***Figura 17B***). El modelo presentó una buena capacidad discriminativa con un índice C de Harrell (corregido por optimismo) de 0,72 (IC95% 0,67 – 0,75) y una buena calibración, con una concordancia adecuada entre el riesgo observado y el riesgo predicho (pendiente de calibración de 0,96, IC95% 0,66 – 1,20). La estimación del riesgo a 2 y 5 años de seguimiento fue correcta (***Figura 17C***). A continuación, se dividió a la cohorte en terciles de puntuación, de manera que comparados con los pacientes de bajo riesgo (< 12 puntos), los de riesgo intermedio (12 – 20 puntos) y especialmente los de alto riesgo (> 20 puntos) presentaron una mayor incidencia de MACE (***Figura 17D***).

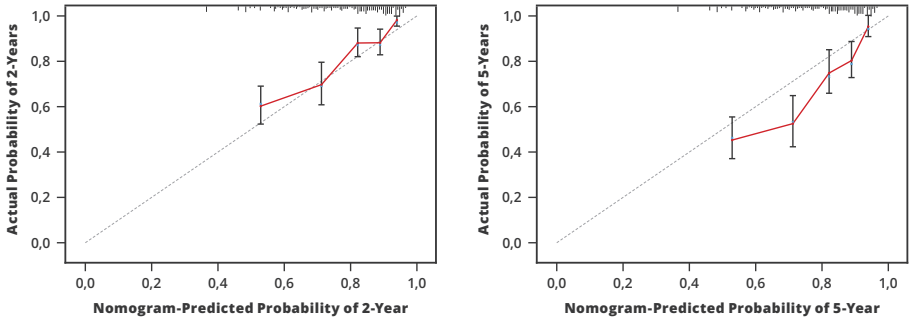
A

Age (years)	Points	Abnormal ECG	Points
≤35	0	N	0
		Y	4
36-54	7	CV Risk Factors	Points
		N	0
≥55	10	Y	3
LVEF (%)	Points	NCCM	Points
≥50	0	N	0
		Y	4
35-50	5	Gender	Points
		Men	3
≤35	10	Women	0

B



C



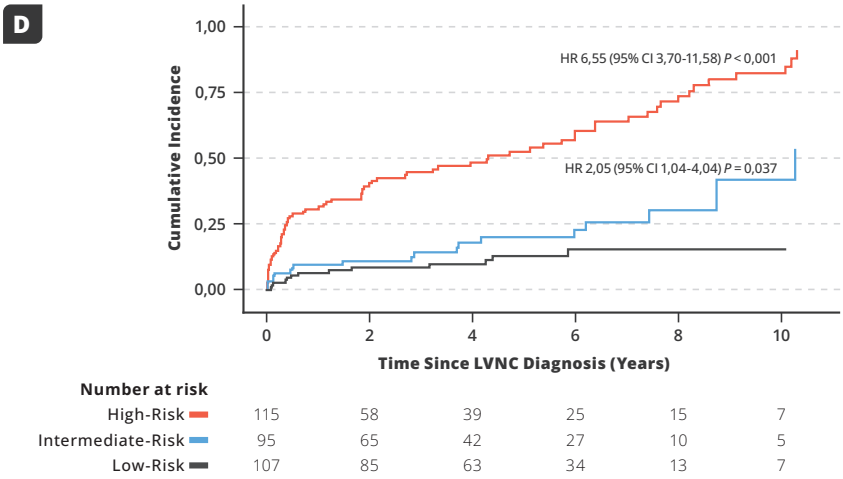


Figura 17: ***A)*** Modelo predictivo de MACE: se muestra la puntuación correspondiente al valor de cada variable. ***B)*** Riesgo de presentar un MACE a lo largo del seguimiento según la puntuación total del modelo predictivo. ***C)*** Nomogramas que muestran la probabilidad predicha de MACE a 2, 5, 10 y 20 años de seguimiento, en comparación con la probabilidad observada. ***D)*** Curvas de Kaplan Meier de incidencia acumulada de MACE, estratificadas por grupos de riesgo del modelo predictivo. Adaptado de Casas *et al* [67].

El modelo de riesgo fue validado en una cohorte externa de 113 pacientes con un seguimiento medio de 2,0 ± 1,0 años y un total de 36 (32%) MACE. Aunque había ciertas diferencias entre las dos poblaciones, notablemente un menor tamaño de la cohorte externa, las características basales eran mayoritariamente comparables (***Tabla 9***). En la cohorte de validación, el modelo predictivo siguió presentando una buena capacidad discriminativa, superponible a la de la cohorte de derivación (índice C de Harrell de 0,72, IC95% 0,71 – 0,73), y una buena calibración (pendiente de calibración 1,04, IC95% 0,80 – 1,28). El modelo también permitió identificar en la cohorte de validación a los pacientes de bajo y alto riesgo, siendo el subgrupo de riesgo intermedio más similar al de bajo riesgo en esta población (***Figura 18***).

Tabla 9: Comparación de las características basales de la cohorte de derivación y de validación. Adaptado de Casas *et al* [67].

	Cohorte de derivación (n = 585)	Cohorte de validación (n = 113)	p Valor	Diferencias estandarizadas
Edad al diagnóstico, años (DE)	45 (20)	43 (18)	0.321	
Sexo masculino, n (%)	334 (57)	70 (62)	0.394	0.099 [-0.102-0.3]
Factores de riesgo cardiovascular, n (%)	279 (48)	46 (41)	0.208	0.141 [-0.061-0.343
ECG anormal, n (%)	271 (62)	46 (41)	<0.001	0.436 [0.234-0.639]
FEVI, % (DE)	48 (17)	45 (15)	0.102	
Miocardiopatía no compactada	462 (79)	67 (59)	<0.001	0.436 [0.233-0.639]

**ECG anormal: ausencia de ritmo sinusal y/o presencia de QRS ancho y/o alteraciones de la repolarización. *Miocardiopatía no compactada: agregación familiar y/o FEVI < 50%.*

*Abreviaciones como en **Tabla 4**.*

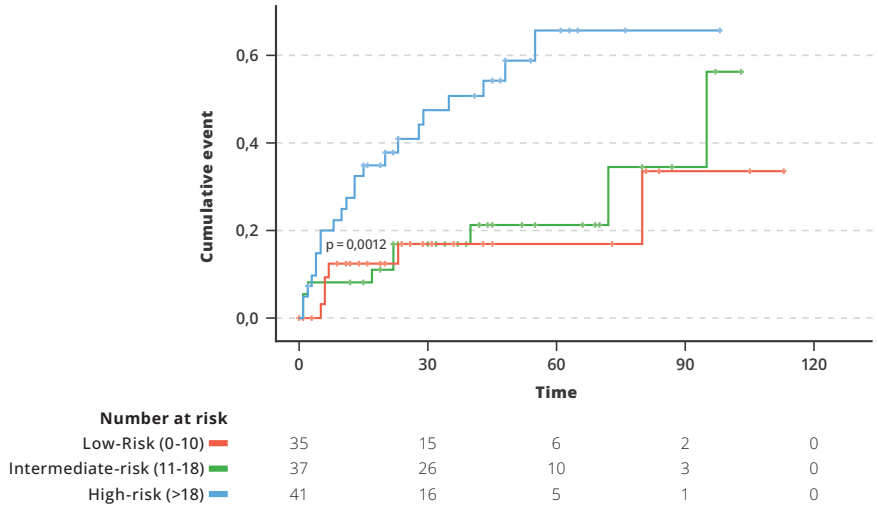


Figura 18: Curvas de Kaplan Meier de incidencia acumulada de MACE, estratificadas por grupos de riesgo del modelo predictivo en la cohorte de validación. Adaptado de Casas *et al* [67]

5.1.4. Algoritmo de bajo riesgo

Una vez demostradas las variables que se asocian al riesgo de eventos cardiovasculares y de haber desarrollado y validado un modelo predictivo de riesgo, se diseñó un algoritmo para intentar identificar a los pacientes de muy bajo riesgo que, a priori, serían sugestivos de no presentar una miocardiopatía asociada. Se utilizaron las mismas variables del modelo previo (ECG, FEVI y agregación familiar), incluyendo además el RTG debido a sus implicaciones pronósticas ampliamente reconocidas (***Figura 19***).

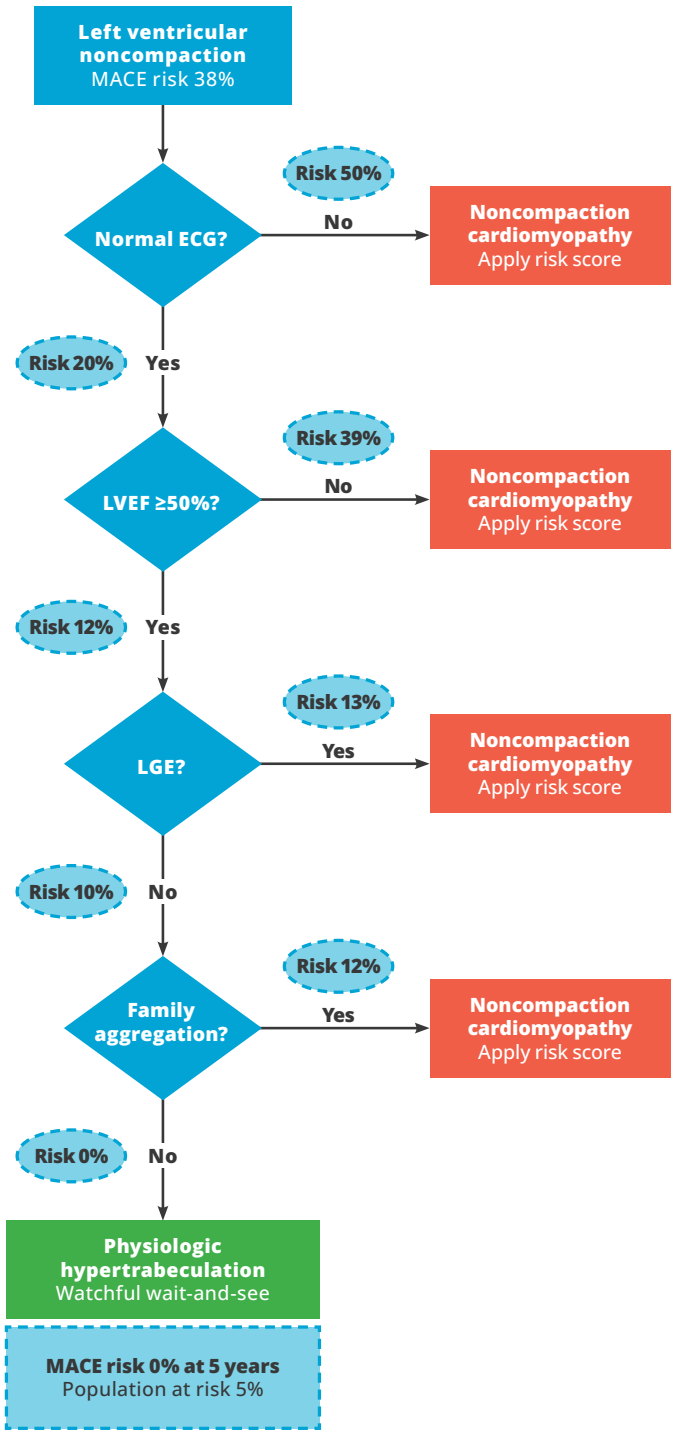


Figura 19: Algoritmo de seguridad en no compactación del ventrículo izquierdo. Adaptado de Casas *et al* [67].

*Abreviaciones como en **Tabla 1** y **Figura 13**.*

De esta manera, un individuo con hallazgos morfológicos de NCVI pero con un ECG normal (ritmo sinusal, QRS estrecho, sin alteraciones de la repolarización), con función sistólica preservada (FEVI ≥ 50%), sin fibrosis miocárdica y sin agregación familiar, no presentó ningún evento a un seguimiento mediano de 5,1 años (riesgo 0% basado en los riesgos observados en nuestra cohorte). Es decir, la NCVI sin ningún otro signo de alarma presenta un pronóstico excelente, sugiriendo que posiblemente se trata de una hipertrabeculación fisiológica o rasgo morfológico aislado, no asociado a una miocardiopatía. En cambio, un paciente con alteraciones en cualquiera de las categorías mencionadas previamente presentó un riesgo claramente mayor de eventos adversos, correspondiendo probablemente a casos de hipertrabeculación patológica asociada a una miocardiopatía (***Figura 19***).

5.2. RESULTADOS DEL SEGUNDO ESTUDIO: DETERIORO DE LA FRACCIÓN DE EYECCIÓN DEL VENTRÍCULO IZQUIERDO Y SU RELACIÓN CON EVENTOS CARDIOVASCULARES EN LA NO COMPACTACIÓN DEL VENTRÍCULO IZQUIERDO

5.2.1. Características basales

Inicialmente se habían reclutado 592 pacientes para el primer estudio, de los cuales 7 (1,2%) se habían excluido por falta de datos clínicos, y 8 (1,4%) se excluyeron del presente estudio por ausencia de información sobre la FEVI al final del seguimiento. Por tanto, finalmente se incluyeron 577 pacientes en este segundo estudio (***Figura 20***; ***Tabla 2***). Las características basales son prácticamente idénticas al primer estudio y se muestran en la ***Tabla 10***.

5.2.2. Deterioro de la FEVI y MACE

El seguimiento ecocardiográfico mediano fue de 4,3 (2,0 – 7,1) años, con una FEVI final del 49 ± 15%. Durante este período, 34 (6%) pacientes desarrollaron un deterioro de la FEVI. Las características de los pacientes con y sin disfunción sistólica progresiva se detallan en la ***Tabla 10***.

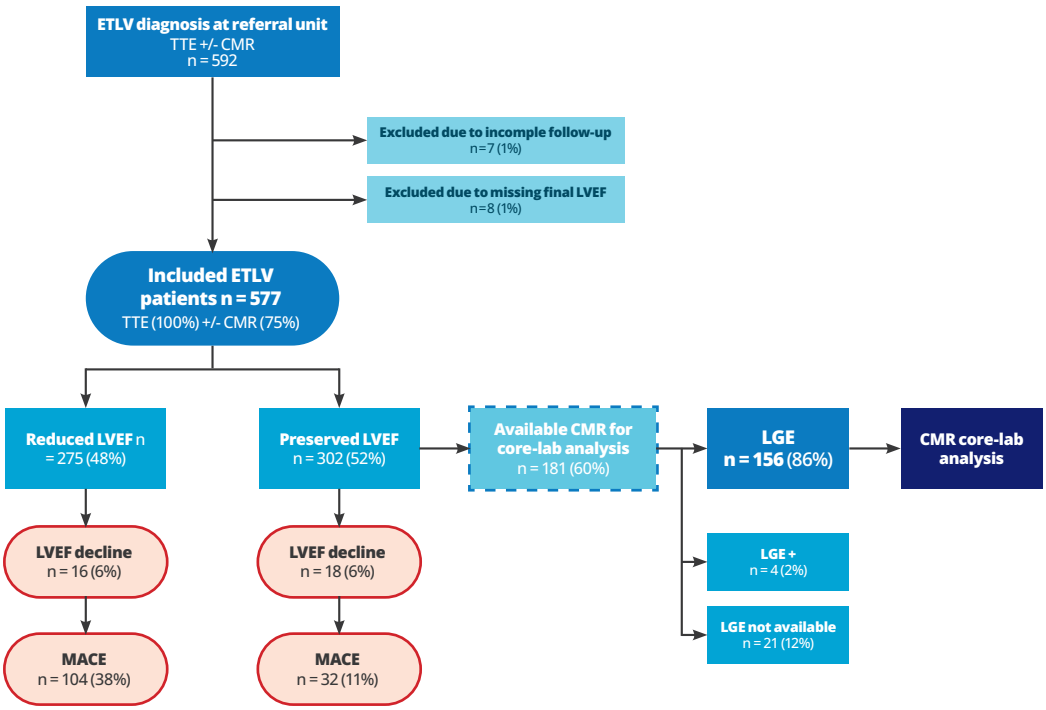


Figura 20: Diagrama de flujo del segundo estudio.

***ETLV**: excessive trabeculation of the left ventricle. Otras abreviaciones como en **Tabla 1** y **Figura 13**.*

En el análisis multivariado, el RTG y la presencia de FA en el ECG basal resultaron ser los únicos factores de riesgo independientes para el deterioro de la FEVI (***Tabla 11***, ***Figura 21A-B***). El modelo se confirmó mediante un análisis por *backward stepwise regression* que mostró que las mismas dos variables mantenían la asociación estadísticamente significativa con el evento (***Tabla 11***). El modelo tuvo una buena capacidad discriminativa para predecir el deterioro de la FEVI con un índice C de Harrell de 0,79 (IC95% 0,74 – 0,84). Los pacientes en ritmo sinusal y sin RTG presentaron un riesgo bajo de desarrollar disfunción sistólica progresiva, mientras que aquellos en FA basal y con RTG mostraron una incidencia significativamente mayor de eventos ($p < 0,001$) (***Figura 21C***).

Tabla 10: Características basales de los pacientes con no compactación del ventrículo izquierdo de acuerdo a la ocurrencia de deterioro de la FEVI

	Cohorte global (n = 577)	Deterioro de la FEVI (n = 34)	No deterioro de la FEVI (n = 543)	HR crudo (IC 95%)	p Valor
Características clínicas					
Edad al diagnóstico, años (DE)	45 (20)	51 (21)	45 (20)	1,02 (1,00-1,04)	0,032
Sexo femenino, n (%)	245 (43)	12 (35)	233 (43)	0,74 (0,37-1,50)	0,406
Probando, n (%)	433 (75)	28 (82)	405 (75)	1,93 (0,80-4,66)	0,146
Screening familiar positivo, n (% de probandos)	106 (42)	8 (44)	98 (42)	1,07* (0,42-2,72)	0,891
Genotipo positivo, n (% de probandos con estudio genético)	99 (42)	8 (57)	91 (41)	0,57† (0,20-1,64)	0,295
Factores de riesgo cardiovascular					
Hipertensión arterial, n (%)	136 (24)	13 (38)	123 (24)	1,90 (0,95-3,79)	0,071
Dislipidemia, n (%)	141 (25)	14 (41)	127 (24)	2,15 (1,08-4,25)	0,029
Diabetes mellitus, n (%)	50 (9)	7 (21)	43 (8)	2,63 (1,14-6,04)	0,023
Tabaquismo, n (%)	76 (19)	3 (14)	73 (20)	0,97 (0,28-3,31)	0,955
IMC, kg/m² (DE)	25 (5)	26 (6)	25 (5)	1,02 (0,95-1,10)	0,549
Electrocardiograma					
Ritmo sinusal, n (%)	495 (91)	26 (77)	469 (92)	0,33 (0,15-0,74)	0,007
QRS, ms (DE)	105 (28)	119 (31)	104 (28)	1,01 (1,00-1,02)	0,015
QRS ≥120 ms, n (%)	155 (35)	15 (52)	140 (34)	1,76 (0,85-3,67)	0,128
BRIHH, n (%)	80 (18)	5 (17)	75 (18)	0,86 (0,33-2,25)	0,754
Ecocardiografía					
FEVI, % (DE)	48 (17)	47 (15)	48 (17)	0,99 (0,97-1,01)	0,473
iDTDVI, mm/m² (DE)	29,6 (5,4)	30,7 (5,4)	29,6 (5,4)	1,03 (0,97-1,09)	0,360
iDTSVI, mm/m² (DE)	20,7 (6,3)	23,0 (6,2)	20,6 (6,3)	1,06 (1,01-1,11)	0,030
TAPSE, mm (DE)	21 (5)	22 (5)	21 (5)	1,06 (0,96-1,16)	0,255
PAPS, mmHg (DE)	34 (12)	44 (14)	33 (12)	1,06 (1,02-1,10)	0,007
Diámetro AI, mm (DE)	39 (9)	40 (11)	39 (9)	1,01 (0,98-1,05)	0,492
Disfunción diastólica grado ≥ 2, n (%)	63 (22)	8 (44)	55 (20)	2,98 (1,17-7,56)	0,022
FEVI final seguimiento, % (DE)	49 (15)	31 (13)	50 (14)	-	-
Resonancia magnética cardiovascular					
FEVI, % (DE)	51 (16)	44 (17)	51 (16)	0,97 (0,95-0,99)	0,005
iVTDVI, ml/m² (DE)	92 (41)	106 (55)	91 (39)	1,01 (1,00-1,02)	0,014
iVTSVI, ml/m² (DE)	48 (35)	62 (49)	47 (34)	1,01 (1,00-1,02)	0,004
iVEVI, ml/m² (DE)	43 (15)	44 (14)	43 (15)	1,00 (0,97-1,03)	0,899
FEVD, % (DE)	54 (12)	53 (12)	54 (12)	0,98 (0,93-1,02)	0,323
iVTDVD, ml/m² (DE)	78 (27)	71 (20)	79 (27)	0,99 (0,96-1,01)	0,394
iVTSVD, ml/m² (DE)	38 (19)	34 (13)	38 (19)	0,99 (0,96-1,03)	0,733
RTG, n (%)	79 (18)	12 (50)	67 (16)	4,85 (2,17-10,80)	<0,001
Tratamiento médico ‡					
Beta-bloqueantes, n (%)	319 (56)	18 (52)	301 (56)	-	-
IECA / ARAII, n (%)	286 (50)	11 (32)	275 (52)	-	-
Sacubitril-valsartan, n (%)	30 (5)	3 (8)	27 (5)	-	-
ARM, n (%)	162 (28)	7 (20)	155 (29)	-	-
Ivabradina, n (%)	42 (8)	4 (11)	38 (8)	-	-
Diuréticos, n (%)	147 (26)	10 (30)	137 (25)	-	-
Anticoagulación oral, n (%)	155 (27)	11 (33)	144 (27)	-	-

**Entre probandos. †Entre pacientes que se sometieron a estudio genético.*
‡El momento de prescripción del tratamiento no estaba disponible, por lo que no se analizaron los HR.

***iDTDVI**: diámetro telediastólico del ventrículo izquierdo indexado por superficie corporal. **iDTSVI**: diámetro telesistólico del ventrículo izquierdo indexado por superficie corporal. **iVEVI**: volumen eyectivo del ventrículo izquierdo indexado por superficie corporal. **iVTDVD**: volumen telediastólico del ventrículo derecho indexado por superficie corporal. **iVTDVI**: volumen telediastólico del ventrículo izquierdo indexado por superficie corporal. **iVTSVD**: volumen telesistólico del ventrículo derecho indexado por superficie corporal. **iVTSVI**: volumen telesistólico del ventrículo izquierdo indexado por superficie corporal. Otras abreviaturas como en la **Tabla 4**.*

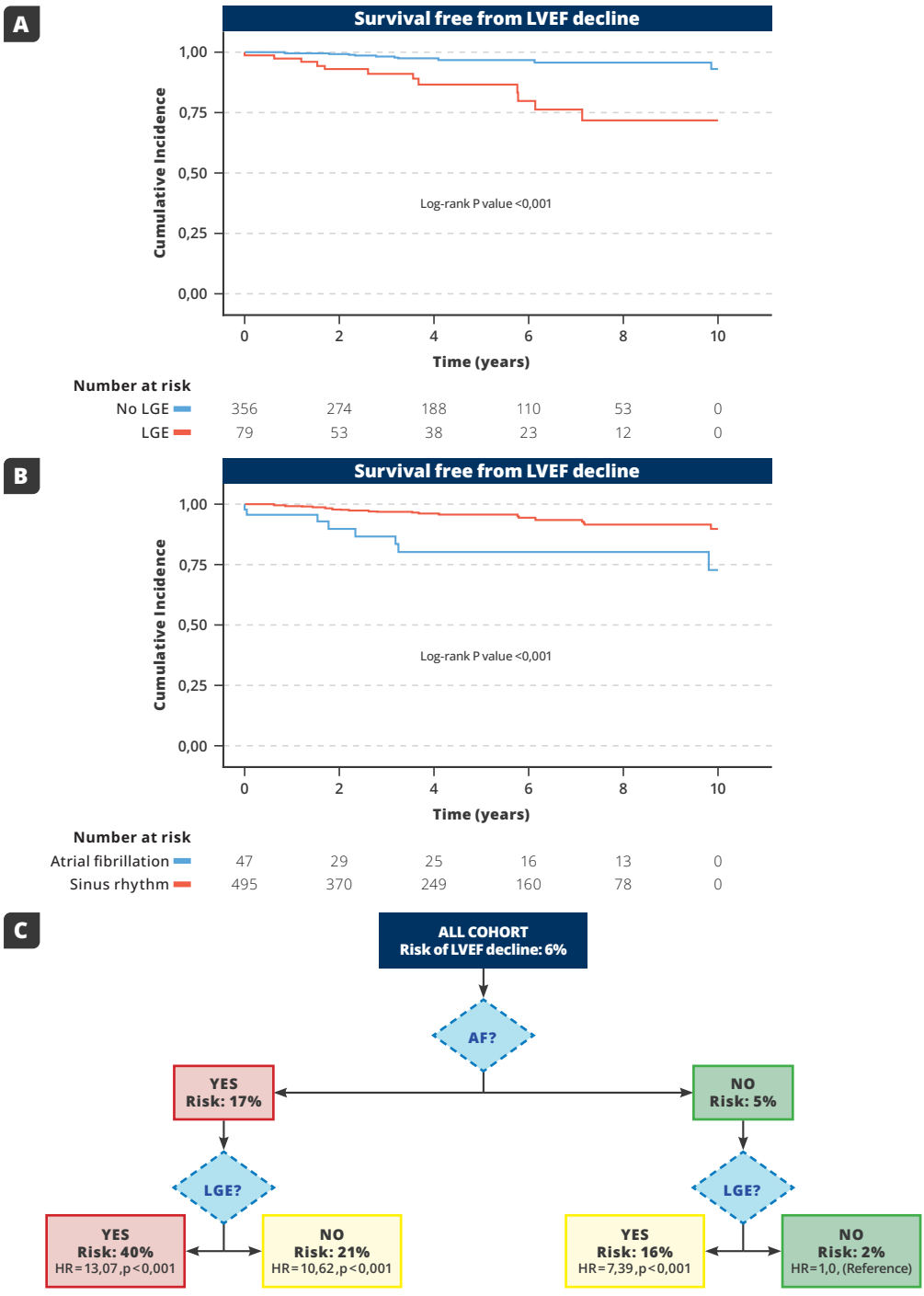


Figura 21: Curvas de Kaplan Meier de supervivencia libre de deterioro de la FEVI, estratificadas por la presencia de ***A)*** realce tardío de gadolinio y ***B)*** ritmo sinusal. ***C)*** Algoritmo de riesgo de deterioro de la FEVI.

*AF: atrial fibrillation. Otras abreviaciones como en **Tabla 1** y **Figura 13**.*

Tabla 11: Análisis multivariado del deterioro de la FEVI y de MACE en no compactación del ventrículo izquierdo

Evento	HR ajustado (IC 95%)	p Valor
Deterioro de FEVI (modelo 1)		
Edad (años)	1,00 (0,98 – 1,03)	0,782
Dislipidemia	1,22 (0,48 – 3,12)	0,669
Diabetes mellitus	1,85 (0,50 – 6,89)	0,359
Fibrilación auricular	4,00 (1,49 – 11,11)	<0,001
Realce tardío de gadolinio	4,60 (1,97 – 10,72)	0,006
Deterioro de FEVI (modelo 2)		
Fibrilación auricular	4,35 (1,69 – 11,11)	0,002
Realce tardío de gadolinio	4,78 (2,12 – 10,78)	<0,001
MACE (modelo 1)		
Edad (años)	0,98 (0,96 – 1,00)	0,104
Sexo masculino	1,23 (0,63 – 2,40)	0,546
Probando	1,14 (0,45 – 2,86)	0,785
Hipertensión arterial	0,56 (0,27 – 1,25)	0,164
Dislipidemia	1,02 (0,50 – 2,09)	0,951
Diabetes mellitus	2,41 (0,91 – 6,42)	0,078
IMC (kg/m^2)	1,02 (0,96 – 1,09)	0,491
Fibrilación auricular	2,50 (1,04 – 5,88)	0,039
QRS ≥ 120 ms	2,33 (1,21 – 4,49)	0,011
FEVI (%)	0,95 (0,92 – 0,98)	<0,001
iDTDVI (mm/m^2)	1,02 (0,98 – 1,06)	0,393
Diámetro AI (mm)	1,00 (0,96 – 1,03)	0,867
Realce tardío de gadolinio	1,20 (0,57 – 2,51)	0,637
Deterioro de la FEVI	3,19 (1,24 – 8,23)	0,016
MACE (modelo 2)		
Fibrilación auricular	2,22 (1,05 – 4,54)	0,037
QRS ≥ 120 ms	2,10 (1,15 – 3,84)	0,016
FEVI (%)	0,95 (0,93 – 0,97)	<0,001
Deterioro de la FEVI	2,68 (1,11 – 6,45)	0,028

***Modelo 1**: análisis de regresión de Cox multivariado incluyendo todas las variables con una p < 0,05 en el análisis univariado. **Modelo 2**: análisis de regresión de Cox multivariado con eliminación hacia atrás (backward stepwise regression). Abreviaturas como en la **Tabla 4** y **10**.*

Posteriormente al evento ecocardiográfico, los pacientes realizaron un seguimiento clínico mediano de 3,8 (1,7 – 6,3) años. Durante este período, 136 (24%) pacientes experimentaron al menos un MACE: 65 (11%) eventos de insuficiencia cardíaca, 70 (12%) arritmias ventriculares, 14 (2%) embolias sistémicas y 33 (6%) muertes. La tasa de incidencia fue de 9,15 (IC95% 7,22 – 11,60) eventos por 100 personas-año. Un total de 16 (47%) pacientes con un deterioro previo de la FEVI desarrollaron posteriormente un MACE, en comparación con 120 (22%) de aquellos sin cambios en la FEVI (p <0,001). De hecho, el deterioro de la FEVI confirió un riesgo tres veces mayor de MACE (HR 2,99, IC95% 1,77 – 5,06, p < 0,001), y una cuarta parte de estos eventos ocurrieron dentro de los dos meses posteriores al deterioro de la FEVI. Otras características de los pacientes con y sin MACE se describen en el Anexo (***Tabla Suplementaria 5***).

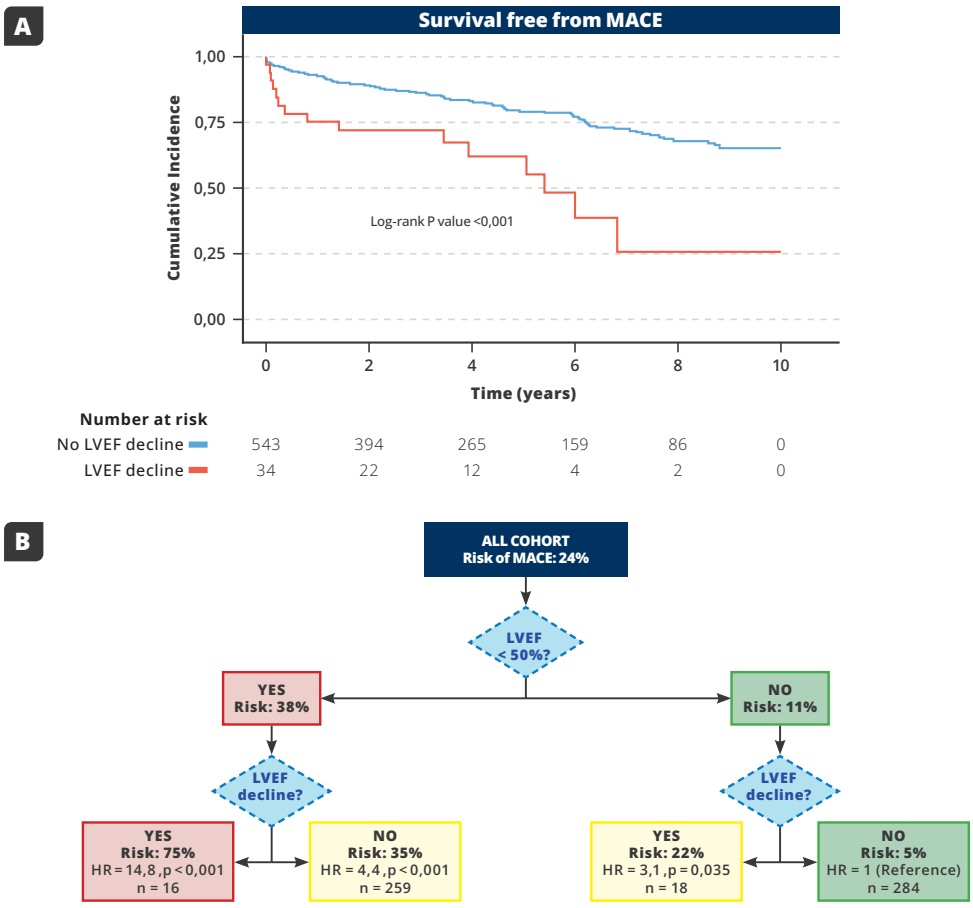


Figura 22: ***A)*** Curvas de Kaplan Meier de supervivencia libre de MACE, estratificadas por deterioro de la FEVI. ***B)*** Algoritmo de riesgo de MACE.

Abreviaciones como en ***Tabla 1****.*

El análisis multivariado mostró que una FEVI inicial más baja, el deterioro progresivo de la FEVI (***Figura 22A***), la presencia de FA y un QRS ancho (≥120 ms) en el ECG basal se asociaron con un mayor riesgo de MACE después del ajuste (***Tabla 11***). El análisis por *backward stepwise regression* confirmó que las mismas cuatro variables mantenían la asociación independiente y estadísticamente significativa (***Tabla 11***). El modelo predictivo demostró una buena capacidad discriminativa para MACE, con un índice C de Harrell de 0,78 (IC95% 0,75 – 0,81). Los pacientes con una FEVIp inicial y sin un deterioro posterior de la FEVI presentaron un riesgo bajo de eventos clínicos adversos, mientras que aquellos con una FEVI reducida y una disminución adicional de la función sistólica mostraron un pronóstico desfavorable (p < 0,001)

Los pacientes con FEVIp inicial pero con posterior deterioro de la FEVI presentaron un pronóstico intermedio, con un 22% de riesgo de MACE (***Figura 22B***).

5.2.3. Subestudio de RMC en individuos de bajo riesgo

Una vez demostrado que algunos pacientes con FEVI inicial preservada, que a priori podrían considerarse de bajo riesgo de tener una miocardiopatía, podían presentar un deterioro de la FEVI durante el seguimiento, y que esto se asociaba a un riesgo posterior aumentado de eventos cardiovasculares, quisimos hacer un estudio de fenotipado profundo de estos casos con FEVI preservada para intentar identificar aquellos que realmente no presentaban una miocardiopatía asociada.

Tabla 12: Características basales de resonancia magnética cardiovascular de los pacientes con no compactación del ventrículo izquierdo de bajo riesgo.

Evento	Cohorte global (n = 156)	MACE y/o deterioro de la FEVI (n = 11)	No MACE ni deterioro de la FEVI (n = 145)	HR crudo (IC 95%)	p Valor
Ventrículo izquierdo					
FEVI, % (DE)	58,6 (5,6)	59,3 (6,9)	58,5 (5,5)	1,00 (0,90-1,11)	0,98
iVTDVI, ml/m² (DE)	83,8 (17,4)	82,2 (20,1)	83,9 (17,2)	1,00 (0,97-1,04)	0,859
iVTSVI, ml/m² (DE)	35,2 (9,5)	33,5 (10,6)	35,4 (9,4)	0,99 (0,94-1,05)	0,809
Masa ventricular indexada, gr/m² (DE)	56,7 (12,1)	51,6 (12,3)	57,1 (12,0)	0,97 (0,92-1,02)	0,233
Ratio NC/C (DE)	2,8 (0,5)	2,8 (0,7)	2,8 (0,5)	1,16 (0,38-3,48)	0,796
% de masa ventricular trabeculada, % (DE)	15,6 (8,2)	16,1 (4,2)	15,6 (8,4)	1,01 (0,94-1,07)	0,875
Masa ventricular trabeculada indexada, gr/m² (DE)	8,7 (5,1)	8,2 (2,4)	8,8 (5,2)	0,97 (0,85-1,12)	0,694
DF apical máxima, (DE)	1,39 (0,10)	1,41 (0,08)	1,39 (0,11)	5,60 (0,01-3608,51)	0,602
DF global media, (DE)	1,30 (0,06)	1,31 (0,05)	1,30 (0,06)	14,32 (0,00-921646,16)	0,638
GLS VI, % (DE)	-12,1 (3,5)	-11,8 (2,7)	-12,2 (3,6)	1,03 (0,86-1,22)	0,765
GCS VI, % (DE)	-16,6 (2,5)	-16,8 (3,0)	-16,6 (2,4)	0,92 (0,71-1,20)	0,551
GRS VI, % (DE)	26,6 (6,0)	27,1 (8,0)	26,5 (5,8)	1,04 (0,94-1,17)	0,445
Ventrículo derecho					
FEVD, % (DE)	53.3 (8.0)	52.8 (9.0)	53.3 (7.9)	1.00 (0.93-1.09)	0.959
iVTDVD, ml/m2 (DE)	87.4 (22.9)	77.9 (27.1)	88.2 (22.5)	0.99 (0.97-1.02)	0.560
iVTSVD, ml/m2 (DE)	41.2 (14.3)	37.5 (17.2)	41.5 (14.0)	0.99 (0.95-1.04)	0.723
NC/C ratio 4 cámaras, (DE)	4.4 (1.4)	4.4 (1.7)	4.4 (1.3)	1.14 (0.74-1.78)	0.554
NC/C ratio eje corto , (DE)	4.2 (1.2)	4.0 (0.9)	4.3 (1.2)	0.87 (0.50-1.51)	0.614
GLS VD, % (DE)	-25.7 (6.1)	-28.3 (8.6)	-25.5 (5.9)	1.01 (0.90-1.13)	0.874
Aurícula izquierda					
Volumen auricular biplano indexado, mL/m² (DE)	47,3 (14,7)	50,0 (16,2)	47,1 (14,6)	1,02 (0,98-1,06)	0,362
FEAI, % (DE)	51,8 (12,9)	45,0 (11,8)	52,3 (12,9)	0,96 (0,91-1,01)	0,069
GLSr AI, % (DE)	33,4 (16,1)	22,9 (11,0)	34,2 (16,2)	0,94 (0,89-0,99)	0,034
GCS AI, % (DE)	27,9 (14,9)	29,6 (15,8)	27,8 (14,9)	1,00 (0,96-1,05)	0,855

***AI**: aurícula izquierda. **DF**: dimensión fractal. **FEAI**: fracción de eyección de la aurícula izquierda. **GCS**: strain circunferencial global. **GLS**: strain longitudinal global. **GLSr**: strain longitudinal reservorio. **GRS**: strain radial global. **NC/C**: no-compactada/compactada. **VD**: ventrículo derecho. **VI** ventrículo izquierdo. Otras abreviaturas como en la **Tabla 4** y **10**.*

Se diseñó un estudio basado en RMC y con análisis centralizado y se reclutaron 181 individuos con NCVI y FEVI ≥ 50%; de estos, 4 tenían RTG (2% de aquellos con secuencias post contraste disponibles) y en 21 (12%) casos no se administró contraste. Por lo que, finalmente, se incluyeron en el estudio 156 individuos con FEVIp y RTG negativo (***Figura 20***). Durante un seguimiento mediano de 3,7 (1,7 – 5,9) años, 11 (7%) casos desarrollaron MACE y/o deterioro de la FEVI: 7 (4%) MACE (1 insuficiencia cardíaca y 7 taquicardias ventriculares) y 5 (3%) deterioro de la FEVI (un paciente desarrolló ambos eventos). Las características basales de RMC se describen en la ***Tabla 12***.

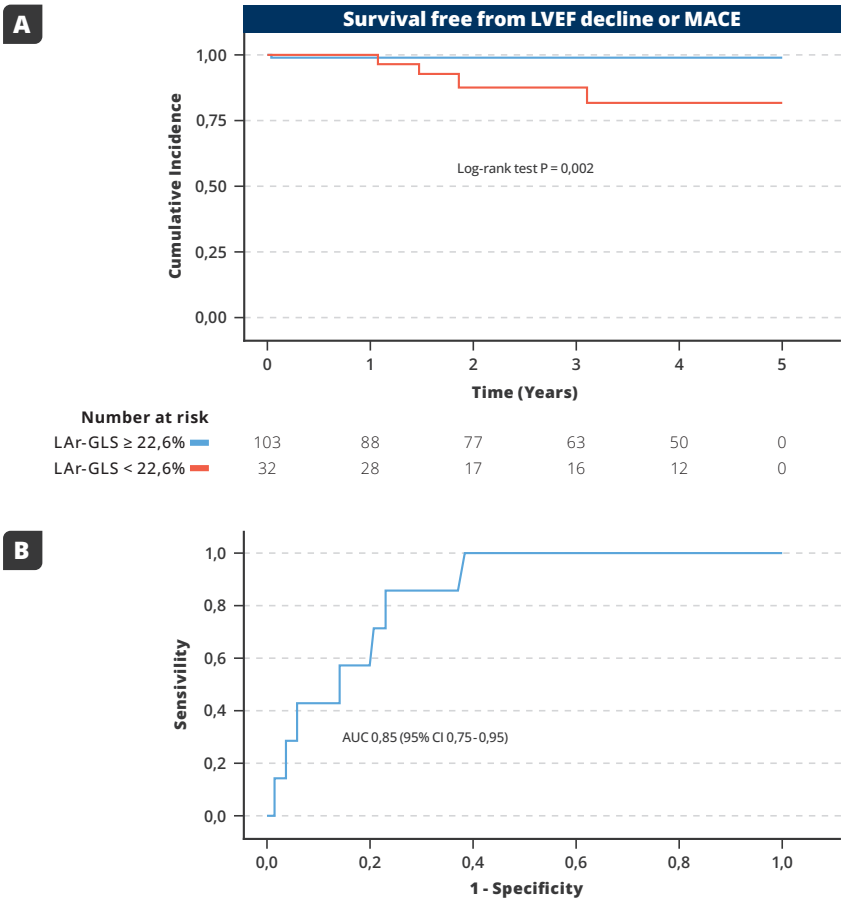


Figura 23: ***A)*** Curvas de Kaplan Meier de supervivencia libre de MACE y/o deterioro de la FEVI estratificado por *strain* longitudinal reservorio de la aurícula izquierda. ***B)*** Curva ROC para MACE según el *strain* longitudinal reservorio de la aurícula izquierda.
LAr-GLS*: strain longitudinal reservorio de la aurícula izquierda. Otras abreviaciones como en* ***Tabla 1***

En el análisis de regresión de Cox univariado, el *strain* longitudinal reservorio de la aurícula izquierda (GLSr AI) fue la única variable asociada significativamente con el evento combinado. Otras variables funcionales o morfológicas, incluyendo el *strain* ventricular o los parámetros de cuantificación de la trabeculación, no se correlacionaron (***Tabla 12***); no se pudo realizar el análisis multivariado debido al bajo número de eventos. Los pacientes en el peor cuartil de GLSr AI (< 22,6%) tuvieron un riesgo significativamente mayor de presentar eventos adversos comparado con el resto de pacientes con GLSr AI ≥ 22,6%, que prácticamente no presentaron eventos durante el seguimiento a largo plazo, lo que podría sugerir que no presentan una miocardiopatía (HR 4,77, IC95% 1,34 – 17,00, p = 0,016) (***Figura 23A***). La diferencia se derivó de una mayor incidencia de MACE, mostrando el GLSr AI una muy buena capacidad discriminativa: índice C de Harrell de 0,80 (IC95% 0,72 – 0,88) y área bajo la curva de 0,85 (IC 0,75 – 0,95) (***Figura 23B***).

6

Discusión

En nuestro proyecto de investigación observacional, retrospectivo, longitudinal y multicéntrico de pacientes con no compactación del ventrículo izquierdo hemos observado que: 1) la evaluación integral permite una estratificación pronóstica precisa; 2) la fracción de eyección del ventrículo izquierdo es una de los principales variables asociadas a eventos y su deterioro a lo largo del tiempo tiene un impacto pronóstico adicional e independiente; y 3) los individuos con criterios morfológicos de NCVI pero sin signos de alarma (ej: FEVI reducida, fibrosis miocárdica, alteraciones en el ECG, historia familiar, alteración del *strain* auricular) constituyen un subgrupo de muy bajo riesgo que sugiere la presencia de una hipertrabeculación fisiológica más que una miocardiopatía.

6.1. MACE: INCIDENCIA Y VARIABLES ASOCIADAS

En nuestro estudio incluimos un total de 585 pacientes con NCVI y durante un seguimiento mediano de 5,1 años, 223 (38%) presentaron al menos un MACE, destacando por su frecuencia la IC (19%) y las AV (15%). La incidencia de eventos cardiovasculares fue superponible a la de un reciente metaanálisis de NCVI con más de 2.500 pacientes[45]: 3,22 vs 3,53 ingresos por IC por 100 personas-año (p = 0,461) y 2,70 vs 2,17 AV por 100 personas-año (p = 0,096). Esta consistencia confirma la validez de nuestros resultados, siendo especialmente relevante dada la heterogeneidad de esta entidad y la discordancia en los datos previamente publicados en la literatura: en algunas series se han reportado porcentajes de eventos muy altos[22,43,44,50], mientras que en otras el número de eventos ha sido muy bajo[36,47,48].

Si comparamos nuestros datos con una población de MCD a partir de un metaanálisis de más de 4.500 pacientes[68], la incidencia de eventos en nuestra cohorte fue superior: 3,22 vs 2,37 ingresos por IC por 100 personas-año (p = 0,014) y 2,70 vs 2,14 AV por 100 personas-año (p = 0,064). Considerando que aproximadamente la mitad de nuestra población tenía FEVIp basalmente, el pronóstico de eventos ajustado por FEVI podría ser significativamente peor en la NCVI que en la MCD. De hecho, previamente se han publicado resultados similares: en un registro multicéntrico de

pacientes sintomáticos con NCVI el riesgo de un evento combinado cardiovascular fue significativamente más alto que el de controles apareados por edad con MCD (HR 2,481, p = 0,002)[43], mientras que en un estudio prospectivo multicéntrico de NCVI, los pacientes con FEVI ≤ 45% presentaron un pronóstico significativamente peor que el de aquellos con MCD y FEVI ≤ 45% (log-rank p = 0,02)[44].

Una de las variables que presentó una asociación más fuerte y consistente con el riesgo de MACE fue la FEVI, en consonancia con publicaciones previas en NCVI[45,50]. En concreto, la FEVI fue el predictor más importante de IC (***Tabla 8***), de manera que especialmente los pacientes con función sistólica severamente deprimida (FEVI ≤ 35%) presentaron un riesgo muy alto y muy precoz de eventos adversos (***Figura 13A***). Estos hallazgos sugieren que este subgrupo se podría beneficiar de un control estricto así como de un inicio y titulación rápidos del tratamiento neurohormonal, tal y como recomiendan las guías de práctica clínica[59,60]. En cambio, la incidencia de IC en pacientes con FEVI > 50% fue prácticamente inexistente (***Figura 13A***).

La FEVI también resultó estar asociada de forma independiente a la aparición de AV (***Tabla 8***), de acuerdo con publicaciones previas[45], si bien con una menor capacidad discriminativa respecto a la IC (***Figura 14A***). Cabe destacar que, en nuestra serie, más de la mitad (54%) de pacientes que presentaron eventos arrítmicos duros (8 episodios de fibrilación ventricular y 8 episodios de taquicardia ventricular sostenida) tenían una FEVI > 35% y por tanto no cumplían criterios para el implante de un DAI en prevención primaria según las guías actuales[6,59–62]. Esto sugiere que la FEVI por sí sola no es un marcador suficientemente preciso del riesgo arrítmico en NCVI, tal y como se comentó en otro artículo[43]: la incidencia de eventos arrítmicos ventriculares (fibrilación ventricular o taquicardia ventricular) en una población de NCVI fue superior a la de un grupo control de MCD, a pesar de que los pacientes con NCVI presentaban una FEVI superior (38 ± 15%). Los autores justificaron este hallazgo por la alta prevalencia de fibrosis miocárdica en su serie (66%), así como por la presencia de genotipos de alto riesgo (*TTN*, *LMNA* y *RBM20*).

En este sentido, es conocido que el uso exclusivo de la FEVI para determinar el riesgo de MSC en la MCD tiene limitaciones, tal y como se comprobó en el estudio DANISH, que no pudo demostrar el beneficio del implante de un DAI profiláctico en cuanto a supervivencia global en este perfil de pacientes[69]. De manera que las últimas guías de práctica clínica de miocardiopatías de la ESC han propuesto un nuevo algoritmo que incluye, más allá de la FEVI, la integración del genotipo y el RTG para una mejor estratificación del riesgo arrítmico, de cara a valorar el implante de un DAI en prevención primaria en pacientes con MCD (***Figura 24***)[6]. En concreto, pacientes con FEVI > 35% pero con un genotipo de alto riesgo (ej: *LMNA*, *FLNC*, *PLN*, etc.) y/o con RTG, pueden ser considerados candidatos a un DAI profiláctico con una recomendación clase IIa / IIb.

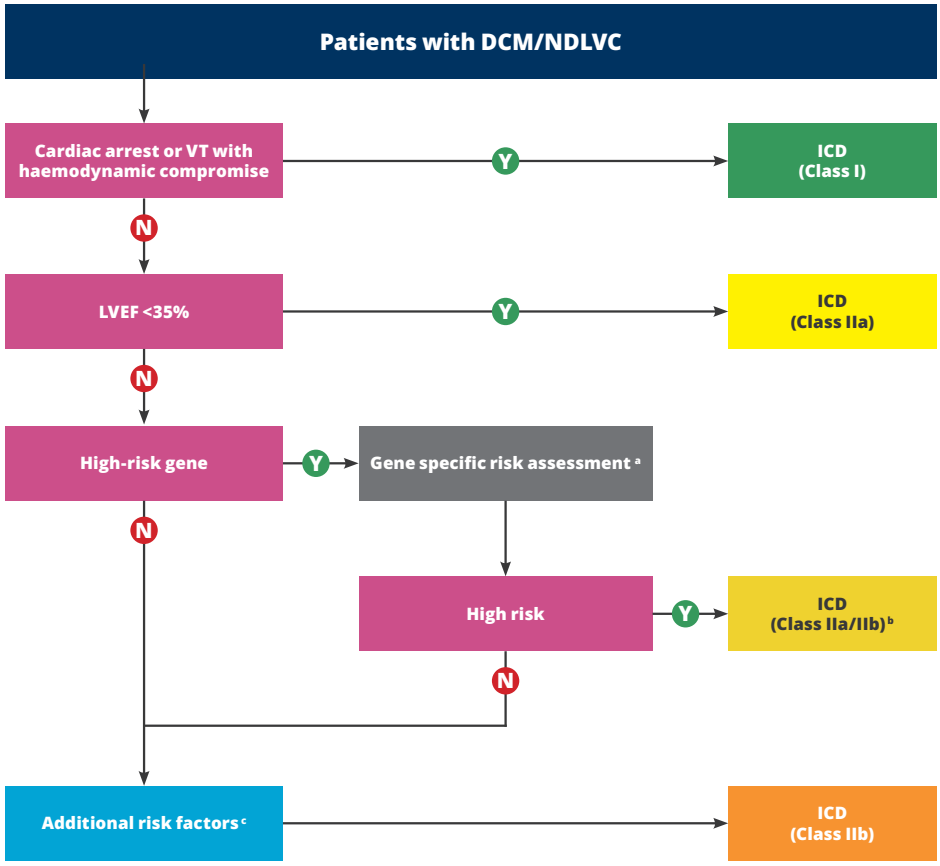


Figura 24: Algoritmo para el implante de un desfibrilador automático implantable en prevención primaria en pacientes con miocardiopatía dilatada. Adaptado de Arbelo *et al*[6].

En lo que respecta al RTG, es un marcador de riesgo bien establecido, que se ha asociado consistentemente y de forma muy potente con un peor pronóstico cardiovascular en múltiples patologías cardíacas. En la MCD un gran metaanálisis ha demostrado su correlación con una mayor incidencia de MACE (OR 5,46, IC95% 3,77 – 7,91), así como un mayor riesgo de un combinado de AV (OR 4,52, IC95% 3,41 – 5,99)[68]. Cabe destacar que la asociación con la MSC se mantiene en pacientes con disfunción ventricular únicamente leve (FEVI ≥ 40%) (HR 9,3, IC95% 3,9 – 22,3, p < 0,0001)[70].

En la NCVI, el RTG se ha asociado con un pronóstico adverso, y en concreto con una mayor incidencia de MACE, independientemente de la dilatación del ventrículo izquierdo (HR 4,02, IC95% 1,64 – 9,83, p = 0,002) o de la FEVI (HR 4,84, IC95% 1,96 – 11,10, p = 0,001)[50,52]. En nuestra serie, el RTG se asoció de forma estadísticamente significativa con el evento combinado de AV en el análisis univariado (***Tabla 7***), pero en el análisis multivariado perdió la significación debido a una fuerte colinealidad con la FEVI (los pacientes con RTG tenían una FEVI significativamente peor) (***Tabla 8***). Conviene destacar que en otros estudios sobre NCVI ya se han documentado interacciones entre la FEVI y el RTG[50,52]. Sin embargo, en aquellos pacientes con FEVI > 35%, el RTG sí se asoció con un mayor riesgo de AV en nuestra serie (***Figura 14B***), de acuerdo con lo descrito en MCD[70].

Este hallazgo también se puede integrar en el mencionado algoritmo de implante profiláctico de DAI (***Figura 24***)[6]: los pacientes con NCVI con FEVI > 35% y RTG se podrían considerar candidatos a un DAI en prevención primaria, debido a que presentan un riesgo aumentado de MSC. Sin embargo, son necesarios estudios prospectivos aleatorizados para demostrar si esta estrategia podría mejorar el pronóstico de este subgrupo de pacientes. Además, existen ciertas limitaciones en la valoración del RTG, ya que no está bien definido a día de hoy si se debe considerar simplemente su presencia, o si bien la cuantificación o el patrón del RTG aportan un papel pronóstico adicional. No está estandarizada tampoco la metodología para cuantificar el RTG ni existen puntos de corte validados que justifiquen por si solos el implante de un DAI.

En lo que respecta a la información del análisis genético, en nuestra serie el 42% de los probandos presentaron una variante patogénica o posiblemente patogénica de acuerdo con las recomendaciones actuales[58]. El rendimiento del estudio genético en nuestra cohorte fue algo superior al de otras series recientes de NCVI, que describieron un porcentaje entre 32-38% de pacientes con genotipo positivo[43,51]. Esta pequeña diferencia se podría explicar por un sesgo de selección, ya que en nuestra serie incluimos únicamente pacientes seguidos en unidades de cardiopatías familiares de referencia, con una alta sospecha de miocardiopatía. Sin embargo, es una cifra comparable a los porcentajes reportados en otras miocardiopatías: entre 30 y 40% tanto en la MCH[20], como en la MCD[21].

Conviene destacar que en nuestra serie las características demográficas basales, así como las variables funcionales de RMC (FEVI y RTG) fueron superponibles entre los grupos de genotipo positivo y negativo (***Tabla Suplementaria 3***), lo que podría justificar que no hubiera diferencias en la incidencia global de MACE entre los dos grupos (***Tabla 5***). En este sentido, otro estudio de NCVI tampoco documentó diferencias en el riesgo de MACE según la presencia o no de mutaciones (posiblemente) patogénicas en pacientes adultos, si bien aquellos con genotipo positivo tuvieron peor FEVI[51]. Otro estudio también describió una mayor prevalencia de disfunción ventricular y fibrosis miocárdica en los pacientes con NCVI y genotipo positivo , comparado con aquellos con genotipo negativo[55]. La discordancia de nuestros datos sobre la correlación genotipo-fenotipo se podría justificar por el pequeño tamaño muestral de la población genotipada, ya que sólo se estudió genéticamente al 61% de la cohorte, lo que podría haber introducido un sesgo de selección y, finalmente, a la gran heterogeneidad genética que existe en esta entidad[17]. En cambio, en la literatura sí que se ha descrito que un genotipo positivo se asocia a un peor pronóstico en otras miocardiopatías como la MCH[71] o la MCD[21].

Haciendo referencia a genes concretos (***Tabla 5***), y en concordancia con trabajos previos, en nuestra serie los pacientes con variantes en *TTN* y con genotipos complejos

presentaron una FEVI más baja [51,55] y un peor pronóstico [24,43]; las variantes en *ACTC1* se asociaron con un mayor riesgo de AV [72]; y los portadores de *MYH7* mostraron un buen pronóstico global [24,51]. No pudimos confirmar las asociaciones previamente descritas para *MYBC3* que han sugerido un alto riesgo de eventos, lo que se podría justificar por el bajo número de portadores en nuestra serie (10 probandos y 8 familiares) [24,51]. En definitiva, el genotipo se podrían considerar para estratificar el pronóstico de pacientes con NCVI, tal y como sugieren Oechslin *et al* en otro trabajo [25]. De hecho, las guías de la ESC ya proponen asesorar el riesgo e individualizar el manejo de los pacientes con MCD según el genotipo [6]. Por tanto, son necesarios más datos en la NCVI, incluyendo series más grandes y prospectivas, que permitan hacer una predicción del riesgo más precisa basada en el genotipo y fenotipo, para poder integrar estas variables en los algoritmos de manejo de los pacientes, de forma análoga a lo que ya ocurre para la MCD [6].

Finalmente, en lo que respecta al estudio familiar, en nuestra serie observamos un 42% de agregación familiar, en concordancia con los porcentajes observados en la literatura [26,27,51]. Conviene destacar que una elevada proporción (63-68%) de los familiares diagnosticados en estas series estaban asintomáticos [26,27], por lo que parece razonable recomendar un screening familiar proactivo en todos los casos de NCVI. La agregación familiar no sólo nos confirmará el diagnóstico del caso índice sino que, de acuerdo a nuestros datos, nos indicará que este individuo presenta un mayor riesgo de MACE, traduciendo la presencia de una probable miocardiopatía y no de una hipertrabeculación fisiológica. En definitiva, el estudio familiar sistemático es recomendable en todos los casos de NCVI ya que tiene un alto rendimiento, permite identificar familiares asintomáticos y ayuda en el manejo del caso índice: un individuo sin familiares afectos ni ningún otro signo de alarma posiblemente no presente una miocardiopatía y puede ser dado de alta, mientras que un caso familiar es más sugestivo de miocardiopatía.

6.2. DETERIORO DE LA FEVI: INCIDENCIA, VARIABLES ASOCIADAS E IMPACTO PRONÓSTICO

Una vez demostrado que la FEVI basal es uno de los principales predictores de riesgo en NCVI, quisimos estudiar si la FEVI es un parámetro estable o si se experimenta cambios a lo largo del tiempo y, especialmente, si estos cambios tienen un impacto pronóstico. En la literatura se han descrito cambios dinámicos de la FEVI tanto en poblaciones con IC [73,74], como en MCD [75,76], pero no hay datos específicos publicados para NCVI. En nuestra serie de 577 pacientes, 34 (6%) presentaron un deterioro de la FEVI durante un seguimiento ecocardiográfico mediano de 4,3 años, de acuerdo a unos criterios estrictos publicados previamente [66]. Esta cifra es menor que la descrita en la literatura y podría justificarse parcialmente por el seguimiento ecocardiográfico relativamente corto en nuestra cohorte, ya que se ha demostrado que en la MCD puede haber un deterioro muy tardío (> 10 años) de la FEVI [73].

Las variables que se asociaron de forma independiente al deterioro de FEVI en nuestra serie fueron el RTG y la presencia de FA en el ECG basal (***Tabla 11***). Por un lado, el RTG traduce la presencia de fibrosis miocárdica y, consecuentemente, una afectación cardíaca más avanzada. Por tanto, desde un punto de vista biológico, parece razonable justificar que los pacientes con NCVI y RTG tienen un mayor riesgo de deprimir la FEVI a lo largo del seguimiento (***Figura 21A***). De forma similar, varios estudios en MCD han mostrado hallazgos comparables: un metaanálisis demostró que su ausencia favorece el remodelado reverso del ventrículo izquierdo (OR 0,15, IC95% 0,06-0,36) [68], mientras que su presencia aumenta el riesgo de recaída de la FEVI en pacientes que habían recuperado previamente la función sistólica (OR 1,09, IC95% 1,03 - 1,16, p = 0,004) [76].

Por otro lado, la presencia de FA basal también se asoció con un mayor riesgo de deterioro de la FEVI (***Figura 21B***). La FA es un factor de riesgo establecido para desarrollar IC y disfunción sistólica, ya que la ausencia de contracción auricular disminuye el gasto cardíaco y aumenta las presiones intracavitarias, pudiendo desembocar en

una miocardiopatía inducida por taquicardia (taquimiocardiopatía) con FEVI reducida [77]. Por lo que nuestro hallazgo es razonable y tiene sentido a nivel fisiopatológico. En este sentido, la ablación de FA ha demostrado mejorar la FEVI en pacientes con disfunción ventricular comparado con la estrategia de control de ritmo farmacológico (mejoría 18 ± 13% vs 4 ± 13%, p < 0,0001) [78]. A destacar del estudio mencionado, que la mejoría de la FEVI fue más marcada en pacientes sin RTG. Igualmente, la ablación de la FA mejora el pronóstico en los pacientes con IC, con una disminución del riesgo de muerte por cualquier causa o ingreso por IC (HR 0,62, IC95% 0,43 - 0,87, p = 0,007) [79].

En definitiva, la caída en FA de un paciente con hipertrabeculación aparentemente benigna podría suponer un marcador precoz de miocardiopatía, especialmente en individuos jóvenes. A nivel práctico, se podría plantear que aquellos pacientes con RTG y/o FA basal deberían seguir un control clínico más estrecho, incluyendo la determinación seriada de biomarcadores como el NTproBNP y la utilización de técnicas de imagen avanzadas como el *strain* longitudinal, para identificar signos incipientes de IC y/o cambios subclínicos en la FEVI. Incluso se podría discutir el uso preventivo de tratamiento neurohormonal para disminuir el riesgo de una eventual caída de FEVI. Además, teniendo en cuenta los estudios mencionados en el párrafo anterior, y que la FA se asocia de forma independiente a la mortalidad en la NCVI [80], se podría plantear un manejo agresivo del ritmo cardíaco mediante la ablación por catéter, aunque la evidencia a día de hoy en NCVI es escasa. Evidentemente, estas hipótesis se tendrían que validar en estudios prospectivos aleatorizados que confirmaran su utilidad, antes de aplicarse en la práctica clínica habitual.

Queda también por aclarar la frecuencia con la que se deberían realizar los controles ecocardiográficos, ya que el seguimiento periódico y a largo plazo de todos los pacientes con hallazgos morfológicos de NCVI supondría una sobrecarga asistencial para los laboratorios de ecocardiografía. Integrando las dos variables, los pacientes con FA y RTG presentan un riesgo muy alto de deterioro de la FEVI, por lo que son los que más

se beneficiarían de un seguimiento estrecho (cada 6 – 12 meses), y los que habría que priorizar desde un punto de vista de eficiencia del sistema de salud. Por otro lado, los pacientes sin FA ni RTG tienen un riesgo prácticamente inexistente de caída de la FEVI, por lo que se podría plantar hacerles un seguimiento más espaciado (cada 2 – 3 años) y evitar controles ecocardiográficos innecesarios.

Presentar un deterioro de la FEVI es especialmente importante porque, según nuestros resultados, se asocia con un mayor riesgo de eventos cardiovasculares en el futuro, independientemente de la FEVI basal y de otras variables como la presencia de FA o un complejo QRS ancho en el ECG basal (***Tabla 11***, ***Figura 22A***). Considerando que la FEVI es uno de los principales marcadores pronósticos en NCVI[45,50,52], su deterioro a lo largo del tiempo emerge como un marcador adicional razonable. De hecho, en la literatura se ha descrito en múltiples trabajos el papel pronóstico de la caída de FEVI. En poblaciones con IC, una mala evolución de la FEVI se ha asociado a la mortalidad global[73] y a un aumento de la mortalidad y/o ingresos por IC (HR 1,15, IC95% 1,01 – 1,30)[74]. En la MCD, el deterioro de la FEVI se ha correlacionado con la mortalidad, trasplante cardíaco y/o implante de un dispositivo de asistencia ventricular izquierda (HR 2,54, IC95% 1,60 – 4,04)[75] y a un aumento de la MSC y/o ingreso por IC (HR 4,30, IC95% 1,63 – 11,31, p = 0,003)[76]. Esta consistencia con la literatura confirma la validez de nuestros hallazgos, que no han sido descritos previamente en la NCVI.

El deterioro de la FEVI se asoció con un riesgo incrementado de MACE incluso en pacientes con FEVI inicial preservada, que a priori podrían considerarse de bajo riesgo y con baja probabilidad de presentar una miocardiopatía como tal, pero que al desarrollar una caída de la FEVI pasan a presentar un riesgo intermedio de eventos cardiovasculares. En cierto modo, el riesgo de este subgrupo sería equiparable al de pacientes con FEVI inicial reducida, pero sin cambios durante el seguimiento, mientras que el peor pronóstico lo presentarían aquellos con FEVI inicial

reducida y con posterior deterioro adicional. En cambio, los pacientes con FEVI inicial preservada y sin deterioro, presentarían un riesgo muy bajo de eventos y podrían considerarse como portadores de un fenotipo benigno no necesariamente asociado a la presencia de una miocardiopatía (***Figura 22B***). Conviene destacar, finalmente, que una vez se ha deteriorado la FEVI, el riesgo de MACE es alto (47%) y muy precoz (25% en dos meses) (***Figura 22A***), por lo que este subgrupo de pacientes debería seguir un control clínico muy estrecho y un manejo rápido del tratamiento para la IC, con el objetivo de mejorar la FEVI y especialmente evitar eventos adversos.

6.3. MODELO PREDICTIVO DE RIESGO

El objetivo final de nuestro trabajo fue desarrollar un modelo predictivo de riesgo (*risk score*) que permitiera estratificar el pronóstico de nuestros pacientes para ofrecer, idealmente, un manejo médico individualizado. El modelo predictivo, basado en las variables asociadas de forma independiente al evento combinado MACE (***Tabla 8***), presentó una buena capacidad discriminativa (índice C de Harrell de 0,72) y una buena calibración (pendiente de calibración de 0,96). Estas variables fueron categorizadas para facilitar su aplicación en la práctica clínica habitual, de manera que el modelo predictivo se transformó en una calculadora (***Figura 17A***), también disponible online.

Conviene destacar de nuestro modelo que está basado en variables simples y fácilmente disponibles en cualquier escenario médico (edad, sexo, antecedentes médicos básicos, ECG, FEVI y agregación familiar), sin requerir de pruebas adicionales complementarias costosas como el estudio genético, o complejas de postprocesar como el *strain* por RMC. Estas varias suelen estar disponibles prácticamente desde la primera visita, con lo cual se puede predecir el riesgo de un individuo con NCVI casi en el momento del diagnóstico (***Figura 17B-D***). Además, la calculadora tiene plausibilidad biológica, ya que todas las variables tienen implicaciones pronósticas reconocidas en NCVI [27,35,42,44,50,54].

El modelo fue validado externamente en una cohorte multicéntrica prospectiva previamente publicada[50], mostrando una capacidad discriminativa y una calibración comparables a la cohorte de derivación, lo cual confirma la validez y aplicabilidad de nuestros resultados. Queda pendiente de realizar una validación prospectiva del modelo, así como determinar su aplicación práctica en cuanto al manejo de los pacientes; es decir, demostrar si un tratamiento guiado por el modelo predictivo (por ejemplo, recomendar un DAI precoz en los pacientes de mayor riesgo), supone un beneficio pronóstico en cuanto a eventos cardiovasculares. A día de hoy, simplemente se podría sugerir un seguimiento más estrecho (cada 6 - 12 meses) a los pacientes de alto riesgo, mientras que se podría adoptar una actitud más conservadora con aquellos de bajo riesgo (controles cada 2 – 3 años). Incluso se podría plantear dar de alta a los individuos con NCVI que no presentan ningún signo de alarma, ya que tienen un pronóstico excelente.

En el mundo de la cardiología, se utilizan modelos de riesgo en la práctica clínica con mucha frecuencia, como por ejemplo la escala CHA_2DS_2-VASc, que determina el riesgo embólico en pacientes con fibrilación auricular de cara a valorar la indicación de anticoagulación oral[81]. A pesar de su amplio reconocimiento y su integración en las guías de práctica clínica[82], la escala CHA_2DS_2-VASc presenta una capacidad discriminativa moderada (índice C de Harrell de 0,67)[83], lo que demuestra la dificultad de desarrollar modelos predictivos potentes y a la vez fáciles de aplicar.

En el ámbito de las miocardiopatías, también son comunes los modelos predictivos. Por ejemplo, es ampliamente conocida y utilizada la calculadora para la predicción de MSC en la MCH (índice C de Harrell de 0,70)[84]. De hecho, este *risk score* está incorporado en las guías de práctica clínica de la ESC, con una recomendación clase I, como pilar principal para la estratificación del riesgo arrítmico y de la decisión de implante de un DAI en prevención primaria[6,85]. Más recientemente, se ha desarrollado y validado un modelo predictivo de arritmias ventriculares para la miocardiopatía arritmogénica[86,87], que también se ha integrado en las guías con una recomendación clase IIa[6].

Existen, además, calculadoras específicas para genes como la *LMNA*[88] e incluso para variantes concretas como la variante p.Arg14del de *PLN*[89], ambas también mencionadas en las guías[6]. En definitiva, el mundo de la cardiología en general, y específicamente el de las miocardiopatías, evoluciona hacia la medicina personalizada e individualizada.

Sin embargo, en lo que respecta a la NCVI no existían previamente modelos predictivos validados, traduciendo la heterogeneidad y falta de consenso en esta entidad. Una serie prospectiva multicéntrica pero de pequeño tamaño (n = 113) describió varios modelos multivariados básicos de MACE, integrando variables clínicas y de RMC (FEVI, volúmenes ventriculares y RTG) (***Figura 25A***)[50]. Un metaanálisis de RMC formuló un modelo bivariado basado en la FEVI y el RTG (***Figura 25B***)[52], mientras que otras series utilizaron biomarcadores como el BNP[54] o la extensión de la hipertrabeculación[42]. Sin embargo, ninguno de estos estudios desarrolló un modelo predictivo o calculadora como tal, ni sus resultados fueron validados en cohorte externas, por lo que sus hallazgos no son tan fácilmente aplicables en la práctica clínica, ni generalizables a otras poblaciones. Estas limitaciones ponen de manifiesto el valor de nuestro modelo predictivo, el único disponible todavía a día de hoy para esta entidad, siendo además sencillo y rápido de aplicar.

Como ya se ha comentado previamente, el objetivo final de estos modelos predictivos es poder ofrecer una atención médica más personalizada a nuestros pacientes. Esta estratificación del riesgo debería permitir un manejo individualizado de cada paciente que, idealmente, repercutiera en una mejoría pronóstica. Evidentemente, nuestro modelo no es perfecto y no pretende cambiar la historia natural de esta entidad, pero supone un cambio de paradigma en la concepción de la NCVI y es un primer paso hacia la medicina de precisión. En el futuro, la mejoría de los conocimientos en genética, la aparición de técnicas de análisis avanzado por RMC y la integración de todas estas variables gracias al uso de la inteligencia artificial, debería permitir la creación de mejores modelos predictivos.

Figura 25: ***A)*** Adaptado de Andreini *et al* [50]. Modelos multivariados de predicción de MACE basados en datos clínicos y variables por resonancia magnética cardiovascular. ***B)*** Adaptado de Grigoratos *et al* [52]. Modelo bivariado de riesgo de MACE y de eventos cardíacos duros, basado en la fracción de eyección del ventrículo izquierdo y el realce tardío de gadolinio.

6.4. ALGORITMOS DE BAJO RIESGO Y CRITERIOS DIAGNÓSTICOS

El siguiente paso en nuestro trabajo fue diseñar un algoritmo que nos permitiera identificar a los pacientes de bajo riesgo. Para eso, utilizamos las mismas variables del modelo predictivo así como el RTG, pero buscando su asociación con la ausencia de eventos a lo largo del seguimiento; es decir, invirtiendo el *risk score*. Diseñamos un algoritmo que incluyó el ECG, la FEVI, el RTG y la agregación familiar (***Figura 19***), de manera que el riesgo de presentar MACE iba disminuyendo progresivamente en cada paso. De hecho, los individuos que no cumplieron ningún criterio de riesgo (alteraciones en las variables mencionadas), no presentaron eventos (0% de riesgo observado de MACE), sugiriendo que corresponden a casos de hipertrabeculación fisiológica con baja probabilidad de presentar una miocardiopatía asociada. Estos individuos no requieren un control clínico estrecho (por ejemplo, visitas cada 3 años), pudiéndose incluso plantear el alta si no se evidencian cambios en la FEVI ni otras alteraciones durante el seguimiento. En cambio, los pacientes con NCVI y algún signo de alarma, presentan un riesgo aumentado de eventos cardiovasculares, sugiriendo que se trata de casos de hipertrabeculación patológica con una alta probabilidad de presentar una miocardiopatía asociada. Estos pacientes requieren un control más estrecho (cada 6 - 12 meses) para evitar complicaciones.

Este algoritmo fue diseñado de forma deliberadamente simplificada para facilitar su aplicación en la práctica clínica, de manera que pudiera considerarse una herramienta rápida de ayuda en la toma de decisiones. Se incluyeron variables fáciles de obtener y disponibles en la gran mayoría de consultas de cardiología. Además, se siguió un modelo secuencial que imita el proceso diagnóstico habitual en las miocardiopatías: empezando por el ECG, continuando con las pruebas de imagen cardíaca (ETT y RMC) y acabando con el estudio familiar (y/o genético).

A continuación, nos centramos en la subpoblación de NCVI clásicamente considerada de bajo riesgo (FEVIp y sin RTG), e hicimos un estudio de fenotipado profundo mediante el análisis avanzado por RMC. La idea de este subestudio era el de identificar de forma

precoz pacientes con una miocardiopatía subclínica, así como descartar individuos sin sospecha de miocardiopatía asociada. En este subgrupo de pacientes, el *strain* auricular (GLSr AI) fue un marcador de riesgo adicional, probablemente indicando una disfunción diastólica o disfunción sistólica subclínica. El GLSr AI ya ha demostrado tener un impacto pronóstico independiente de la FEVI y el RTG, en un pequeño estudio retrospectivo de NCVI[90]. En MCD, un gran estudio multicéntrico prospectivo mostró hallazgos superponibles[91]. En nuestra serie, el GLSr AI permitió diferenciar a los individuos con riesgo realmente bajo (aquellos con FEVIp, sin RTG y con un GLSr AI normal) de aquellos con un riesgo intermedio de eventos (FEVIp, sin RTG pero con un GLSr AI alterado) (***Figura 23A***), es decir diferenciar la hipertrabeculación fisiológica de la miocardiopatía subclínica. Por tanto, de forma análoga a lo comentado en el algoritmo previo, un individuo con NCVI, FEVI conservada, sin RTG y con un *strain* auricular normal no requeriría necesariamente controles periódicos, ya que tiene un pronóstico muy benigno y una baja probabilidad de presentar una miocardiopatía asociada. En cambio, aquellos con FEVIp, sin RTG pero con *strain* auricular anormal no deberían ser dados de alta, porque están en riesgo de acabar desarrollando una miocardiopatía establecida.

En la literatura se han sugerido algoritmos de bajo riesgo parecidos, como los propuestos por Gati *et al*[40] y por Oechslin *et al*[28] (***Figura 7***), así como los publicados por Caselli *et al*[92] y por Garcia-Pavia *et al*[41]. En definitiva, todos estos modelos sugieren un abordaje integral de los pacientes con NCVI que incluya síntomas, historia familiar, variables de ECG, imagen cardíaca (FEVI, RTG, *strain*, función diastólica), holter, ergometría y genética, entre otros. De manera general, los individuos que muestran hallazgos morfológicos de NCVI pero que no presentan ningún otro signo de alarma, corresponden a casos de muy bajo riesgo, probablemente atribuibles a una hipertrabeculación fisiológica o rasgo fenotípico aislado (baja probabilidad de miocardiopatía)[11,46,47]. En cambio, aquellos pacientes con criterios de NCVI y alguna alteración adicional, constituyen casos de más riesgo, lo que sugiere la presencia de una hipertrabeculación patológica o miocardiopatía[43,50,51] (***Tabla 13***).

Tabla 13: Algoritmo para el diagnóstico diferencial de individuos con hallazgos morfológicos de no compactación del ventrículo izquierdo. Adaptado de Casas *et al* [8].

Favors cardiomyopathy	Variable	Favors phenotypic
Dilated and/or hypertrophic LV	LV dimensions	Nondilated and nonhypertrophic LV
Reduced	LVEF	Preserved
Abnormal (even if pEF)	GLS	Normal
Abnormal (even if pEF)	Diastolic function	Normal
+	LGE	-
Elevated	ECV	Normal
+	Past family history and/or family aggregation	-
+	Genotype	-
Shortness of breath, syncope, palpitations...	Symptoms	Asymptomatic
Heart failure, supraventricular/ventricular arrhythmias, systemic embolisms, death	Cardiovascular events	No events
LBBB, T wave inversion...	ECG	Narrow QRS, no repolarization abnormalities
Elevated	Biomarkers (NT-proBNP, hs-cTn)	Normal
Non-sustained VT, frequent ventricular ectopic beats..	Holter	Normal
Inducible VT, decrease in LVEF at peak stress	Treadmill test / stress TTE	Normal
Progressive LV dilatation/dysfunction	Change in LV dimensions / LVEF	No significant changes in LV dimensions or LVEF

***ECG**, electrocardiogram; **ECV**, extracellular volume; **GLS**, global longitudinal strain; **hs-cTn**, high-sensitivity cardiac troponin; **LBBB**, left bundle branch block; **LGE**, late gadolinium enhancement; **LV**, left ventricle; **LVEF**, left ventricular ejection fraction; **NT-proBNP**, N-terminal pro-B-type natriuretic peptide; **pEF**, preserved ejection fraction; **TTE**, transthoracic echocardiography; **VT**, ventricular tachycardia.*

En este sentido, otra forma de interpretar estos algoritmos es que, más allá del riesgo de eventos, nos ayudan a definir la probabilidad pretest de miocardiopatía, es decir la probabilidad que un individuo con hallazgos de NCVI tenga una hipertrabeculación patológica (y por tanto, riesgo de eventos adversos) o una hipertrabeculación fisiológica (muy bajo riesgo). Esta diferenciación es controvertida y todavía no está bien definida a día de hoy. Sin embargo, es importante plantearse el diagnóstico diferencial en todos los casos ya que, tal y como sugieren los documentos de consenso de expertos [1] y las guías de práctica clínica de la ESC [6], la no compactación o excesiva trabeculación del ventrículo izquierdo no se asocia necesariamente a una miocardiopatía de base. Además, esta diferenciación es importante desde el punto de vista práctico, ya que un individuo con hipertrabeculación fisiológica presenta un pronóstico benigno y debería ser dado de alta, evitando de esta manera una carga psicológica innecesaria personal y familiar, así como un gasto sanitario innecesario. En cambio, un paciente con hipertrabeculación patológica debe realizar un seguimiento periódico en una

unidad de referencia debido al riesgo de complicaciones cardiovasculares. A día de hoy, el grado de hipertrabeculación no permite hacer esta diferenciación, por lo que son necesarios más estudios con nuevas técnicas (*radiomics*, inteligencia artificial, etc.) que ayuden en el diagnóstico diferencial y nos permitan también predecir qué pacientes tendrán un estudio genético positivo.

En definitiva, se deberían redefinir los criterios diagnósticos de la NCVI integrando todos las variables anteriormente comentadas, más allá de la valoración de la hipertrabeculación per se, que en nuestra seria no ha demostrado tener implicaciones pronósticas (***Tabla 12***), tal y como está publicado en la literatura [47,52]. Idealmente, se debería crear un *score* diagnóstico, parecido al diagnóstico *Task Force* propuesto para la miocardiopatía arritmogénica [93], de manera que una mayor puntuación conllevaría una mayor probabilidad de tener una miocardiopatía (y en paralelo, un mayor riesgo de eventos adversos). De esta forma, evitaríamos las incongruencia de los diferentes criterios existentes [40] y el sobrediagnóstico de casos [12], aumentando la especificidad del diagnóstico. Por tanto, nuestro algoritmo de bajo riesgo, y el resto de algoritmos comentados, tendrían una finalidad tanto diagnóstica como pronóstica.

6.5. LIMITACIONES

Este trabajo corresponde a un estudio retrospectivo, con todos los sesgos inherentes a este diseño, y con el cual no podemos establecer relaciones de causa - efecto. Serán necesarios en el futuro estudios prospectivos que validen nuestros hallazgos, como ya se ha comentado en la discusión, incluyendo la validación prospectiva del modelo predictivo de riesgo en una cohorte externa de mayor tamaño. No podemos asegurar la validez externa, ya que solo se incluyeron pacientes seguidos en unidades de referencia de cardiopatías familiares, por lo que nuestros hallazgos podrían no ser generalizables a cualquier individuo con hallazgos morfológicos de NCVI. Además, debido a la ausencia de un grupo control, no podemos asegurar si las variables pronósticas descritas en nuestra cohorte son específicas para NCVI, o si

por el contrario serían aplicables a otras poblaciones. Sin embargo, todas estas limitaciones son comunes en la mayoría de artículos publicados sobre miocardiopatías.

No se realizó un análisis centralizado de las ecocardiografías con lo que se utilizaron diferentes equipos para la adquisición y postprocesado de las imágenes, y por tanto no se puede descartar cierta variabilidad a la hora de calcular la FEVI, tanto en el momento basal como a lo largo del seguimiento. Sin embargo, los estudios se realizaron en centros de referencia por expertos en imagen cardíaca, por lo que se asume que esta variabilidad no es clínicamente significativa. No se realizó RMC a todos los pacientes (de forma análoga a la mayoría de artículos sobre NCVI), pero al ser una técnica menos disponible, su uso sistemático en cualquier caso de NCVI sin sospecha de miocardiopatía no parece justificado. Además, se hizo un análisis centralizado sólo de los individuos de bajo riesgo. Para el resto, se utilizaron los datos de RMC proporcionados por cada centro, por lo que tampoco se puede descartar cierta variabilidad. Sin embargo, la reproducibilidad de la RMC es superior a la ETT, de manera que su asume que esta variabilidad no es clínicamente relevante. Específicamente, la valoración del RTG sólo se hizo de forma visual cualitativa, lo que, junto con la colinealidad descrita con la FEVI, muy posiblemente infraestimó su valor pronóstico.

No disponíamos de información sobre el momento de prescripción del tratamiento médico, por lo que no se pudo utilizar para el análisis de supervivencia, pero al ser pacientes seguidos en centros de referencia se asume que se siguieron las guías de práctica clínica. De la misma manera, tampoco disponíamos de información sobre biomarcadores de todos los pacientes y había inconsistencias en el biomarcador utilizado según el centro (BNP y NTproBNP), por lo que se omitió esa información en el estudio. No se realizó estudio genético y familiar en todos los casos, con lo cual los resultados podrían no ser generalizables. Sin embargo, se hizo un estudio fenotípico familiar y genotípico en una proporción elevada de pacientes (60% aproximadamente), en consonancia con otros estudios de NCVI. Además, la realización

indiscriminada de un estudio genético a cualquier paciente con hallazgos morfológicos de NCVI no parece razonable, por lo que nuestro estudio refleja la práctica clínica habitual de muchos centros de referencia del país.

7

Conclusiones

1. La no compactación del ventrículo izquierdo conlleva un riesgo aumentado de eventos cardiovasculares adversos mayores (38% a un seguimiento mediano de 5,1 años). La edad, el sexo, los factores de riesgo cardiovascular, las alteraciones en el electrocardiograma, la fracción de eyección del ventrículo izquierdo y la agregación familiar se asocian de forma independiente a la incidencia de eventos adversos y permiten predecir el riesgo de forma precisa.

2. La fracción de eyección del ventrículo izquierdo es una de las principales variables asociadas al riesgo de eventos cardiovasculares, incluyendo la insuficiencia cardíaca y las arritmias ventriculares. La FEVI puede disminuir (6% a un seguimiento ecocardiográfico mediano de 4,3 años) y este deterioro se asocia al riesgo de MACE, independientemente de la FEVI basal.

3. En la no compactación del ventrículo izquierdo, el electrocardiograma, la fracción de eyección del ventrículo izquierdo, el realce tardío de gadolinio y la agregación familiar permiten identificar los casos de bajo riesgo. Los individuos sin ningún signo de alarma tienen un pronóstico excelente (0% de eventos a 5,1 años) y corresponden a casos de hipertrabeculación fisiológica. En pacientes con FEVI conservada y sin realce tardío de gadolinio, un *strain* auricular anormal sugiere una miocardiopatía subclínica.

4. La valoración integral del fenotipo de no compactación del ventrículo izquierdo permite estimar la probabilidad de ser portador de una miocardiopatía, mejorando la especificidad de los criterios diagnósticos actuales, así como asesorar el riesgo de eventos adversos para ofrecer un manejo individualizado. Sin embargo, a día de hoy sigue siendo una entidad heterogénea y mal definida, tanto a nivel fenotípico como genotípico. Son necesarios estudios prospectivos que confirmen nuestros hallazgos y mejoren el diagnóstico diferencial y la estratificación pronóstica.

8

Líneas de investigación futuras

En paralelo al desarrollo de los estudios mencionados en esta tesis doctoral, durante este tiempo hemos iniciado un estudio internacional específico de RMC, coordinado por el Hospital Universitari Vall d'Hebron, con un análisis centralizado de las imágenes en nuestro departamento de imagen cardíaca. Se han reclutado más de 350 pacientes de centros españoles (cohorte interna), así como más de 240 pacientes de centros internacionales (EEUU, Italia y Suiza; cohorte externa). Se ha realizado un análisis integral de las RMC, incluyendo variables avanzadas como el *strain* ventricular y auricular, fuerzas hemodinámicas y cuantificación de RTG, que han permitido desarrollar un modelo predictivo de MACE con una excelente capacidad discriminativa en la cohorte de derivación (índice C de Harrell de 0,83). Está pendiente en el momento actual completar el análisis de las RMC externas para validar los hallazgos descritos en la cohorte interna.

También hemos establecido una colaboración con un grupo de bioingenieros la Universitat de Barcelona, liderados por Karim Lekadir, que trabaja en técnicas de *radiomics*. Hemos realizado una publicación conjunta sobre resultados preliminares en NCVI [94]. Nuestra intención es proseguir con esta línea de investigación basada en técnicas de inteligencia artificial y aprendizaje automático (*machine learning*) aplicadas a la imagen cardíaca, y actualmente tenemos en revisión un artículo al respecto ("Radiomics analysis of cardiac magnetic resonance images for the detection of genetic and familial cases in excessive trabeculation of the left ventricle"; Journal of Cardiovascular Magnetic Resonance).

Basándonos en las RMC reclutadas, se han diseñado tres proyectos más que se iniciarán en el futuro. Primero, intentar definir un nuevo algoritmo diagnóstico basado exclusivamente en RMC que mejore el bajo rendimiento de los criterios diagnósticos actuales, y permita identificar aquellos casos con una miocardiopatía asociada (genética positiva, agregación familiar y/o eventos cardiovasculares adversos). Este análisis utilizará variables morfológicas, funcionales avanzadas (*strain* y fuerzas

hemodinámicas) y de caracterización tisular (presencia, cuantificación y patrones de RTG). Segundo, un estudio específico sobre arritmias ventriculares, para intentar optimizar el uso de DAI en esta población. Tercero, un trabajo para intentar identificar mediante RMC a los pacientes que presentarán un resultado positivo del estudio genético, para optimizar la indicación del mismo debido a su alto coste, de forma análoga a lo publicado en MCD [95].

Finalmente, nos gustaría establecer nuevas colaboraciones tanto nacionales como internacionales para poder reclutar una gran cohorte que nos permitiera realizar una validación prospectiva de todos nuestros hallazgos. En este sentido, hemos contactado con Steffen E. Petersen del Barts Hospital (Londres, Reino Unido), unos de los mayores expertos mundiales sobre NCVI, y estamos valorando posibles colaboraciones.

9

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10

Anexos

10.1. PUBLICACIONES

10.1.1. Artículo 1

Casas G, Limeres J, Oristrell G, Gutierrez-Garcia L, Andreini D, Borregan M, et al. Clinical Risk Prediction in Patients With Left Ventricular Myocardial Noncompaction. J Am Coll Cardiol. 2021;78(7):643–62.

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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).

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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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Javed Butler, MD, MPH, MBA, served as Guest Editor-in-Chief for this paper.

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

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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

Continued on the next page

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

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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*

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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).

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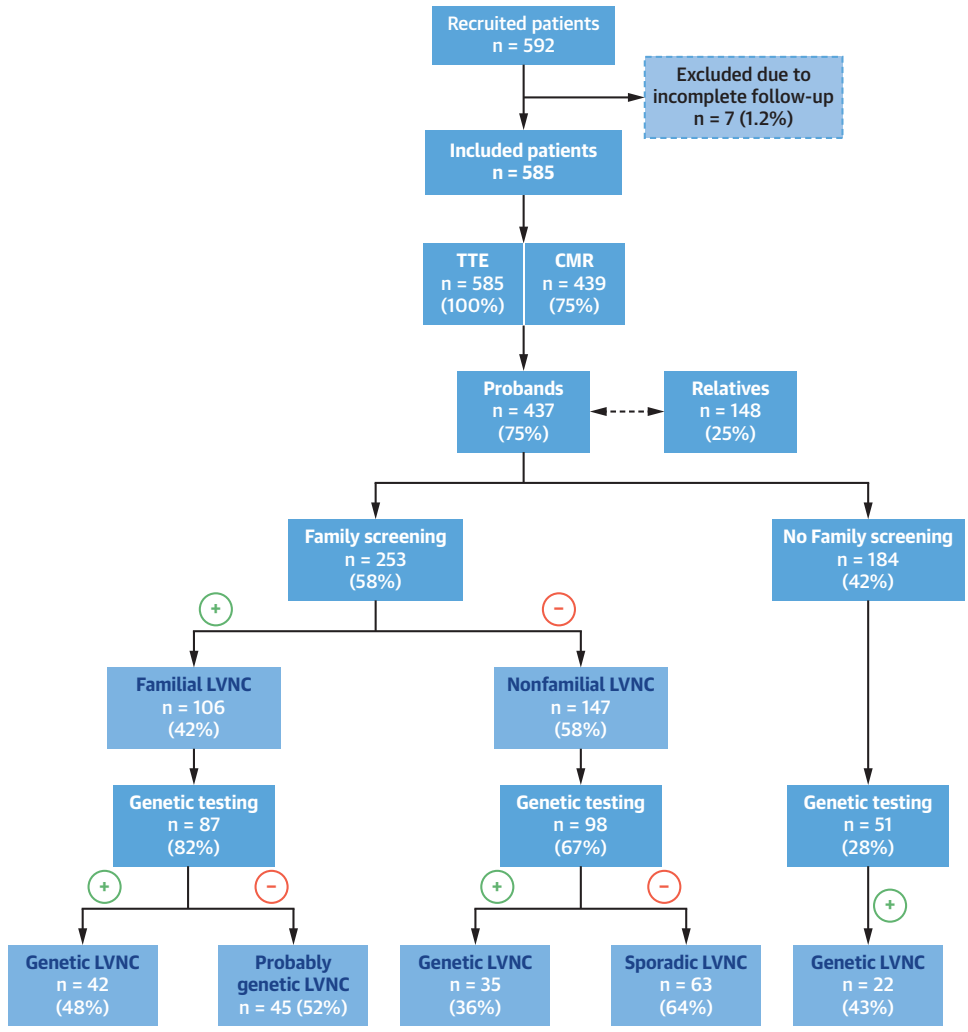
FIGURE 1 Study Flowchart



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

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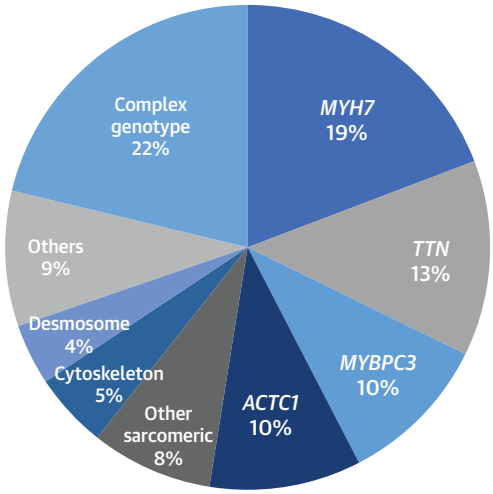
FIGURE 2 Genetics of Left Ventricular Noncompaction



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

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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

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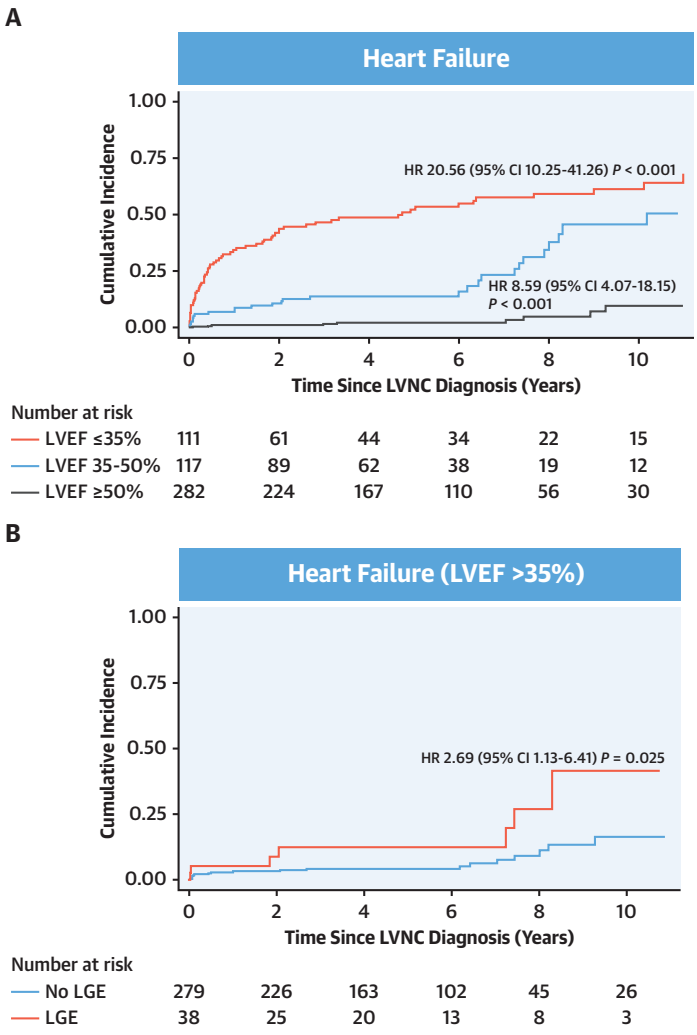
FIGURE 3 Cumulative Incidence of Heart Failure and Ventricular Arrhythmias



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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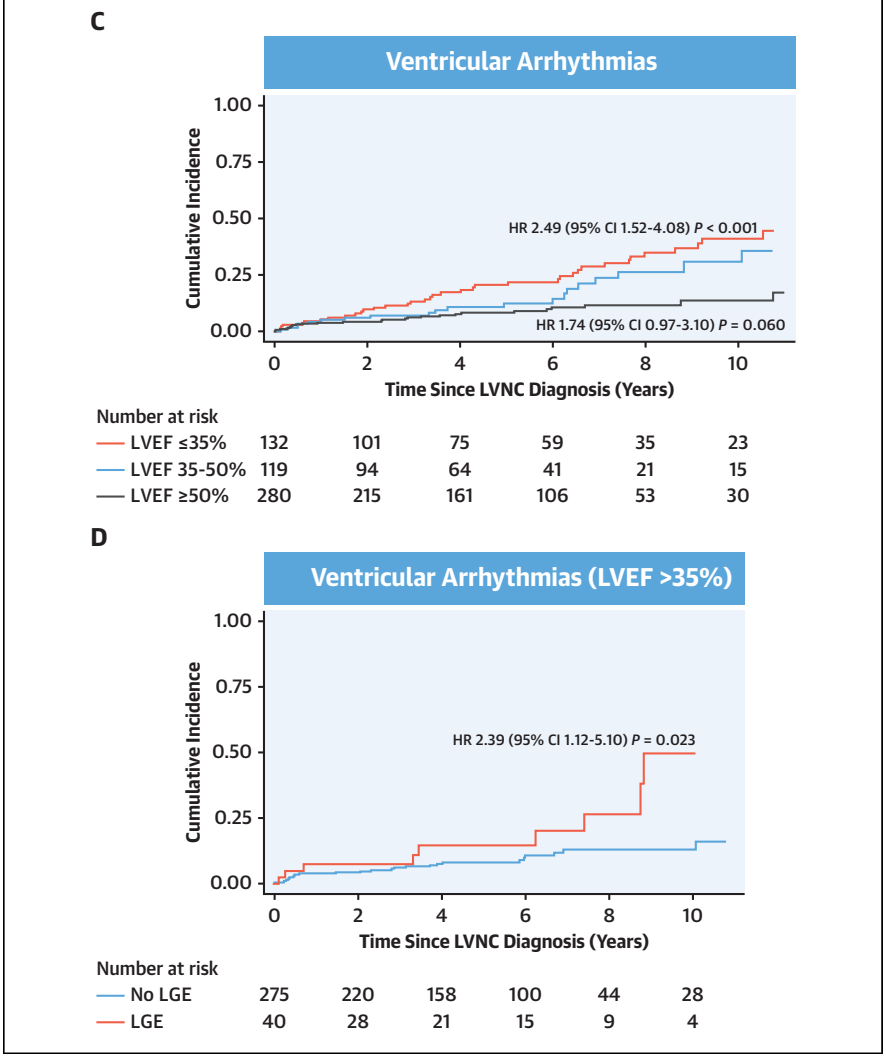
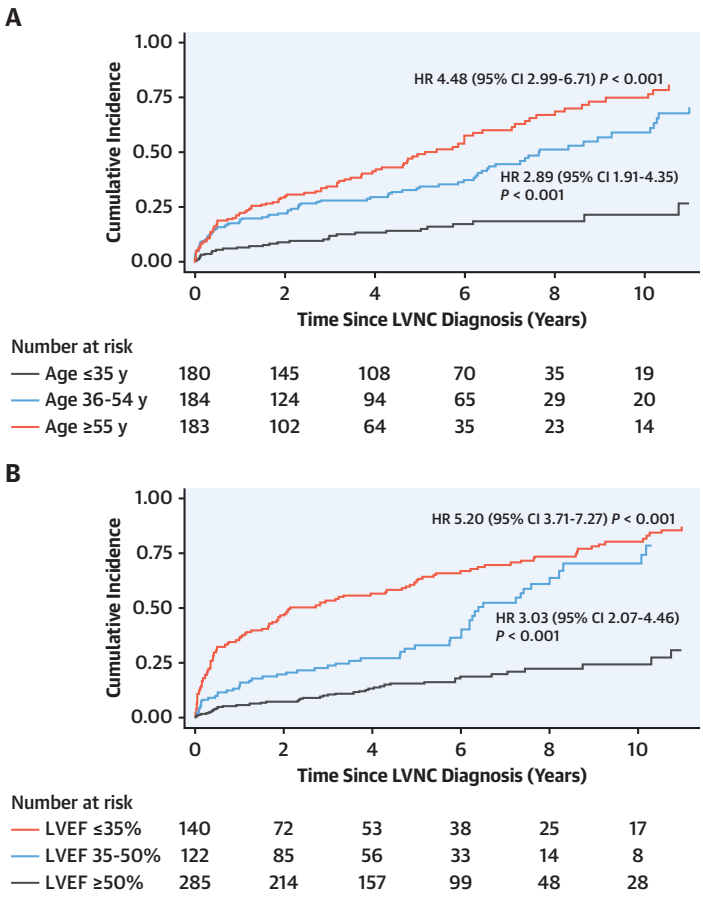
FIGURE 3 Continued



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,

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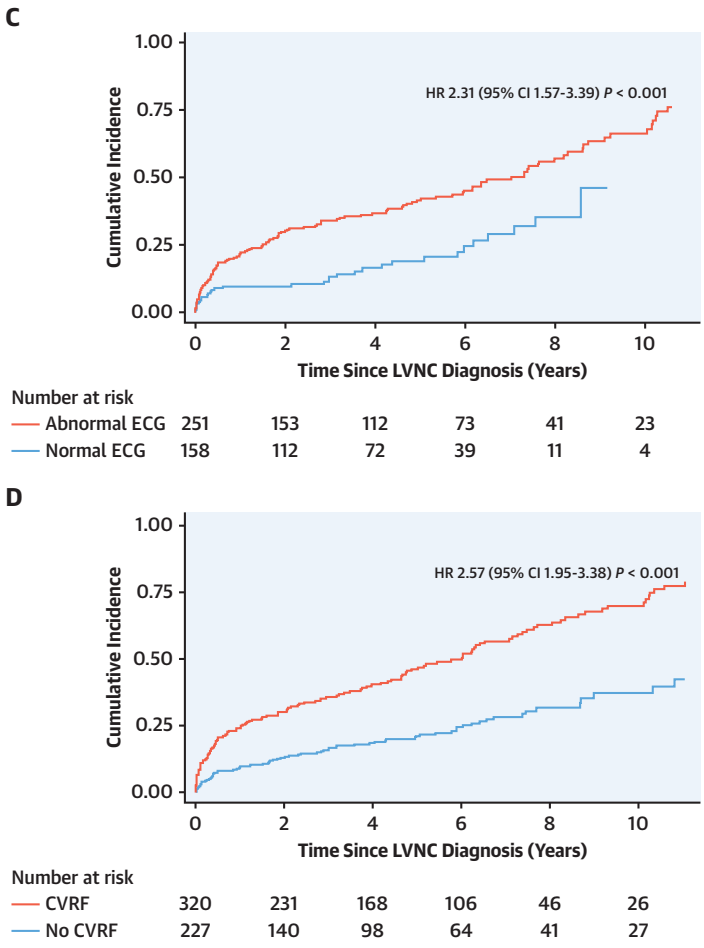
FIGURE 4 Continued



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

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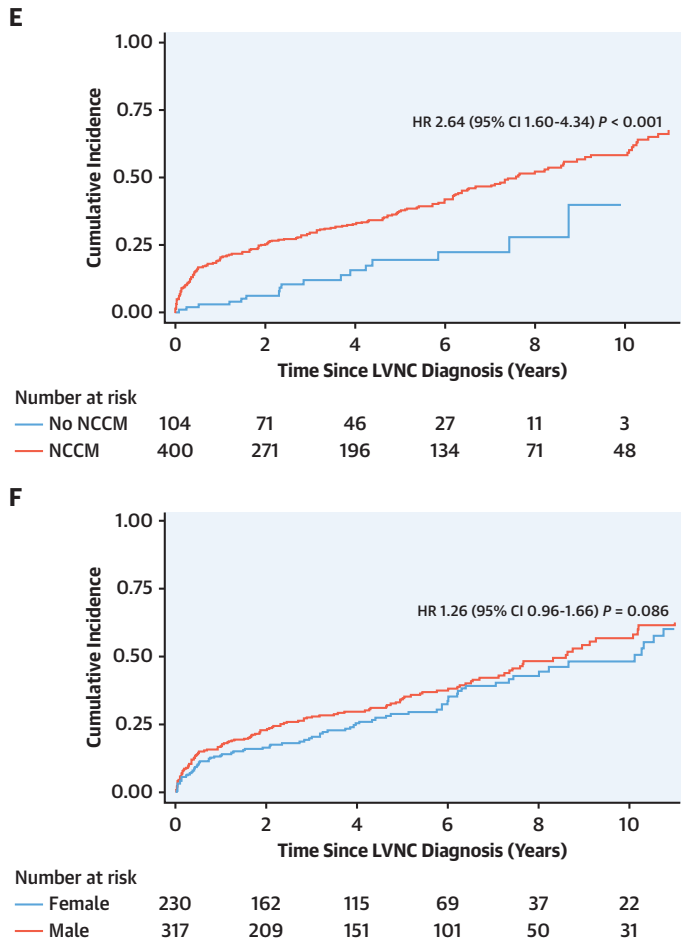
FIGURE 4 Continued



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

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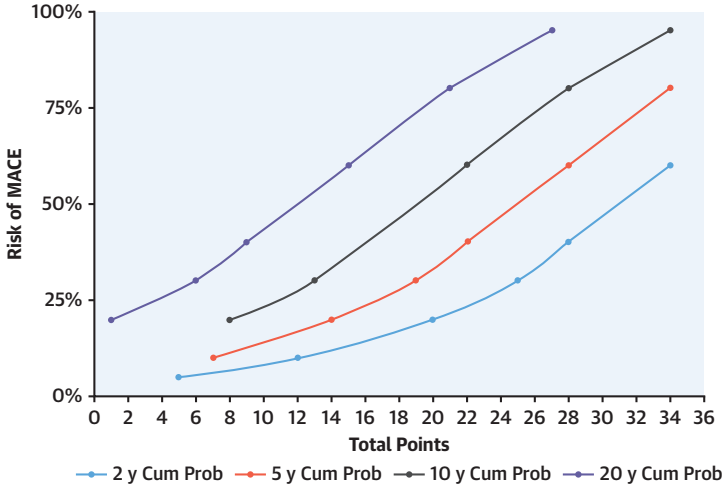
FIGURE 5 Risk Prediction Model of MACE in LVNC

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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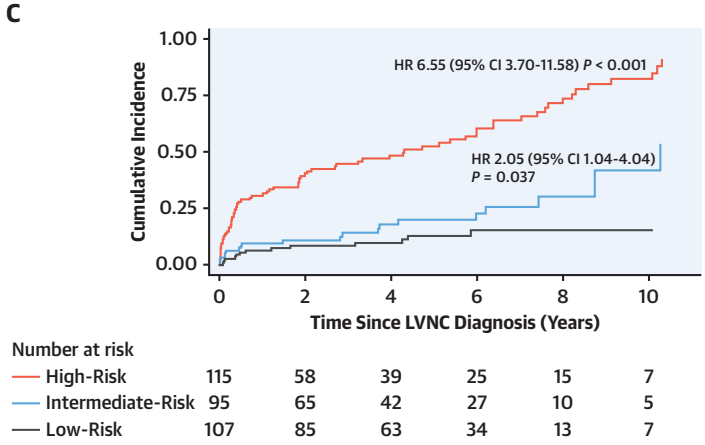
FIGURE 5 Continued



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

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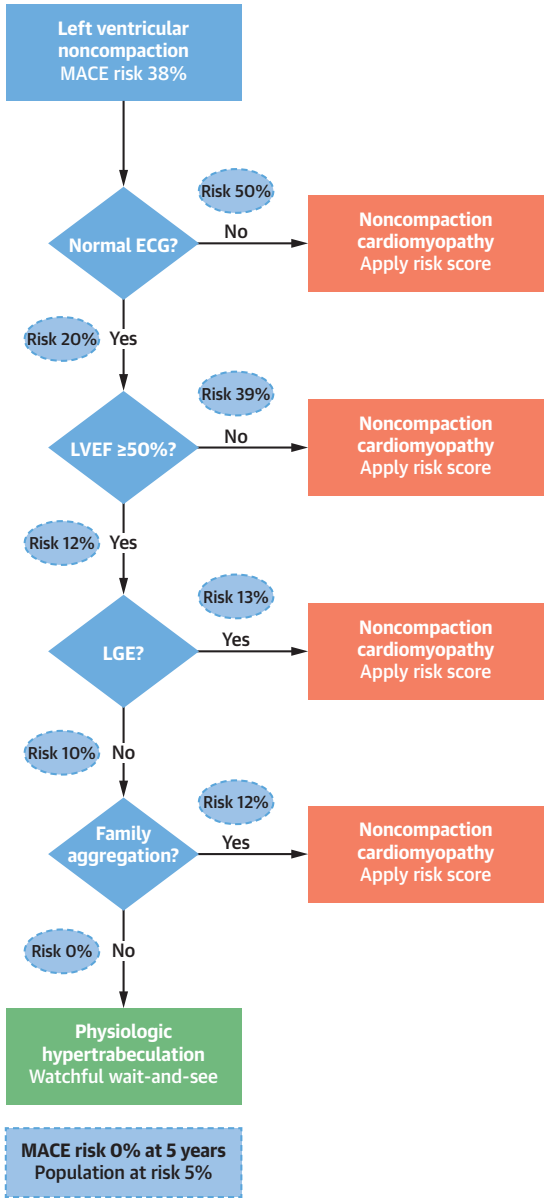
FIGURE 6 **LVNC Safety Algorithm**



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.

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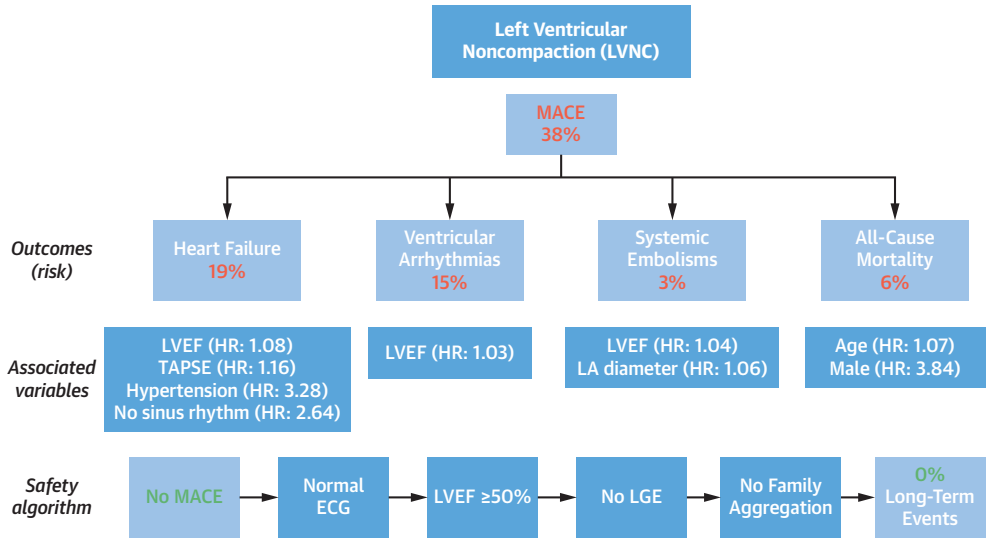
CENTRAL ILLUSTRATION **Outcomes of LVNC**



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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

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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.

10.1.2. Artículo 2

Casas G, Rodríguez-Palomares JF, Ferreira-González I. Left ventricular noncompaction: a disease or a phenotypic trait? Rev Esp Cardiol (Engl Ed). 2022 Dec;75(12):1059–69.

Rev Esp Cardiol. 2022;75(12):1059–1069

Review article

Left ventricular noncompaction: a disease or a phenotypic trait?

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Differential diagnosis
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ABSTRACT

Left ventricular noncompaction is a poorly defined and controversial entity, with wide phenotypic expression: from a simple anatomical trait to a disease with overt cardiac affection. Current diagnostic criteria rely exclusively on morphologic features of hypertrabeculation, which have low specificity for identifying true cardiomyopathy cases. The management of left ventricular noncompaction is also heterogeneous, and there are no dedicated clinical practice guidelines. The most common cardiovascular complications are heart failure, ventricular arrhythmias, and systemic embolisms. In this review, we discuss the diagnostic limitations of the available criteria, and propose a comprehensive alternative approach (including functional imaging variables, tissue characterization, genetics, and family screening) that may help in the differential diagnosis of hypertrabeculation cases. We also describe the genetic background of the disease and discuss the overlap with other cardiomyopathies. Finally, we focus on controversial issues in clinical management and suggest the use of the previously-mentioned variables for risk stratification and for individualization of patient follow-up.

Miocardio no compactado: ¿una enfermedad o un rasgo fenotípico?

Palabras clave:
Miocardiopatía
Tratamiento clínico
Diagnóstico diferencial
Estratificación pronóstica

RESUMEN

El miocardio no compactado es una entidad mal definida y en controversia, con una amplia expresividad fenotípica: desde un simple rasgo anatómico hasta una enfermedad con grave afección cardiaca. Los criterios diagnósticos actuales se basan únicamente en hallazgos morfológicos de hipertrabeculación y tienen una baja especificidad para identificar casos de miocardiopatía. El tratamiento del miocardio no compactado también es heterogéneo y no existen guías de práctica clínica específicas. La insuficiencia cardiaca, las arritmias ventriculares y las embolias sistémicas son las complicaciones cardiovasculares más frecuentes. En esta revisión, se tratan las limitaciones diagnósticas de los diferentes criterios disponibles y se propone una aproximación holística alternativa (que incluye variables funcionales por imagen, de caracterización tisular genética y estudio familiar) que puede ayudar en el diagnóstico diferencial de casos con hipertrabeculación. Se describe la genética de esta entidad y el solapamiento con otras miocardiopatías. Por último, se centra en aspectos debatidos del tratamiento clínico y se propone utilizar las mismas variables ya comentadas para la estratificación pronóstica e individualizar el seguimiento de los pacientes.

INTRODUCTION

Left ventricular noncompaction (LVNC) is a heterogeneous entity characterized by prominent left ventricular (LV) trabeculae, deep intertrabecular recesses, and a thin compacted myocardial layer.[1] Even though it was first described more than 30 years ago,[2] LVNC is still a poorly defined and understood disorder, considered a nonclassified familial cardiomyopathy by the European Society of Cardiology,[3] and a genetic cardiomyopathy by the American Heart Association.[4]

Several diagnostic imaging parameters have been proposed, but there are no standardized criteria. The different criteria are inconsistent, and focus only on morphologic traits, which has resulted in an overdiagnosis of LVNC.[5] Additionally, this heterogeneity has led to highly variable LVNC outcomes being reported in the literature. All in all, no clinical practice guidelines are available for such a controversial entity, which makes clinical management highly challenging.

In this review, we focus on the various available diagnostic criteria and the complexity of reaching a correct diagnosis. In

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1885-5857/

Abbreviations

CMR: cardiovascular magnetic resonance
LGE: late gadolinium enhancement
LVEF: left ventricular ejection fraction
LVNC: left ventricular noncompaction
MACE: major adverse cardiovascular events
TTE: transthoracic echocardiography

addition, we discuss the difficulties and controversies of specific clinical management.

DIAGNOSTIC CRITERIA AND DIFFERENTIAL DIAGNOSIS

Definition of the entity

LVNC diagnosis is currently based on cardiac imaging techniques, both with transthoracic echocardiography (TTE) and cardiovascular magnetic resonance (CMR). Different diagnostic criteria have been proposed, which focus on morphologic traits to compare the compacted and noncompacted myocardial layers, without considering functional parameters. These criteria are inconsistent, not standardized, and based on small series of patients, which makes the diagnosis of LVNC widely heterogeneous (table 1).

Chin et al.[2] first reported LVNC TTE diagnostic criteria based on a series of 8 patients. These authors proposed measuring the distance from the epicardial surface to the trough of the trabeculae (X), and the distance from the epicardial surface to the peak of the trabeculae (Y) on short-axis views. The authors defined that a ratio of X/Y $\leq$ 0.5 at end-diastole was suggestive of LVNC (figure 1A). Later, Jenni et al.[2] published a series of 34 patients, and suggested measuring the compacted (C) epicardial layer and the noncompacted (NC) endocardial layer. A ratio of NC/C $\geq$ 2 measured on short-axis views at end-systole was considered to be consistent with LVNC[6] (figure 1A). The third relevant TTE criterion was reported by Stöllberger et al.[2] in a series of 62 patients. Based on their observations, the presence in 1 apical plane of more than 3 trabeculations protruding from the LV wall (apically from the insertion of the papillary muscles) was considered suggestive of LVNC[7] (figure 1B). This criterion was later updated to also include a ratio of NC/C $\geq$ 2 measured on short-axis views at end-diastole.[8] Of all these proposed criteria, Jenni's criterion has become the most widely used in clinical practice with TTE.

With CMR, at least 5 different diagnostic criteria have been described, although only 2 of them (Petersen and Jacquier) are usually applied in clinical practice. Petersen et al.[9] first reported CMR-derived diagnostic criteria in a series of 7 patients who showed hypertrabeculation on TTE and/or CMR. The authors reported that a ratio of NC/C layers $>$ 2.3 measured on long-axis views at end-diastole was suggestive of LVNC (figure 2A). Jacquier et al. later published other criteria based on a series of 16 patients meeting Jenni's TTE criteria. According to their observations, a trabeculated mass $>$ 20% of the total LV mass showed an excellent diagnostic accuracy for LVNC[10] (figure 2B). The criteria of Jacquier et al. seem more robust than Petersen's criteria considering that the global hypertrabeculated myocardium is measured and not only the ratio of hypertrabeculation in a specific region. Even though Jacquier's criteria have excellent interobserver reproducibility, their assessment is time-consuming. Therefore, Petersen's criteria have become the most widely used in routine clinical practice. Indeed, due to increased spatial resolution and better tissue characterization compared with TTE, CMR is always recommended to confirm LVNC diagnosis.

Some other CMR diagnostic approaches have been described. Stacey et al.[11] proposed measuring the NC/C ratio in short-axis cine sequences at end-systole. Based on a series of 122 patients, they described that a ratio $\geq$ 2 was suggestive of LVNC. Grothoff et al.[12] published a small series of 12 LVNC patients and concluded that a cutoff point of 15 grams of trabeculated mass/m^2 showed an excellent diagnostic accuracy for LVNC. Finally, Captur et al.[13] published a series of 30 patients and described a new diagnostic method based on fractal analysis, a semiautomatic tool to quantify the degree of hypertrabeculation. Fractal dimension, a marker of geometric complexity, is obtained after contouring the LV endocardium at end-diastole, and a maximal apical fractal dimension $\geq$ 1.30 is diagnostic of LVNC (figure 2C). Fractal analysis has excellent inter- and intraobserver reproducibility, although its use has not been widely adopted because of the limited availability of the software needed for its assessment.

Limitations of the current definition

As previously mentioned, none of these criteria include functional LV parameters such as LV size, systolic function (LV ejection fraction, left ventricular ejection fraction [LVEF]), or the presence of late gadolinium enhancement (LGE) (figure 3). This has probably resulted in an overdiagnosis of LVNC cases,[5] even in asymptomatic patients with no established cardiovascular disease: in a population-based study, 15% fulfilled at least 1 LVNC criteria.[14] It should also be noted that the sole presence of

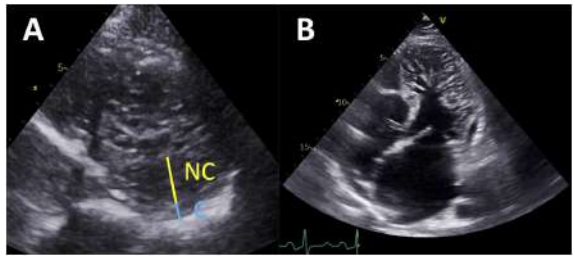

Figure 1. Left ventricular noncompaction diagnostic criteria with transthoracic echocardiography. A: measurement of the wall thickness of the compacted (C) and noncompacted (NC) myocardial layers on a short-axis view, at end-diastole (Chin criteria) or end-systole (Jenni Criteria). B: apical 4-chamber view showing numerous and prominent trabeculations protruding from the left ventricle apically from the papillary muscles (Stöllberger criteria).

Table 1
Summary of different diagnostic criteria for left ventricular noncompaction

Criteria	Chin	Jenni	Stöllberger	Petersen	Jacquier	Stacey	Grotthoff	Captur
Reference	2	6	7, 8	9	10	11	12	13
Number of patients	8	7	62	7	16	122	12	30
Gold-standard diagnosis	Necropsy, 3 (38)	Anatomical examination, 7 100)	> 3 trabeculations protruding from the LV wall and intertrabecular spaces	TTE or CMR evidence of a 2 -layered myocardium and 1 additional feature	Jenni criteria	Jenni and Petersen criteria	Jenni criteria and 1 additional feature	Jenni criteria and 1 additional feature
Age, y	9 [11-22]	39 ± 17	50 [18-75]	29 ± 13	48 ± 17	57 ± 17	35 ± 18	41 ± 13
Females	3 (38)	2 (29)	13 (21)	2 (29)	6 (38)	50 (41)	9 (75)	14 (47)
Left ventricular systolic function	FS range 10%-33%	LVEF 29% ± 6%	FS < 30% in 43 (69) patients	LVEF 53% ± 17%	Not reported	LVEF 44% ± 16%	LVEF 51% ± 16%	LVEF 52% ± 17%
Cardiovascular events	5 (63)	7 (100) death and/or heart transplant	45 (73) heart failure	3 (43)	Not reported	36 (30) heart failure	6 (50) ventricular tachycardia	20 (67)
Imaging technique	TTE	TTE	TTE	CMR (1.5 T)	CMR (1.5 T)	CMR (1.5 T)	CMR (1.5 T)	CMR (1.5 T)
View	Short-axis	Short-axis	Apical views	Longitudinal-axis	Short-axis stack	Short-axis	Short-axis stack	Short-axis stack
Cardiac cycle phase	End-diastole	End-systole	End-diastole	End-diastole	End-diastole	End-systole	End-diastole	End-diastole
Trabeculation measurement	Distance between the epicardial surface and trough of a trabecular recess (X) and the distance between the epicardial surface and peak of the trabeculation (Y)	Measurement of the wall thickness of the NC and C myocardial layers	Presence of more than 3 trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in 1 image plane and measurement of the wall thickness of the NC and C myocardial layers	Measurement of the wall thickness of the NC and C myocardial layers	Semiautomatic outlining of endocardial and epicardial contours, including papillary muscles	Measurement of the wall thickness of the NC and C myocardial layers	Manual tracing of epicardial borders in 4-chamber and vertical long-axis views, propagation algorithm in short-axis and manual tracing of trabeculations	Segmentation of the endocardial border and box-counting method for fractal analysis
Cutoff point	X/Y ≤ 0.5	NC/C ≥ 2	NC/C ≥ 2	NC/C ≥ 2.3	Trabeculated mass > 20% of the total LV mass	NC/C ≥ 2	Trabeculated mass > 15 g/m^2 or > 25% of the total LV mass or NC/C ≥ 3	Maximal apical fractal dimension ≥ 1.30
Interobserver variability	Significant at apical segments, insignificant at mid and basal segments	Not reported	Not reported	Not reported	Intraclass correlation coefficient 0.95 (95%CI, 0.89-0.97)	Spearman correlation 0.82 and 0.78 for the compacted and noncompacted layers, respectively	Not reported	Intraclass correlation coefficient 0.96 (95%CI 0.93-0.97)
Figure	1A	1A	1B	2A	2B			2C

95%CI, 95% confidence interval; C, compacted; CMR, cardiovascular magnetic resonance; FS, fractional shortening; LVEF, left ventricular ejection fraction; NC, noncompacted; TTE, transthoracic echocardiography.
Unless otherwise indicated, the data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

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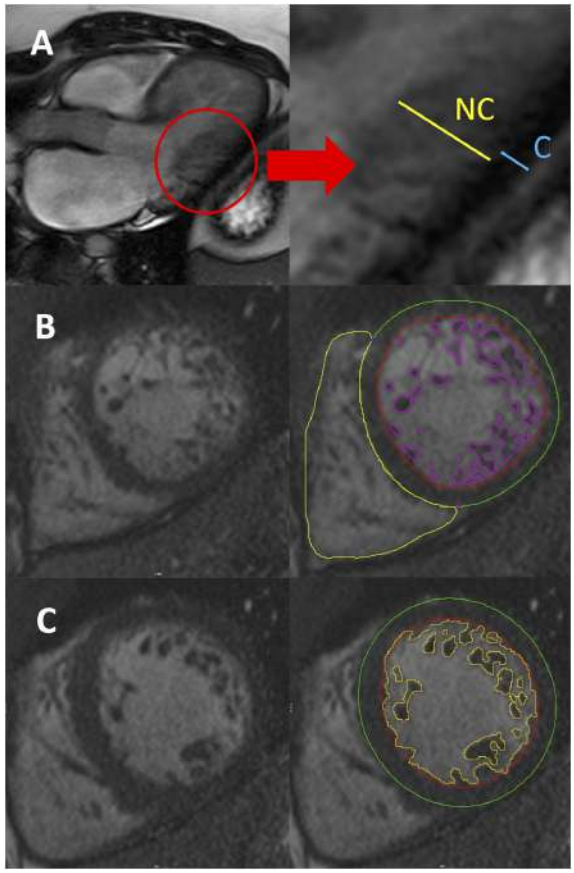

Figure 2. Left ventricular noncompaction diagnostic criteria with cardiovascular magnetic resonance. A: measurement of the wall thickness of the compacted (C) and noncompacted (NC) myocardial layers on a longitudinal-axis view at end-diastole (Petersen criteria). B: endocardial (red) and epicardial (green) contours, including semiautomatic outlining of the trabeculae (purple) for trabeculated mass quantification, in a short-axis view (Jacquier criteria). C: endocardial (red) and epicardial (green) contours, including the automatic outlining of the trabeculae (yellow) for fractal analysis, in a short-axis view (Captur criteria).

hypertrabeculation fulfilling LVNC criteria has not been associated with either long-term LV remodelling[15] or outcomes.[16,17] A substudy of the MESA registry analyzed 2742 patients with a baseline CMR and a follow-up at 9.5 years. Patients were divided into quintiles of hypertrabeculation following Petersen's assessment,[9] and no differences were found among groups in terms of changes in LV volumes or LVEF.[15] When considering clinical endpoints, a study of 700 patients referred to CMR found that fulfilling any of the 4 aforementioned CMR criteria was not associated with major adverse cardiovascular events (MACE) at 7 years of follow-up.[16] Similar findings were observed in a large meta-analysis of 574 patients with LVNC: diagnostic criteria per se had no prognostic value beyond LVEF or the presence of LGE.[17] In addition, hypertrabeculation in nonischemic dilated cardiomyopathy (DCM) has not been associated with a worse outcome.[18]

Furthermore, there have been reports of acquired and reversible hypertrabeculation. In particular, a high prevalence has been observed in athletes: 8% to 10% of highly-trained athletes fulfil LVNC criteria.[19,20] Indeed, a large population-based study showed that vigorous physical activity was progressively associated with hypertrabeculation: individuals undertaking more activity showed a higher proportion of LVNC criteria, irrespective of LV volumes.[21] In addition, another study showed that pregnancy was frequently associated with hypertrabeculation: 8% of women developed LVNC during pregnancy, which mostly disappeared after childbirth.[22] Similarly, a large proportion of patients with sickle cell anemia were found to have hypertrabeculation, and at least 8% fulfilled LVNC criteria.[23] These findings suggest that certain changes in loading conditions might lead to physiological remodeling with marked LV hypertrabeculation without prognostic implications.

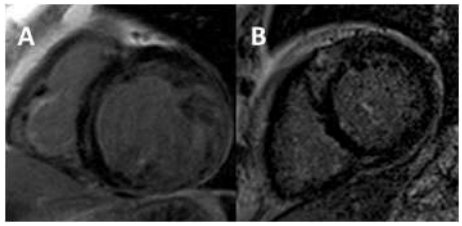

Figure 3. Cardiovascular magnetic resonance post-contrast T_1 images showing different late gadolinium enhancement patterns in left ventricular noncompaction. A: linear intramyocardial basal septum uptake. B: focal intramyocardial basal anteroseptal uptake.

In contrast, some other studies have shown discordant results and have suggested that hypertrabeculation might not be considered a benign finding, reinforcing the fact that LVNC is a highly heterogeneous entity. In a large population-based study of 10 097 patients who underwent cardiac computed tomography, patients with hypertrabeculation were at increased risk of MACE at 4.0 years of follow-up, and the degree of hypertrabeculation (measured as the indexed trabeculated LV mass) was independently associated with outcomes.[24] Similarly, another study of 339 LVNC patients followed up for 6.3 years showed that LV hypertrabeculation (defined by Petersen's criteria) extending from the apex to mid-basal segments was independently associated with all-cause mortality.[25] In addition, in a series of 328 patients with LVNC followed up for 3.1 years, the authors found that the presence of myocardial thinning (defined as an abrupt thinning of compacted myocardium by 50% or greater compared with a contiguous segment) was independently associated with a higher risk of MACE.[26]

Little is known about the involvement of the right ventricle (RV) in LVNC. The RV is a naturally more hypertrabeculated chamber than the LV and therefore applying the same LV criteria might lead to a considerable overlap with the healthy population. Specific cutoff values have not been published or validated, and quantification of RV trabeculae with TTE is technically challenging. Several CMR measurements of the RV hypertrabeculation have been proposed, including the RV end-diastolic trabeculated area and volumes, as well as the RV NC/C ratios in short-axis and 4-chamber views.[27] However, a strong overlap with controls has been observed and, without prognostic implications, caution is recommended when analyzing these variables.

One step further: the holistic approach

All this controversial data has prompted some authors to question whether LVNC is a true cardiomyopathy or a simple morphologic trait.[28,29] Consequently, some algorithms combining LVEF, LGE presence, electrocardiogram data, family history, or genetic testing, have been proposed to differentiate physiologic hypertrabeculation (a phenotypic trait) from pathologic forms[30–32] (table 2). In a recent large multicentre study, a stepwise algorithm has been proposed to identify low-risk LVNC patients: cases with no electrocardiogram abnormalities, with a preserved LVEF, no LGE, and no family history did not show MACE at 5 years of follow-up. This suggests that those cases might correspond to physiologic or "benign" hypertrabeculation rather than a cardiomyopathy. However, patients with any of the aforementioned abnormalities presented an increased risk of cardiovascular events, confirming the pathological nature of such hypertrabeculation.[33]

Additionally, other imaging parameters, such as deformation and mapping variables have been proposed, but they have only been tested in small case series and are not recommended in routine clinical practice. Global strain, LV rotation, and torsion on TTE are impaired in LVNC even with a preserved LVEF, and significantly lower compared with controls.[34] Similar results have

Table 2
Differential diagnosis of patients with morphologic features of hypertrabeculation

Favors cardiomyopathy	Variable	Favors phenotypic trait
Dilated and/or hypertrophic LV	LV dimensions	Nondilated and nonhypertrophic LV
Reduced	LVEF	Preserved
Abnormal (even if pEF)	GLS	Normal
Abnormal (even if pEF)	Diastolic function	Normal
+	LGE	-
Elevated	ECV	Normal
+	Past family history and/or family aggregation	-
+	Genotype	-
Shortness of breath, syncope, palpitations...	Symptoms	Asymptomatic
Heart failure, supraventricular/ventricular arrhythmias, systemic embolisms, death	Cardiovascular events	No events
LBBB, T wave inversion...	ECG	Narrow QRS, no repolarization abnormalities
Elevated	Biomarkers (NT-proBNP, hs-cTn)	Normal
Non-sustained VT, frequent ventricular ectopic beats..	Holter	Normal
Inducible VT, decrease in LVEF at peak stress	Treadmill test / stress TTE	Normal
Progressive LV dilatation/dysfunction	Change in LV dimensions / LVEF	No significant changes in LV dimensions or LVEF

ECG, electrocardiogram; ECV, extracellular volume; GLS, global longitudinal strain; hs-cTn, high-sensitivity cardiac troponin; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pEF, preserved ejection fraction; TTE, transthoracic echocardiography; VT, ventricular tachycardia.

been described with CMR with a good correlation with the degree of hypertrabeculation, and with incremental diagnostic value.[35,36] In addition, native T_1 and extracellular volume are higher in LVNC patients compared with controls, even in the absence of LGE.[37]

Genetic tests are also very useful in the diagnosis of pathologic forms of LVNC. Even though 189 genes have been reported in relation to LVNC, only 32 have been found to be significantly associated with the entity in a recent review (list on table 3).[38] Genetic variants usually involve sarcomeric genes (between one third and half of the cases, most often *MYH7*, *MYBPC3*, *ACTC1* and *TTN*), but may also affect transcriptional/translational regulators, mitochondrial and cytoskeleton genes,[38,39] ion channelsn[40] and copy number variations.[41] Most of the genetic causes are missense mutations (55%), and the most frequent inheritance pattern is autosomal dominant (83%), while X-linked and mitochondrial patterns are less prevalent.[39] Thus, if there is clinical suspicion of LVNC, genetic testing is reasonable to confirm the diagnosis, as recommended by an expert consensus document with a class IIB recommendation.[42] The presence of a pathogenic or likely pathogenic genetic variant will confirm the diagnosis, avoiding unnecessary examinations in genotype-negative relatives. However, pathogenic variants are described in approximately 30% to 40% of cases only.[33,43,44] Most importantly, certain genotypes have been associated with phenotype and prognosis: specifically, *MYBPC3* and *TTN* variants, as well as other genes, correlate with a higher risk of MACE, while *MYH7* and *ACTC1* variants have more favorable outcomes.[39]

However, LVNC shares a common genetic background with other cardiomyopathies such as DCM and hypertrophic cardiomyopathy (HCM), which usually also involve sarcomeric genes.[28,38,39] This finding explains the large overlap among all these cardiomyopathies: some patients with DCM or HCM also meet the diagnostic criteria for LVNC, while patients with definite LVNC may also display features of DCM or HCM,[1] even with different phenotypes among relatives.[45] Some authors have proposed that there is a continuum of phenotypical expression between LVNC, DCM, and HCM, and that both genetic factors and nongenetic triggers interact with the final phenotype.[38,46] However, no clear features have been proposed to differentiate these phenotypes in clinical practice, which often makes imaging-based diagnosis challenging. LVNC may also occur in association with congenital heart diseases or with neuromuscular disorders.[28] In addition, cases of isolated LVNC with no phenotypic features of other cardiomyopathies have been described in infantile taffazinopathies (eg, Barth syndrome)[47] or in mutations of the NOTCH pathway regulator *MIB1* gene.[48] Indeed, genetic pathways that are uniquely associated with LVNC and not DCM or HCM are often involved in cardiomyocyte development and differentiation, such

Table 3
List of genes associated with left ventricular noncompaction. Only genes with a definitive or moderate association with left ventricular noncompaction according to a recent review [38] are shown in the table

Gene function	Gene	Gene name
Sarcomere	*ACTC1*	Actin alpha cardiac muscle 1
	DES	Desmin
	LDB3	LIM domain binding 3
	MYBPC3	Myosin binding protein C3
	MYH7	Myosin heavy chain 7
	PLN	Phospholamban
	OBSCN	Obscurin
	RYR2	Ryanodine receptor 2
	TNNT2	Troponin T_2, cardiac type
	TPM1	Tropomyosin 1
	TTN	Titin
Cytoskeleton	*DMD*	Dystrophin
	DTNA	Dystrobrevin alpha
	LMNA	Lamin A/C
Desmosome	*PKP2*	Plakophilin 2
Intracellular trafficking	*LAMP2*	Lysosomal associated membrane protein 2
	PLE-KHM2	Pleckstrin homology and RUN domain containing M2
Ion channel	*HCN4*	Hyperpolarization activated cyclic nucleotide gated potassium channel 4
	SCN5A	Sodium voltage-gated channel alpha subunit 5
Mitochondria	*NNT*	Nicotamide nucleotide transhydrogenase
	TAZ	Tafazzin
	TMEM70	Transmembrane protein 70
Protein degradation	*MIB1*	Mindbomb E3 ubiquitin protein ligase 1
Signal transduction	*ALPK3*	Alpha kinase 3
	DMPK	DM1 protein kinase
Transcriptional/translational regulator	*NKX2.5*	NK2 homebox 5
	NONO	Non-POU domain containing octamer binding
	PRDM16	PR/SET domain 16
	RBM20	RNA binding motif protein 20
	TBX20	T-box transcription factor 20
	TBX5	T-box transcription factor 5

DM1, myotonic dystrophy 1; LIM, acronym of LIN-11, Isl-1 and MEC-3; RNA, ribonucleic acid.

as the NOTCH pathway.[38] This finding supports the hypothesis that LVNC may be a consequence of an abnormal embryogenesis.

Some cardiac imaging studies have attempted to define markers that allow differentiating between different cardiomyopathies. A characteristic deformation pattern on TTE, with higher values in the LV base compared with the apex (where hypertrabeculation is more pronounced) could differentiate LVNC from DCM, which shows uniformly reduced strain values.[49] The combination of fractal analysis and global longitudinal strain on CMR allowed accurate differentiation of LVNC from DCM patients.[50] Recently, a study based on radiomics (an emerging imaging analysis technique for deeper phenotyping in CMR) showed that artificial intelligence allowed excellent differentiation of DCM, HCM, and LVNC in an automatic and highly-efficient way.[51]

Finally, family aggregation has been described in approximately 40% to 50% of LVNC cases,[33,43,45] and therefore family screening is recommended in all patients to confirm the index diagnosis and to identify asymptomatic relatives.[52] According to expert consensus,[42] if a disease-causing genetic variant is described in a patient, first-degree relatives should undergo clinical and genetic assessment with a class I recommendation.

Therefore, based on the different published series collected in this review, the presence of a marked myocardial hypertrabeculation should not be considered, a priori, as a normal morphological trait and should instead be studied in an integral manner. Most importantly, the diagnosis should not only be based on morphologic imaging criteria, but should also consider clinical status, the electrocardiogram, family history, genetic testing, functional imaging variables, and the presence of myocardial fibrosis, among other parameters. Such a holistic approach will allow for the differentiation of physiologic hypertrabeculation cases from those with true LVNC cardiomyopathy (table 2). Only those patients with morphological criteria who do not show other red flags can be considered as a normal variant, whereas only those with definite pathologic features (electrocardiogram changes, reduced LVEF, LGE and/or family aggregation) should be diagnosed with LVNC. This differential diagnosis is clinically relevant because individuals with a simple phenotypic trait have favorable outcomes and might not require periodic follow-up, avoiding unnecessary costs and the psychological burden of an incorrect diagnosis. In contrast, patients with cardiomyopathy are at increased risk of developing cardiovascular events, and should therefore be carefully monitored and managed appropriately (see next section) (figure 4).

RISK STRATIFICATION AND CLINICAL MANAGEMENT

Prognosis and clinical management: scope of the problem

Because of the lack of universal diagnostic criteria, outcomes in LVNC are uncertain. Some series confer LVNC a poor prognosis,[2,44,53] while others suggest a more benign profile.[15,16,54] Additionally, there are no specific clinical practice guidelines, which contributes to the heterogeneous management of these patients. However, some expert consensus recommendations are available,[42] with subtle changes in clinical management compared with other cardiomyopathies (figure 5), reinforcing the importance of a correct diagnosis.

The main complications associated with LVNC are heart failure (HF), ventricular arrhythmias, systemic embolisms, and death. Some patients may also be asymptomatic, diagnosed incidentally or during family screening. The most common clinical manifestation of this disease is HF, which is found in 14% to 21% of adult patients.[26,33,43] The incidence is higher than that observed in the DCM population (4.05 events per 100 person-years).[33,55] LVEF is the strongest predictor of HF, and patients with reduced LVEF are at increased risk, especially those with an LVEF $\leq$ 35%.[33] Thus, patients with reduced LVEF should be promptly treated with guideline-directed medical therapy to reduce the risk of death and HF hospitalization and to improve clinical and functional status with a class I recommendation according to international guidelines[56,57] (figure 5). In addition, the presence of LGE (a marker of myocardial fibrosis on CMR), has been associated with HF risk, even in the absence of severe systolic dysfunction.[33] Other variables that correlate with HF are a higher degree of hypertrabeculation[24] and certain genotypes, specifically *TTN*[33,39] and *MYBPC3*[39] variants. Therefore, it seems reasonable that these

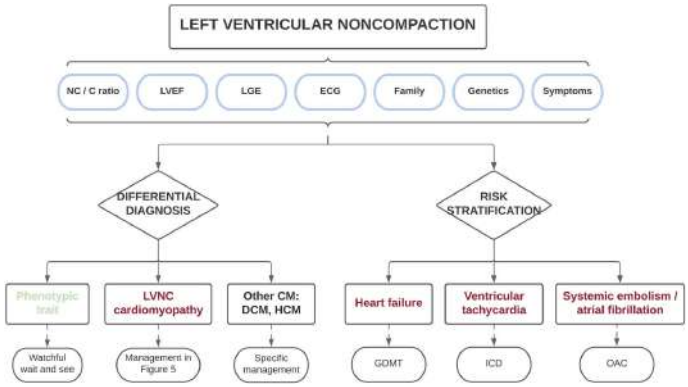

Figure 4. Central illustration. Clinical approach in individuals with morphologic features of left ventricular noncompaction. A comprehensive diagnostic evaluation is recommended to exclude patients with a simple phenotypic trait and those with other cardiomyopathies. The same variables used in the differential diagnosis may be applied for risk stratification to individualize patient treatment and follow-up. C, compacted; CM, cardiomyopathy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVNC, left ventricular noncompaction; NC, noncompacted; OAC, oral anticoagulation.

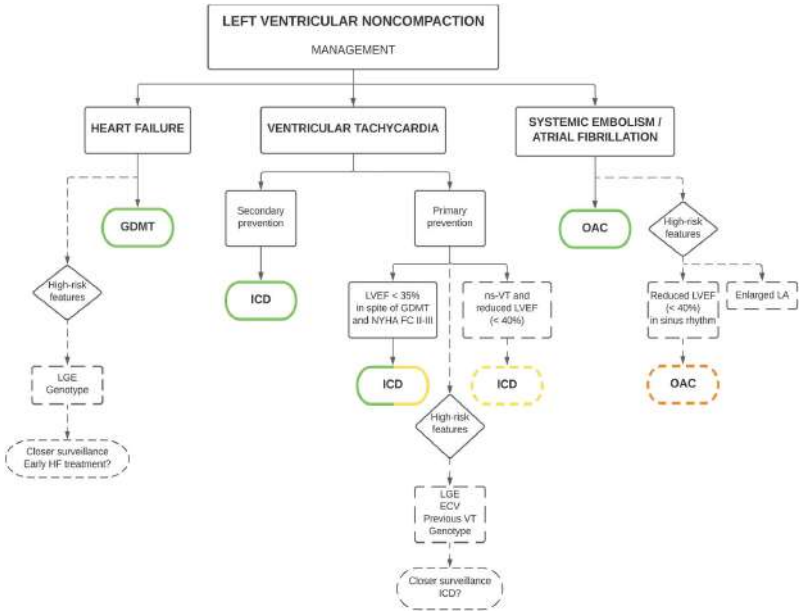

Figure 5. Clinical management of patients with left ventricular noncompaction. Green stands for a class I recommendation, yellow for a class IIa recommendation and orange for a class IIb recommendation. ECV, extracellular volume; ICD, implantable cardioverter-defibrillator; GDMT, guideline-directed medical therapy; HF, heart failure; ns, non-sustained; LA, left atrium; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NYHA FC, New York Heart Association Functional Class; VT, ventricular tachycardia; OAC, oral anticoagulation.

patients undergo closer clinical surveillance (including natriuretic peptides and echocardiography) to detect early symptoms and signs of HF. However, prospective studies should clarify whether early initiation of HF treatment would improve prognosis (figure 5). At this stage, the recommended management is comparable to that of patients with HF and reduced LVEF.[56,57]

Ventricular arrhythmias are another frequent and feared complication, being present in 19% to 21% of patients,[26,33] with sudden cardiac death (SCD) in 5% to 6%.[58,59] A multicenter retrospective study estimated the incidence of arrhythmic events at around 2.79 events per 100 person-years,[33] which is statistically similar to the numbers reported for DCM.[55] LVEF remains the strongest predictor of ventricular arrhythmias,[33] and indications for primary prevention of SCD and implantable cardioverter-defibrillator (ICD) implantation are comparable to those in the general population: patients with an LVEF $\leq$ 35% despite optimal medical therapy for $\geq$ 3 months, in New York Heart Association functional class II and III, and expected survival longer than 1 year, with a class IIa recommendation in the latest European guidelines, and with a class I recommendation in the American guidelines.[56,57,60,61] The weaker European recommendation in nonischemic patients was changed after the results of the DANISH trial.[62] Additionally, an expert consensus document recommends prophylactic ICD in cases of reduced LVEF and nonsustained ventricular tachycardias, even in the absence of LGE, with a class IIa recommendation[42] (figure 5). Indications for secondary prevention are more homogeneous in different guidelines: patients surviving an SCD, and those with documented ventricular fibrillation or hemodynamically not tolerated/sustained ventricular tachycardias should receive an ICD with a class I recommendation if expected survival is longer than 1 year, according to international guidelines (figure 5).[56,57,60,61] It is worth mentioning that high rates of appropriate ICD shocks have been reported in LVNC patients, after both primary and secondary prevention,[44,63,64] and consequently it seems to be an effective therapy in this cardiomyopathy. Therefore, a low threshold for ICD implantation is suggested, even if evidence of its benefits in nonischemic etiology is still unclear.

LGE is another important predictor of ventricular arrhythmias in LVNC,[17,33,65] and myocardial fibrosis seems to be an arrhythmic substrate. Consistent with other cardiomyopathies,[55,66,67] LGE has been associated with poor outcomes and SCD risk in LVNC, even in the absence of severe systolic dysfunction.[33] However, LGE has not yet been incorporated into clinical practice guidelines, which are solely based on LVEF.[56,57,60,61] In a small study, extracellular volume on CMR was also associated with the risk of ventricular arrhythmias even in the absence of LGE.[37] In addition, the presence of preceding arrhythmias, including ventricular tachycardias, has been correlated with an increased risk of SCD in a pediatric LVNC population.[59] Finally, certain genotypes have also been associated with ventricular arrhythmias: *ACTC1*,[33] *MYBPC3*, arrhythmogenic genes (*ABCC9, ANK2, CACNA2D1, CASQ2, HCN4, KCNE3, KCNH2, KCNQ1, RYR2*, and *SCN5A*), and nonarrhythmogenic nonsarcomere genes (*DMPK, DSP, DTNA, FKTN, HFE, JUP, LMNA, PKP2, PLEC, PLN, PRDM16, RBM20*, and *SGCD*).[39]

All of these risk factors identify patients at increased risk of arrhythmic events. Therefore, closer clinical surveillance and proactive detection of subclinical arrhythmias, including Holter

monitoring and treadmill tests, is recommended. At present, no recommendations can be made on early ICD implantation in these patient subgroups, and future prospective studies should investigate whether a more aggressive approach might improve clinical outcomes (figure 5). A combined approach with LVEF and LGE, similar to that proposed in DCM patients, might be considered to identify high-risk patients.[68]

Systemic embolisms are another classic manifestation commonly associated with LVNC, with an estimated prevalence of approximately 15%.[69] However, recent series have reported a lower risk around 3.1% to 4.6%,[26,33] which could be explained by more aggressive anticoagulation therapy. Beyond traditional embolic factors such as atrial fibrillation (AF) and systolic dysfunction, LVNC has an intrinsic embolic risk. This has been considered to be secondary to blood stasis in the intertrabecular recesses, even though a greater degree of hypertrabeculation has not been associated with a higher risk of stroke.[24] The presence of previous systemic embolisms in LVNC is an indication for oral anticoagulation therapy (OAC) with a class I recommendation according to an expert consensus (figure 5).[42]

AF is also common in LVNC, with a prevalence of up to 29% of patients,[70] and is associated with an increased risk of systemic embolism.[69] In patients with LVNC, AF is an indication for OAC irrespective of thromboembolic risk assessed by traditional scores (CHA_2DS_2-VASc), with a class I recommendation according to the European guidelines and expert consensus (figure 5).[42,71] Left atrial dilatation has also been associated with systemic embolisms risk in LVNC,[33] which could be an early marker of AF. Although no recommendations for the use of prophylactic OAC can be made based on left atrial dimensions, patients with enlarged left atria might be considered to undergo a more proactive search for subclinical AF, as has been suggested in HCM.[72] A reduced LVEF is another consistent risk factor for SE,[33,69] and patients with an LVEF $\leq$ 40% might be considered for prophylactic OAC, even in sinus rhythm, with a class IIB recommendation according to an expert consensus document (figure 5).[42] Based on the increased embolic risk, proactive screening of intraventricular thrombi with contrast echocardiography is recommended if there is reduced LVEF. If a thrombus is detected, vitamin K antagonists are usually the first choice treatment due to the lower embolic risk compared with direct oral anticoagulants.[73] Otherwise, direct oral anticoagulants are usually preferred over vitamin K antagonists, owing to a better safety profile, even though their evidence in LVNC is limited to case reports.[74] Recently, an algorithm has been proposed for prophylactic OAC in LVNC, which includes all the aforementioned variables.[75]

Table 4 describes the most important LVNC series discussed in this review.

The need for an integrated prognostic score

All in all, it seems clear that the incidence of MACE in patients with confirmed LVNC (determined not only by morphologic traits) is not negligible. In an attempt to establish risk scores in this population, our group conducted a large multicenter retrospective study of 585 patients, of whom 223 (38%) experienced MACE during a median follow-up of 5.1 years. On multivariate analysis, the variables independently associated with MACE were age, LVEF, and the presence of electrocardiogram changes. These variables, combined with sex, family aggregation, and cardiovascular risk factors were incorporated to develop a risk prediction model that was also validated in an external population. The performance of the score was very high (C-index 0.72; 95% confidence interval, 0.67-0.75), and allowed for correct risk estimation of up to 5 years differentiating between low- and high-risk patients.[33] A study by

Table 4
Summary of the main left ventricular noncompaction studies cited in the review

First author	Number of patients	Women, n (%)	Age, y	Diagnostic criteria	LVEF, % (SD or IQR)	Positive genotype	Family aggregation	Follow-up, y	Heart failure	Ventricular arrhythmias	Systemic embolisms	Death	MACE, n (%)
Stacey, 2013[11]	122	50 (41)	57 ± 17	Stacey	44 ± 16	Not reported	Not reported	Not reported	36 (30)	6 (5)	10 (8)	6 (5)	Not reported
Vaidya, 2021[25]	339	157 (46)	47 [34-61]	Jenni, Chin and Petersen	45 [30-58]	Not reported	Not reported	6.3 [3.1-10.8]	Not reported	Not reported	Not reported	59 (17)	Not reported
Ramchand, 2021[26]	328	136 (42)	43 ± 17	Petersen	45 ± 14	Not reported	Not reported	3.1	41 (13)	70 (21)	15 (5)	15 (5)	102 (31)
Casas, 2021[33]	585	251 (43)	45 ± 20	Jenni and Petersen	48 ± 17	99 (42)	106 (42)	5.1 [2.3-8.1]	110 (19)	87 (15)	18 (3)	34 (6)	223 (38)
van Waning, 2018[43]	327 (275 adults)	152 (46)	45 [33-56]	Jenni and Petersen	174 (53) with LV systolic dysfunction	104 (32)	120 (37)	2.1 [0.3-4.8] in adults	72 (22)	19 (6)	38 (12)	24 (7)	72 (22)
Sedaghat-Hamedani, 2017[44]	95	20 (19% of index patients)	41 ± 14	Stöllberger, Jenni and Petersen	38 ± 15	36 (38)	22 (23)	5.1	Not reported	24 (35)	7 (10)	9 (13)	Not reported
Brescia, 2013[59]	242 children	97 (40)	9 [0-14]	Jenni	150 (62) with LV systolic dysfunction	Not reported	56 (23)	4.0 [1.8-15.9]	Not reported	42 (17)	Not reported	31 (13)	Not reported
Andreini, 2016[65]	113	43 (38)	44 ± 17	Jenni and Petersen	45 ± 15	Not reported	17 (15)	3.8 [2.2-5.7]	16 (14)	10 (9)	5 (4)	5 (4)	36 (32)
Stöllberger, 2011[69]	144	43 (30)	54 ± 16	Stöllberger	88 (61) with LV FS < 25%	Not reported	Not reported	Not reported	Not reported	Not reported	22 (15)	Not reported	Not reported

FS, fractional shortening; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; SD, standard deviation.
The data are presented as No. (%), mean ± standard deviation, or median [interquartile range].

Ramchand et al.[26] reported a large single-center retrospective series of 328 patients, with 102 (31%) MACE during a mean follow-up of 3.1 years. After adjustment for medical history, the variables independently associated with outcomes were compacted myocardial thinning, elevated NT-proBNP levels, and increased LV end-systolic volumes. The combination of the 3 variables conferred a higher accuracy for risk stratification. Although these 2 approaches do not imply specific changes in clinical management, they can identify high-risk patients who might benefit from closer surveillance or low-risk patients who might not require strict follow-up. Most importantly, they are based on readily available variables that do not require complex assessment and which can therefore be easily applied in clinical practice. Future studies should elucidate whether the prospective application of such risk scores improves prognosis in this disease.

CONCLUSIONS

Final remarks

LVNC is a poorly defined, heterogeneous, and controversial entity. Diagnosis is currently based on morphologic imaging variables, which have low specificity for identifying true cardiomyopathy cases. Evidence suggests that a comprehensive holistic diagnostic approach with clinical information, functional imaging variables, family screening, and genetics will more accurately differentiate physiologic hypertrabeculation from LVNC cardiomyopathy. Clinical management is also challenging due to uncertain prognosis and lack of specific guidelines. Risk stratification, using LVEF and LGE among other parameters, is recommended to identify low- and high-risk patients and to tailor follow-up.

Future directions

We are facing a paradigm shift in cardiomyopathies due to the constantly growing knowledge of cardiovascular genetics and a deeper understanding of genotype-phenotype correlations. Therefore, we will ultimately refer to the phenotypic expression of a specific genetic variant, instead of using the terminology of traditional heart diseases. In addition, the never-ending development of cardiac imaging techniques and the application of artificial intelligence algorithms will allow for a better identification of pathologic hypertrabeculation cases, which will result in an optimization of health system resources.

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AUTHORS' CONTRIBUTIONS

J.F. Rodríguez-Palomares and I. Ferreira-González conceived the review, G. Casas and J.F. Rodríguez-Palomares wrote the manuscript, I. Ferreira-González critically reviewed the manuscript.

CONFLICTS OF INTEREST

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10.1.3. Artículo 3

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MDPI

Review

Multimodality Cardiac Imaging in Cardiomyopathies: From Diagnosis to Prognosis

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Abstract: Cardiomyopathies are a group of structural and/or functional myocardial disorders which encompasses hypertrophic, dilated, arrhythmogenic, restrictive, and other cardiomyopathies. Multimodality cardiac imaging techniques are the cornerstone of cardiomyopathy diagnosis; transthoracic echocardiography should be the first-line imaging modality due to its availability, and diagnosis should be confirmed by cardiovascular magnetic resonance, which will provide more accurate morphologic and functional information, as well as extensive tissue characterization. Multimodality cardiac imaging techniques are also essential in assessing the prognosis of patients with cardiomyopathies; left ventricular ejection fraction and late gadolinium enhancement are two of the main variables used for risk stratification, and they are incorporated into clinical practice guidelines. Finally, periodic testing with cardiac imaging techniques should also be performed due to the evolving and progressive natural history of most cardiomyopathies.

Keywords: cardiomyopathy; multimodality cardiac imaging techniques; diagnosis; prognosis; left ventricular ejection fraction; late gadolinium enhancement

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1. Introduction

Cardiomyopathies constitute a heterogeneous group of diseases that affect the muscle of the heart and present a very diverse etiology. Classically, the European Society of Cardiology (ESC) classifies these diseases as hypertrophic, dilated, arrhythmogenic, restrictive, or other cardiomyopathies [1]. Additionally, all of them are subclassified as familial/genetic or non-familial/non-genetic. Cardiomyopathies present variable expressions and symptoms that can change over time. Thus, periodic evaluation using cardiac imaging techniques is essential throughout follow-up. These techniques can help us to diagnose, guide treatment, and optimize patients' prognosis.

The patient evaluation includes anamnesis, physical examination, an electrocardiogram, and transthoracic echocardiography (TTE) that may raise suspicion of cardiomyopathy. This information is usually complemented with a cardiovascular magnetic resonance (CMR) that provides more precise anatomic and functional evaluation, as well as excellent tissue characterization with prognostic implications. Additionally, some patients may require a nuclear medicine test or cardiovascular computed tomography (CT).

In this manuscript, we will review the information that the different imaging techniques offer in the diagnosis and management of these patients.

2. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined by an increase in left ventricular (LV) wall thickness and/or LV mass, unexplained by LV loading conditions. HCM is the most prevalent cardiomyopathy, affecting approximately 1:500 of the adult population, and is usually caused by mutations in sarcomeric genes [2,3].

TTE is the first-line imaging modality for HCM evaluation: a maximal wall thickness >15 mm (or higher than two standard deviations from normal corrected for age, gender, and height) or asymmetric septal hypertrophy (septal/posterior wall thickness) ratio >1.3 (or >1.5 in hypertensive patients) is suggestive of HCM (Figure 1) [4]. A wall thickness ≥30 mm is associated with a higher risk of sudden cardiac death (SCD) [2,3].

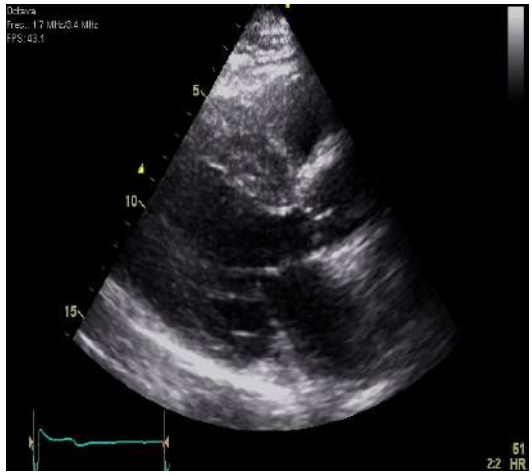

Figure 1. A parasternal long-axis view of a patient with septal HCM. Note the marked increase in septal wall thickness and the asymmetry compared to the posterior wall.

TTE allows for localization of the hypertrophy and hence identification of different phenotypes: septal, septal reverse, apical, or diffuse HCM, among others (Figure 2). In addition, patients with HCM present ancillary signs that, although non-specific, can help in the diagnosis: papillary muscle abnormalities (hypertrophic, bifid or trifid, and with an apical insertion), false tendons, myocardial clefts or crypts, aneurysms, or mitral valve and subvalvular structure abnormalities (elongated mitral leaflets with/without systolic anterior motion -SAM-) (Figure 3) [5].

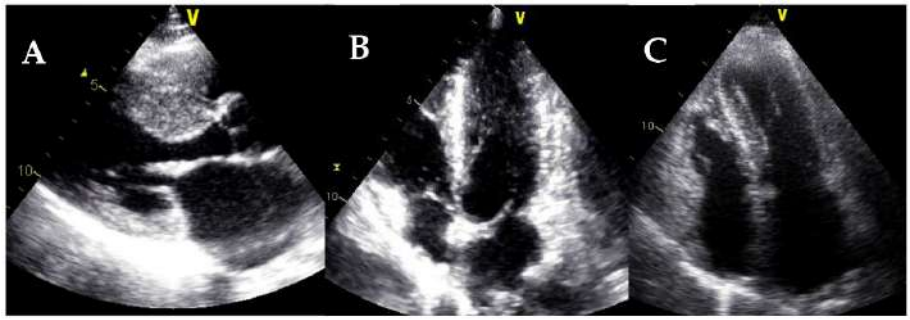

Figure 2. Different hypertrophic cardiomyopathy phenotypes. (**A**) Septal HCM. (**B**) Apical HCM. (**C**) Diffuse HCM.

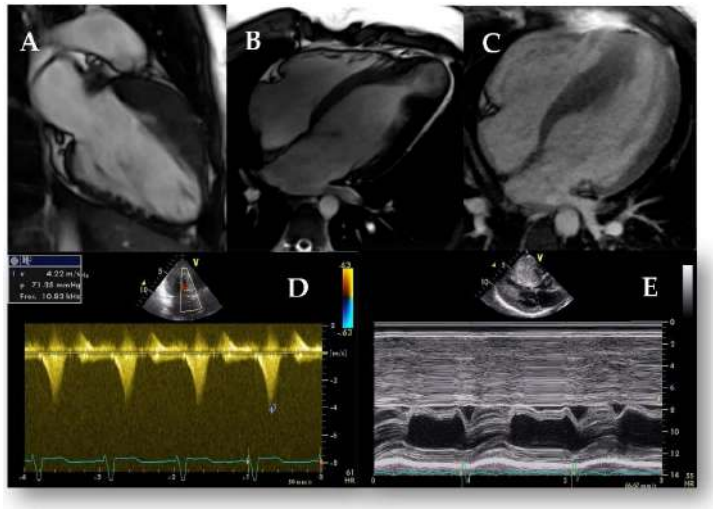

Figure 3. Ancillary signs in HCM. (**A**) Myocardial crypts in the inferior wall. (**B**) Apical aneurysm in a patient with apical HCM. (**C**) Apical insertion of the papillary muscles in a patient with septal HCM. (**D**) Outflow tract obstruction measured on Doppler CW, note the dagger-shaped curve. (**E**) SAM evidenced on M-mode: see the movement of the anterior mitral leaflet towards the septum in systole.

Moreover, the presence of LV outflow tract obstruction (LVOTO) can be easily evaluated and is defined as a peak gradient higher than 30 mm Hg at rest or after provocative maneuvers (typically observed as a dagger-shaped curve on continuous wave Doppler, Figure 3D). LVOTO differentiates between obstructive and non-obstructive HCM, with important therapeutic and prognostic implications [2,3]. Assessment of LV systolic function or LV ejection fraction (LVEF) is also important because it remains an important predictor of events [6]. Patients with an LVEF <50% present a poor prognosis [7] and should be considered for prophylactic implantable cardioverter-defibrillator (ICD) according to the recent American guidelines [3]. In addition, the anteroposterior left atrial diameter should be measured, and the diastolic function should be assessed. The maximal wall thickness, the left atrial diameter, and LVOTO have been incorporated into the risk prediction model of SCD [8] endorsed by the ESC [2].

Strain parameters from speckle-tracking TTE constitute markers of LV systolic function and are more sensitive than LVEF to systolic impairment. An abnormal global longitudinal strain (GLS) has been associated with worse outcomes in HCM [9], even though clear cut-off values are not available due to lack of standardization. Other techniques, such as circumferential strain or LV rotation and twist mechanics, are not routinely recommended.

CMR has become the gold standard technique for HCM evaluation and should be performed in all patients [4]. Beyond more accurate measurement of LV wall thickness and LVEF, CMR allows for tissue characterization with late gadolinium enhancement (LGE) sequences (Figure 4). Artificial intelligence and machine learning could further improve the accuracy of wall thickness measurements [10].

LGE is a frequent finding in HCM (about 60% of patients) [6,11–13], correlates with the presence of myocardial fibrosis [14], and usually affects the most hypertrophied segments with an intramural pattern. In addition, its location in areas of septal-free wall junctions is a common finding. The presence of LGE has been consistently associated with adverse outcomes and especially with SCD risk [11,15,16].

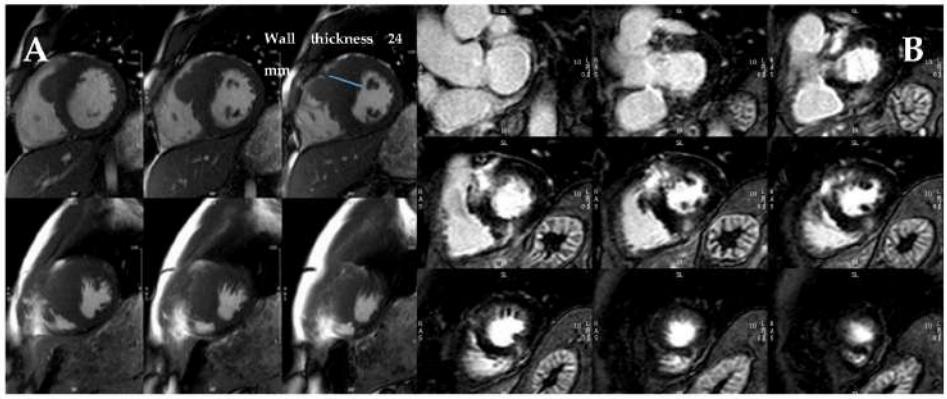

Figure 4. CMR study of a patient with septal HCM. (**A**) Maximal wall thickness measured on the short-axis cine stack at end-diastole. (**B**) Post-contrast T1 sequences showing extensive basal and mid-anteroseptal LGE with an intramyocardial pattern.

Quantification of LGE, usually as the percentage of total LV mass using the five standard deviation method [17], has emerged as a powerful predictor of SCD, both in obstructive and non-obstructive, low- and high-risk HCM [6,11–13,18] and with better predictive value than the ESC calculator [8]. An LGE >15% has been proposed as a risk marker for SCD [3,16,19]. Contrarily, outcomes of patients with a low LGE amount (<5%) are comparable to those without LGE [6,12]. Progression of LGE extension throughout follow-up has also been reported in HCM patients and has been related to adverse cardiac remodeling and worse prognosis [18]. Owing to the strong evidence, "extensive" LGE has been incorporated as a parameter for prophylactic ICD implantation in the recent American guidelines, which also recommend performing a CMR every 3–5 years to evaluate disease progression [3].

Emerging CMR sequences, such as T1 and T2 mapping and extracellular volume (ECV), allow for quantitative analysis of tissue characteristics and are more sensitive than LGE for the detection of myocardial fibrosis, especially in case of diffuse interstitial fibrosis (Figure 5) [20]. Further, T1 and T2 mapping are useful in the differential diagnosis of left ventricular hypertrophy [21]. Small studies have so far reported prognostic implications of T1 mapping [22] and ECV [23] values. However, further studies are needed to validate the prognostic implications of mapping sequences to fully incorporate them into daily clinical practice.

Stress echocardiography (SE) is another useful technique in the assessment of HCM because one-third of patients have latent LVOTO. SE is safe and usually performed in a semi-supine position, while the use of dobutamine is not recommended in HCM. LVOTO, LV systolic function (LVEF and GLS), LV diastolic function (E/E′), dynamic mitral regurgitation (usually secondary to SAM) and tricuspid regurgitation (TR) velocity should be evaluated at rest, at peak stress, and post-exercise (Figure 6) [24]. Exercise-induced significant LVOTO (>50 mmHg) is a marker of worse prognosis and can be used to guide treatment [2,3,24]. A diastolic stress test may also be performed; an increase in E/E′ > 14 and peak TR velocity >2.8 m/s has been invasively correlated with elevated LV filling pressures during exercise [25] and is a marker of poor exercise tolerance [24]. The role of SE in the detection of inducible ischaemia in HCM is controversial. In this scenario, stress CMR with vasodilators is usually preferred, and signs of microvascular dysfunction may be observed [4].

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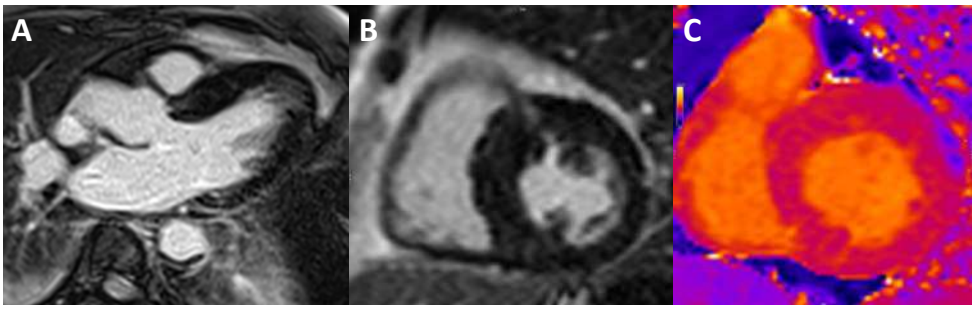

Figure 5. CMR study of a patient with septal HCM. (**A**,**B**) LGE sequences with heterogeneous contrast uptake in the basal and mid-anteroseptal segments. (**C**) Native T1 mapping sequence with an increased native T1 value of 1108 ms in the basal anteroseptal segment (reference range 950–1050 ms).

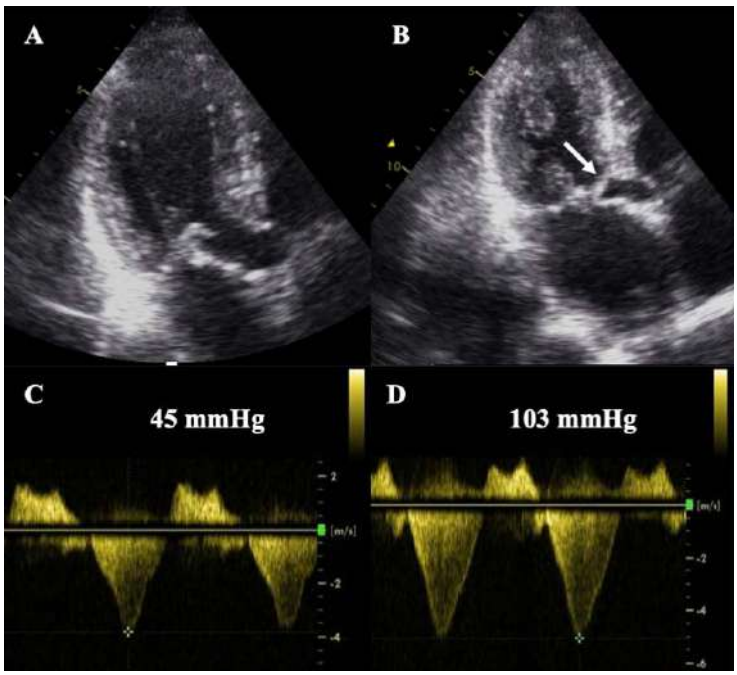

Figure 6. Stress echocardiography in a patient with HCM. Note the marked increase in SAM (**B**, white arrow) and the significant increase in LVOTO (**D**) at peak stress compared to the basal situation (**A**,**C**).

The role of cardiac CT in HCM is secondary and may be considered to exclude coronary artery disease. Recently, assessment of myocardial fibrosis by delayed enhanced CT has been described with an adequate agreement with LGE by CMR [26]. Even though data is still scarce, and no clinical implications should be attributed, it might become an alternative for those patients who have a contraindication for CMR.

Table 1 describes the main imaging diagnostic and prognostic findings in HCM.

Table 1. Summary of imaging findings in HCM.

Diagnostic Criteria	Ancillary Signs	Prognostic Markers
Maximal wall thickness >15 mm (>13 mm in relatives of HCM patients)	Papillary muscle abnormalities	Maximal wall thickness (>30 mm)
Asymmetric septal hypertrophy (ratio septal/posterior wall thickness >1.3 or >1.5 in hypertensive patients)	Mitral valve and subvalvular structure abnormalities	Left atrial size (anteroposterior diameter)
	Myocardial clefts/crypts	Maximum LVOT gradient (at rest or induced by exercise)
	Aneurysms	LVEF < 50%
		Abnormal GLS
		Presence, extension, and progression of LGE
		Increased T1/ECV values

3. Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is defined by LV (or biventricular) systolic dysfunction (LVEF < 45%) and dilatation (LV end-diastolic volumes or diameters >2 standard deviations from normal corrected by age, gender, and body surface area) not attributed to loading conditions or coronary artery disease (Figure 7). DCM affects approximately 1:2500 adults, can be both genetic and acquired, and is a leading cause of heart failure [27].

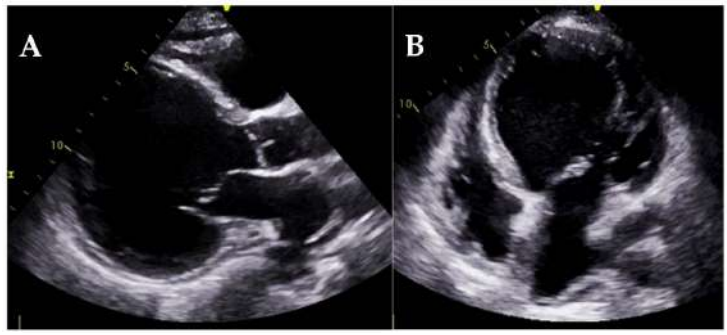

Figure 7. Transthoracic echocardiography of a patient with dilated cardiomyopathy, showing a parasternal long-axis view (**A**) and an apical 4-chambers view (**B**). Note the marked dilatation of the left ventricle and the spherical pattern.

TTE allows for both anatomical and functional assessment. Three-dimensional transthoracic echocardiography (3D TTE) is increasingly used due to improvements in technology and automated software and has the advantage of direct LV measurements with no geometric assumptions (Figure 8). Most importantly, 3D TTE is more accurate and reproducible than conventional two-dimensional (2D) TTE and shows better agreement with CMR values. However, 3D TTE depends on good image quality, requires more advanced technical skills, and normal values are less well established [28].

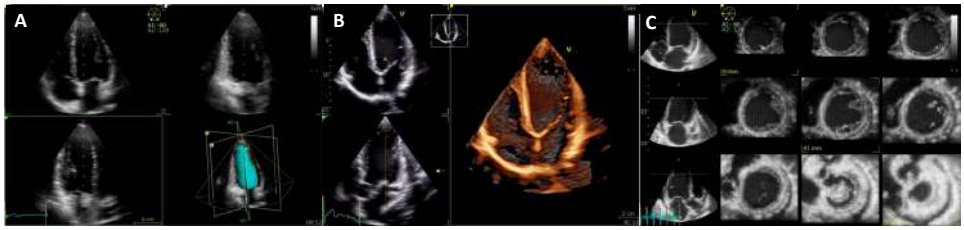

Figure 8. Three-dimensional transthoracic echocardiography of the left ventricle. (**A**) Triplane view of the LV allows simultaneous and single-beat acquisition of the three apical views. By tracing the endocardial borders, the LV volume is obtained (surface rendering, bottom right). (**B**) Real-time single-beat 3D acquisition of the LV from the apical window. Volume renders allow for offline reconstructions. (**C**) Tomographic multislice obtained from a multiple-beat apical view. Wall motion abnormalities can be assessed with this technique.

LVEF remains the strongest predictor of events in DCM; thus, patients with an LVEF ≤35% must be considered for optimal medical treatment and prophylactic ICD (with/without cardiac resynchronization therapy, CRT) [29,30]. However, an LVEF ≤35% has proven to have a low sensibility and specificity for SCD prediction, so additional predictors are required. Strain parameters, both GLS (Figure 9) and global circumferential strain (GCS) have been associated with cardiovascular events and present an incremental prognostic value over LVEF [31]. Myocardial work (MW) is a novel quantitative parameter that incorporates both strain and LV pressure variables (Figure 10) [32]. Initial reports suggest that not only MW is related to outcomes, but also has an additional prognostic role over both LVEF and GLS in DCM [33].

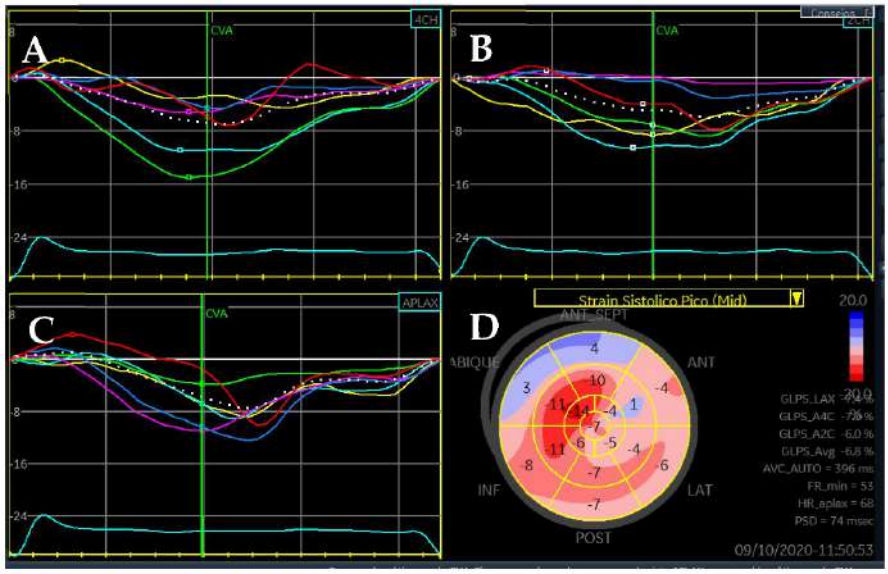

Figure 9. Longitudinal strain analysis of a patient with DCM: 4 chambers (**A**), 2 chambers (**B**), 3 chambers (**C**), and bull's eye plot (**D**). Note the diffusely affected longitudinal strain, consistent with depressed LVEF, and positive values in the basal septum suggestive of dyskinesia in these segments.

Stress echocardiography (SE) is also useful for risk stratification in DCM. Dobutamine is most often used, with either low or high-dose protocols (10 or 40 μg/kg/min), and the contractile response is assessed. An increase by ≥5% in LVEF at peak stress is defined as a contractile reserve and is associated with improved outcomes and reverse remodeling in DCM [24,34]. SE may also be used to exclude ischaemic etiology.

CMR should be performed at least once in all DCM patients since it is the gold standard technique for the assessment of biventricular volumes, systolic function, and tissue characterization. LGE is common in DCM and traduces myocardial fibrosis [35,36], usually with a septal mid-wall pattern (Figure 11). LGE has been consistently described as a strong and independent predictor of outcomes in DCM [35–37], and specifically for SCD [35,37,38]. The absence of LGE is also associated with reverse remodeling [37], which confers improved survival in DCM. Of note, LGE shows incremental prognostic value over LVEF [39], even in patients with only mild or moderate systolic dysfunction [40].

The extension, localization, and pattern of LGE have also been associated with prognosis [41,42]; a higher burden of LGE, septal LGE, and multiple patterns (combined septal

and free-wall, epicardial, and transmural LGE) are related to higher mortality or SCD. The risk of adverse outcomes is also higher in patients with progression of LGE over time [43]. Considering the important prognostic role of LGE and the aforementioned limitations of LVEF, a combined algorithm has recently been proposed to enhance the identification of patients at high risk for SCD who should be considered for prophylactic ICD [42]. However, clinical guidelines are only based on LVEF [29,30].

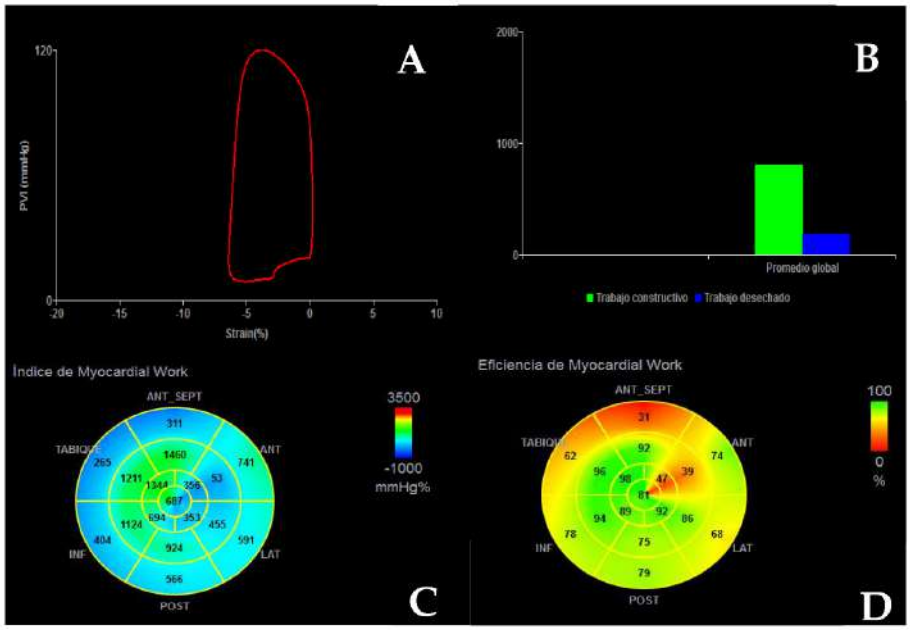

Figure 10. Myocardial work analysis in a patient with DCM. (**A**) Strain—pressure loop. (**B**) Comparison of constructive work (green) and wasted work (blue). (**C**) Bull's eye plot of myocardial work index (mmHg%). (**D**) Bull's eye plot of myocardial work efficiency (%).

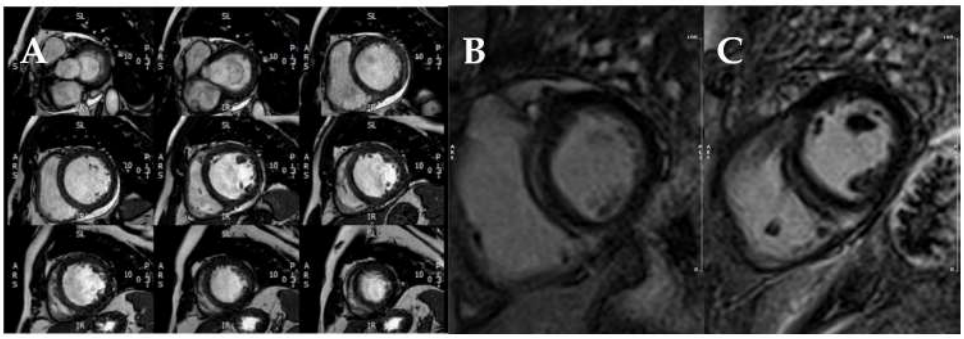

Figure 11. CMR study of a patient with DCM. (**A**) Short-axis cine stack. (**B**,**C**) Post-contrast T1 sequences showing a typical LGE pattern with a lineal mid-septum uptake as well as a focal uptake in the septum-free wall inferior junction.

GLS by CMR (Figure 12) has been shown to be associated with outcomes in DCM, and most importantly to improve risk classification beyond LVEF and LGE [44]. However, it has not been standardized and no cut-off points have been proposed, so routine clinical use is not yet recommended. Mapping techniques have also been evaluated in DCM; higher T1 and ECV values have been shown to have prognostic implications irrespective of LVEF and LGE [45]. Furthermore, an increased native T2 value indicates the presence of myocardial edema, which could suggest the presence of inflammatory cardiomyopathy [46]. These techniques offer promising new tools for risk stratification, but further validation is still required.

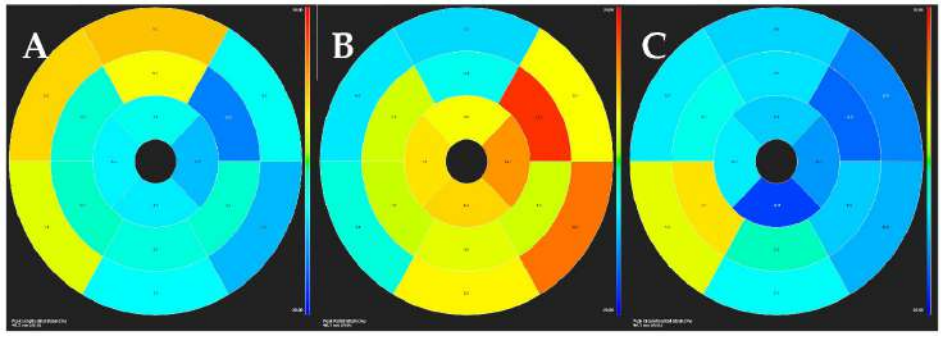

Figure 12. Strain analysis by CMR obtained with feature-tracking software in a patient with DCM. Endocardial and epicardial segmentation of short and long-axis is required, both at end-diastole and end-systole. Thus, longitudinal (**A**), radial (**B**), and circumferential (**C**) strain are simultaneously acquired.

Assessment of right ventricle (RV) size and systolic function is recommended in all patients since RV systolic dysfunction is a common finding and an independent predictor of poor outcome [47]. Different techniques may be applied: fractional area change [48], peak longitudinal strain of RV free wall [49] by TTE, or RV ejection fraction (RVEF) by CMR [47]. The same advantages and limitations previously mentioned in 3D TTE also apply to the RV; specifically, global chamber including RV inflow and outflow tracts and apical regions can only be assessed by 3D TTE and not 2D TTE (Figure 13) [28]. Secondary (functional) mitral regurgitation and diastolic dysfunction should also be evaluated since they are associated

with cardiovascular events [50]. LV GLS [51], left atrial strain [52] and MW [53,54] by TTE, as well as septal viability on CMR [54], have been identified as predictors of response to CRT.

Other imaging modalities are rarely used in DCM. Nuclear imaging can analyze cardiac sympathetic innervation, which has been associated with ventricular arrhythmias and adverse prognosis [55]. Cardiac CT is commonly used to exclude coronary artery disease. Recent studies have shown the ability of delayed enhancement CT to detect myocardial fibrosis, with comparable performance to LGE by CMR [56]. However, results are still preliminary, and no clinical studies are available, so routine use is not recommended.

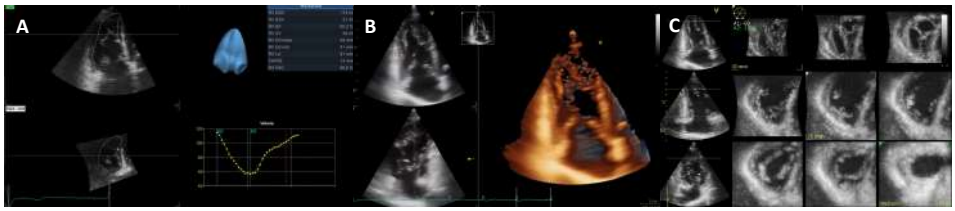

Figure 13. Three-dimensional transthoracic echocardiography of the right ventricle. (**A**) By tracing the endocardial RV borders (top and bottom left), a 3D volume of the RV (top right) is obtained throughout the cardiac cycle (bottom right) and 3D RVEF is calculated. Note the RV inflow and outflow tract in the 3D model. (**B**) Real-time single-beat 3D acquisition of the RV from the dedicated apical window. (**C**) Tomographic multislice obtained from a multiple-beat apical view.

Table 2 describes the main imaging prognostic findings in DCM.

Table 2. Summary of prognostic imaging markers in DCM.

LVEF ≤ 35%
RV systolic dysfunction (RVEF < 45%)
Significant (secondary) mitral regurgitation
Advanced diastolic dysfunction
Abnormal strain and myocardial work values
Presence, extension, pattern, and progression of LGE
Increased T1 and ECV values

4. Restrictive Cardiomyopathies

Restrictive cardiomyopathies (RCM) account for less than 5% of all cardiomyopathies and have a highly varied etiology (Table 3).

Table 3. Classification of restrictive cardiomyopathies.

Restrictive Cardiomyopathy			
Non-Infiltrative Disorders	**Infiltrative Disorders**	**Storage Diseases**	**Endomyocardial Diseases**
• Idiopathic • Hereditary (sarcomere mutations . . .) • Systemic sclerosis	• Amyloidosis • Sarcoidosis • Hereditary hyperoxaluria	• Anderson–Fabry disease • Danon disease • Pompe disease • Gaucher disease • Iron overload • Hereditary hemochromatosis	• Carcinoid • Endomyocardial fibrosis • Endocardial fibroelastosis • Metastatic tumor • Chemotherapy • Radiation therapy

RCM is characterized by a marked alteration of myocardial compliance: severe diastolic dysfunction and a preserved systolic function (at least in early stages). The initial diagnosis is performed by TTE showing a normal/increased LV wall thickness (generally with a concentric/symmetric distribution), a restrictive pattern by Doppler, absence of left ventricular dilatation, preserved LVEF, and a marked biatrial dilatation [57]. However, although TTE is crucial for the initial approach and raising diagnostic suspicions, its role is limited when establishing the differential diagnosis, in which case CMR is highly relevant.

4.1. Idiopathic Restrictive Cardiomyopathy

Idiopathic restrictive cardiomyopathy is a very uncommon disease affecting predominantly children and young adults with a familial pattern. It is characterized by the presence of a restrictive diastolic filling pattern (increased left ventricular end-diastolic pressure), normal left ventricular dimensions, absence of an increased left ventricular mass, normal left and right ventricular function, and absence of any other cardiac or pericardial diseases [58].

4.2. Cardiac Amyloidosis

Cardiac amyloidosis (CA) is an infiltrative disease caused by an extracellular accumulation of amyloid fibers. Most patients are affected by light chains (primary or AL amyloidosis) or by transthyretin (ATTR amyloidosis), either the hereditary form (ATTRm) or the wild type (ATTRwt) [59].

Among the main TTE findings, the following "red flags" should raise suspicion of CA [60]: left ventricular wall thickness > 12 mm, myocardial sparkling (Figure 14), increased valvular thickness, thick interatrial septum, low stroke volume, paradoxical low-flow low-gradient aortic stenosis, restrictive filling pattern by Doppler, and apical sparing pattern on strain analysis (a reduced global longitudinal strain with an apical to basal deformation ratio >2.1) (Figure 14), abnormal left atrial strain and pleural or pericardial effusion.

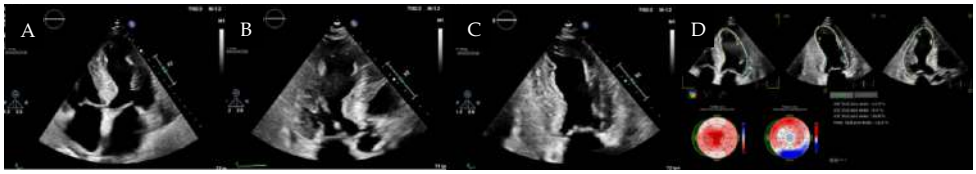

Figure 14. Apical 4-chamber (**A**), 3-chamber (**B**), and 2-chamber (**C**) views in a patient with cardiac amyloidosis (left ventricular wall thickness and sparkling). On the bull's eye strain images (**D**), the apical sparing pattern is displayed (right image).

The presence of a reduced GLS presents prognostic implications; a GLS >−14.8% has been associated with an increase in global mortality [61]. Although the apical sparing pattern is quite suggestive of CA, this pattern may not be present in patients with concomitant significant aortic stenosis [62].

CMR provides high-resolution structural and functional information, allows tissue characterization [60], and permits diagnosis at early stages compared to TTE [63]. The main findings, in addition to those described by TTE, are the difficulty to null the myocardial signal in LGE sequences, a global or diffuse LGE, and a marked increase in native T1 and ECV values (>40%) (Figure 15) [60,63,64].

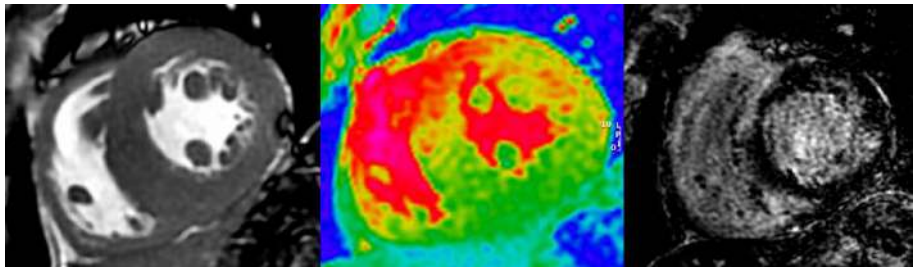

Figure 15. CMR findings in a patient with CA: left ventricular concentric hypertrophy (left), increased native T1 mapping values (red color in the central image), and diffuse LGE (right image).

As the disease progresses, there is an increase in LGE uptake, which is initially subendocardial and progressively becomes transmural (which is associated with an increase in overall mortality regardless of the type of amyloidosis) [65]. Additionally, a recent meta-analysis showed that ECV is the strongest diagnostic and prognostic imaging biomarker in CA [66], and an ECV >58% is associated with increased mortality in ATTR [67]. CMR cannot distinguish ATTR and AL forms, but there are characteristically-associated signs (Table 4) [64,65,67,68].

Either 99m technetium diphosphonate (Tc-DPD) or pyrophosphate (Tc-PYP) scintigraphy play a relevant role in diagnosing ATTR amyloidosis and allow early detection of cardiac involvement before TTE and CMR, however, false positives can be present [69]. Results are evaluated based on the Perugini scale: a grade 2 or 3 uptake (cardiac uptake similar to or greater than the ribs with/without a reduction in the bone uptake) has a positive predictive value around 100% [70]. Another means of quantification is the assessment of cardiac uptake compared to the contralateral chest (C/CL): a ratio $\geq$1.5 suggests the diagnosis of ATTR [68,70]. Prognostic implications of scintigraphy are still limited, however, a C/CL uptake >1.6 [71] or an apical sparing pattern [72] are associated with lower survival.

Table 4. Main differences between ATTR and AL amyloidosis.

	ATTR	AL
Left ventricular wall thickness and LV mass	++++	++
Asymmetrical septal hypertrophy	79%	14%
Transmural LGE	63%	27%
Subendocardial LGE	24%	39%
Native T1 elevation	++	++++
Native T2 relaxation time	++	++++
ECV	++++	++

++ Mildly abnormal. ++++ Severely abnormal.

Table 5 describes the main imaging findings that should raise suspicion of cardiac amyloidosis.

Table 5. Main imaging red flags in cardiac amyloidosis.

Echocardiography	CMR	Scintigraphy
• Left ventricular wall thickness > 12 mm. • Myocardial sparkling • Pleural/pericardial effusion • Increased valvular thickness • Thick interatrial septum. • Low stroke volume. • Paradoxical low-flow low-gradient aortic stenosis. • Restrictive filling pattern. • Apical sparing pattern. • Abnormal left atrial strain.	• Increased LV wall thickness. • Increased myocardial LV mass • Bi-auricular enlargement • Difficulty to null the myocardial signal • Global or diffuse LGE, • Marked increase in native T1 values • Elevated extracellular volume (> 40%) • Presence of pleural or pericardial effusion	• Grade 2 or 3 uptakes in the Perugini scale. • C/CL uptake ≥ 1.5

4.3. Fabry Disease

Anderson–Fabry disease (FD) is a rare (approximate incidence 1:40,000) genetic lysosomal storage disorder caused by a mutation in the alpha-galactosidase A (GLA) gene with an X-linked inheritance.

The presence of concentric left-ventricular hypertrophy (LVH) is the most common finding in FD, however, other patterns have also been described: septal, asymmetric, or apical [73]. LVH is higher in men than in women, and it tends to appear at younger ages. Another common finding is the presence of a binary septum: a hyperechoic endocardium adjacent to a hypoechoic subendocardium (Figure 16A). Prominent papillary muscles have also been described, as well as RV hypertrophy. There is also dilation and left atrial dysfunction (systolic and early diastolic strain) that is associated with a higher incidence of supraventricular arrhythmias. Mitral and aortic valvular thickening are also frequent.

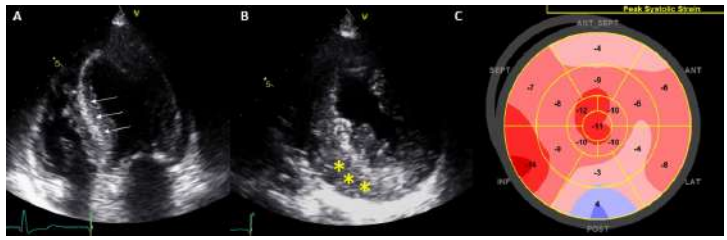

Figure 16. Echocardiographic signs in Fabry disease. (**A**) Binary septum (arrows), (**B**) concentric hypertrophy, and inferolateral fibrosis (*), (**C**) abnormal longitudinal strain more pronounced in the inferolateral wall (blue area) correlated with the fibrosis.

Generally, the biventricular systolic function is preserved until advanced stages of the disease, at least in terms of LVEF. However, FD patients show reduced values of GLS

and GCS compared to controls, which are more reduced in those with inferolateral LGE (Figure 16C); thus, an inferolateral longitudinal strain peak value <−12.5% suggests the presence of fibrosis with a sensitivity of 90% and a specificity of 97% [74].

Table 6 describes the main imaging findings in Fabry disease.

Table 6. Main echocardiographic findings in Fabry disease.

CARDIAC STRUCTURE	FINDINGS
Left ventricle	Concentric left ventricular hypertrophy Binary septum (low sensitivity and specificity for FD) Prominent papillary muscles Preserved LV function until end-stages Diastolic dysfunction Abnormal global longitudinal or radial strain, even in the absence of LVH
Right ventricle	Right ventricular hypertrophy Preserved RV function until end-stages Abnormal global longitudinal strain even with preserved EF
Atrium	Biauricular dilation Increased end-diastolic pressure Reduced auricular strain
Valves	Increase in mitral and aortic valve thickness Valvular regurgitation (generally, mild)
Aorta	Dilation of the aortic root and the ascending aorta (not descending aorta)

The most common finding in CMR is also the presence of concentric LVH. The typical LGE pattern is an intramyocardial uptake at the basal LV inferolateral wall, which is present in up to 50% of patients [75], and may progress to transmural extension together with a marked thinning of the myocardial wall (Figure 17).

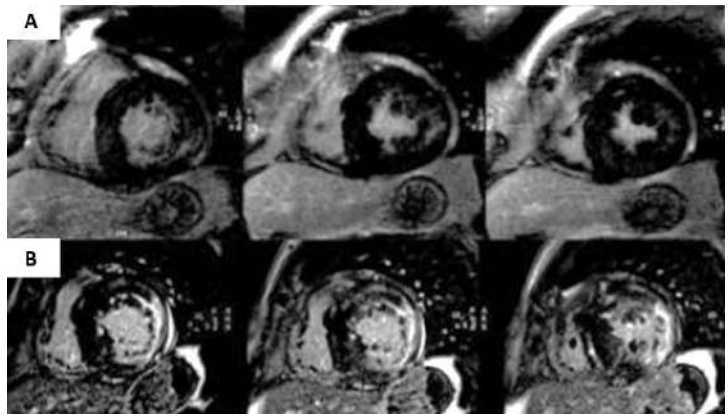

Figure 17. Late gadolinium enhancement pattern in a patient with Fabry disease. (**A**) Presence of LGE in the inferolateral wall. (**B**) Evolution of the same patient 5 years later, the presence of a thinning of the wall, a more extensive and transmural LGE pattern is observed.

The presence of LGE is indicative of irreversible myocardial damage; tfhus, clinical practice guidelines recommend starting treatment with a class I indication when there is

no or minimal fibrosis [76]. The presence of LGE is associated with a poorer response to medical treatment and an increased risk of cardiovascular events including SCD [74]. For this reason, some authors have suggested an ICD implantation in patients with a significant LGE mass; however, there are no available guidelines.

T1 and T2 mapping techniques may identify the presence of early myocardial damage before the onset of myocardial fibrosis. Given that the degree of myocardial infiltration is diffuse, it is recommended to assess the value of native T1 in all myocardial segments (Figure 18) [77]. Native T1 time has been inversely correlated with wall thickness, so that, the more hypertrophy the lower T1. Additionally, patients with ECG abnormalities present shorter T1 [77]. In the early stages, ECV is normal, suggesting that LVH is due to myocyte hypertrophy and not to extracellular fibrosis.

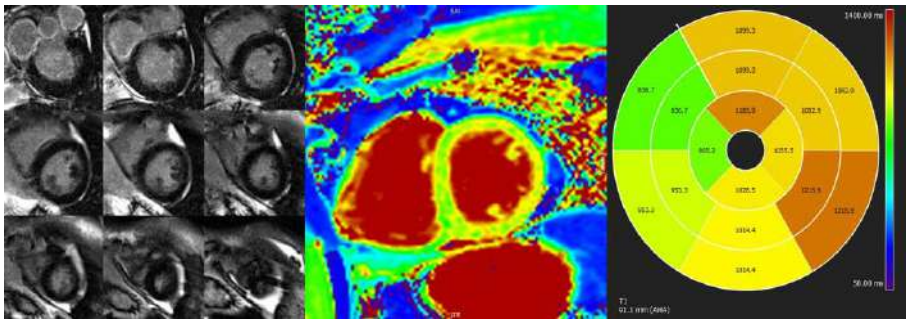

Figure 18. CMR findings in a patient with Fabry disease: (Left panel) presence of concentric left ventricular hypertrophy with no LGE. (Central panel) T1 mapping image of the same patient. (Right panel) bull's eye representation of the T1 mapping showing a short native T1 in the septum (glycosphingolipid accumulation) and a long T1 value in the inferolateral wall (diffuse fibrosis). T1 mapping abnormalities appear earlier than LGE.

FD must also be considered a chronic inflammatory disease. Thus, unlike patients with HCM, the presence of high native T2 values suggest FD, initially affecting the inferolateral wall and becoming progressively diffuse. Using 18F-fluorodeoxyglucose positron emission tomography (PET), an increase in the uptake of the tracer has also been described, confirming the presence of myocardial inflammation [78]. Finally, patients with FD also present a reduction in sympathetic activity, and 123I-meta-iodobenzylguanidine (MIBG) scintigraphy studies can differentiate stages of the disease [79]. The absence of myocardial denervation could play a relevant role in assessing the risk of developing ventricular arrhythmias and SCD.

4.4. Iron Overload Cardiomyopathy

Iron overload cardiomyopathy (IOC) is a secondary form of cardiomyopathy resulting from iron accumulation in the myocardium mainly because of genetically-determined iron metabolism disorders or multiple transfusions [80]. It has been described as a dilated cardiomyopathy, characterized by LV remodeling with chamber dilatation and reduced LVEF. However, primary hemochromatosis, a genetically determined condition leading to iron overload, is classically categorized as an infiltrative cause of restrictive cardiomyopathy. Moreover, secondary hemochromatosis may lead to severe diastolic LV dysfunction in the early stages of the disease, before LVEF is affected [80].

IOC can be very difficult to diagnose by TTE, therefore, CMR T2* imaging is considered the reference standard for detecting and quantifying myocardial iron overload. Abnormalities in CMR T2* can occur before the development of systolic or diastolic dysfunction and may be used to guide iron chelation therapy to prevent heart failure or death [81].

For easy classification into different IOC risk groups, the following classification has been adopted using a 1.5 Tesla MR scanner: patients with T2* >20 ms are regarded as not having cardiac iron overload, between 10–20 ms have mild to moderate cardiac iron load and those <10 ms are considered to have a heavy cardiac iron load [82].

4.5. Cardiac Sarcoidosis

Sarcoidosis is an inflammatory granulomatous disease that can involve any organ, with cardiac involvement (cardiac sarcoidosis, CS) in a quarter of patients. Clinical manifestations include heart block, atrial and ventricular arrhythmias, and heart failure. Diagnosis can be challenging but with the increased availability of advanced cardiac imaging, more cases are being identified.

TTE has limited sensitivity and specificity for the diagnosis of CS, however, it is often the initial imaging study. The TTE main findings include ventricular hypertrophy, diastolic dysfunction/restrictive filling pattern, wall motion abnormalities with a non-coronary distribution, aneurysms, and LV or RV systolic dysfunction [83]. CS patients who need pacing and have an LVEF <50% should be considered for CRT with ICD according to the recent ESC guidelines [84].

CMR plays an important role in the diagnosis and risk stratification of patients with CS. Although the presence of LGE may be non-specific, the subepicardial location, multifocal distribution, high signal intensity, and contiguous extension from the left to the right ventricle may increase the specificity of this finding for the diagnosis of CS [85]. Many studies have also demonstrated its prognostic value; LGE is associated with an increased risk of ventricular arrhythmias and all-cause mortality [85].

Cardiac PET using 18F-FDG has emerged as a cornerstone in the clinical diagnosis, prognostic evaluation, and monitoring of therapy in CS. FDG-PET/CT has a fair diagnostic accuracy for CS [86]. The classic pattern is one of 'perfusion–metabolism' mismatch, in which areas of 18F-FDG uptake correspond to areas of reduced or absent perfusion. FDG-PET/CT has a fair diagnostic accuracy for CS with a sensitivity of 89% and specificity of 78% [86]. An abnormal FDG uptake is associated with increased rates of ventricular arrhythmias and death, especially when located in the right ventricle [87] (Figure 19). Serial PET imaging is useful in monitoring disease activity and response to immunosuppressive therapy. Additionally, hybrid CMR-PET imaging has shown incremental value in determining disease activity and pattern [88].

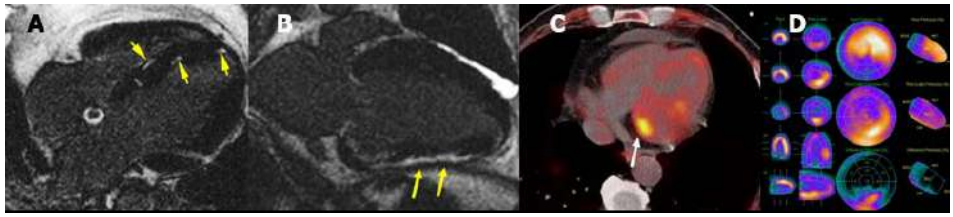

Figure 19. (**A**) Patchy LGE distribution in the septum (arrows) and (**B**) subepicardial LGE (arrows) in a patient with sarcoidosis. (**C**) 18F-FDG uptake in a patient with sarcoidosis (arrow). (**D**) Perfusion-metabolism mismatch in a patient with sarcoidosis (perfusion defect in the upper image, metabolism uptake in the mid image, and mismatch in the lower image).

4.6. Endomyocardial Fibrosis

Endomyocardial fibrosis (EMF) is a rare form of RCM characterized by an abnormal thickening of the endocardium due to fibrous tissue deposit [89] secondary to infections (typically in the tropical regions), inflammation, or toxic agents among others. Echocardiographic findings include apical obliteration due to endocardial thickening, a small ventricular cavity, and a marked restrictive diastolic pattern. EMF may affect primar-

ily the left ventricle, both left and right ventricles (in approximately half of the cases), or predominantly the right ventricle [90]. Apical thrombus is also a common finding and echocardiographic contrast may be used to differentiate them from the thickened myocardium (Figure 20).

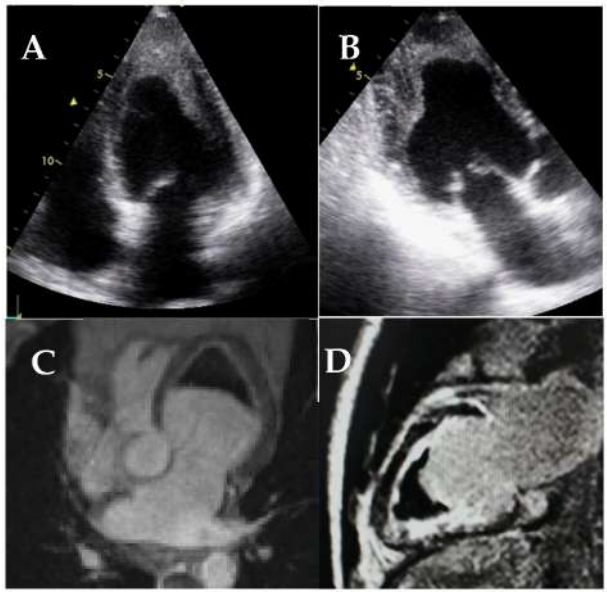

Figure 20. Transthoracic echocardiography (**A**,**B**) and cardiac magnetic resonance (**C**,**D**) of patients with endomyocardial fibrosis. Note the marked endocardial thickening of the mid and apical segments and apical obliteration of the left ventricle (**A**,**B**), the apical thrombus (**C**,**D**), and the endomyocardial fibrosis on LGE sequences (**D**).

CMR is the gold standard for EMF evaluation and specifically for localization, characterization, and quantification of fibrous tissue by LGE sequences. LGE strongly correlates with histopathological findings and its extension is associated with increased mortality risk [91]. CMR may also identify apical thrombus or calcifications.

5. Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is an inherited heart muscle disorder predisposing to SCD, particularly in young patients and athletes. It is a cell-to-cell junction cardiomyopathy, typically caused by genetically-determined abnormalities of cardiac desmosomes. Pathological features include loss of myocytes and fibrofatty replacement of right or left ventricular myocardium. ACM diagnosis does not rely on a single gold standard test but is classically achieved using a scoring system, which encompasses familial and genetic factors, ECG abnormalities, arrhythmias, and structural/functional ventricular alterations [92]. The score was recently updated and simplified [93].

TTE is the initial diagnostic approach in ACM patients. A thorough RV assessment with dedicated RV planes is recommended if clinical suspicion is high (Figure 21). The presence of regional RV akinesia, dyskinesia, or aneurysms and either RV dilatation or RV systolic dysfunction are considered diagnostic criteria on the 2010 Task Force Criteria, with different cut-off points for TTE and CMR major or minor criteria (Table 7) [92]. These were

changed slightly in the Padua criteria [93], where RV dilatation and systolic dysfunction were defined according to nomograms, with no specific cut-off points.

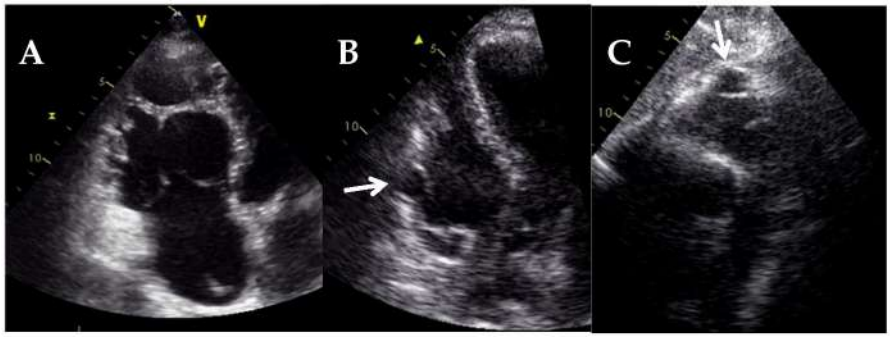

Figure 21. Transthoracic echocardiography of a patient with right ventricular arrhythmogenic cardiomyopathy. (**A**) RV dedicated apical 4-chamber view shows severe dilatation of the RV. RV dedicated apical 4-chamber view (**B**) and subcostal view (**C**) show the presence of aneurysms in the RV free wall (arrow).

Table 7. 2010 Task Force Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy. Adapted from [92].

	Global and/or Regional Dysfunction and Structural Alterations
Major	By 2D TTE: regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): • PLAX RVOT $\geq$ 32 mm (corrected for body size [PLAX/BSA] $\geq$ 19 mm/m^2) • PSAX RVOT$\geq$ 36 mm (corrected for body size [PSAX/BSA] $\geq$ 21 mm/m^2) • Or fractional area change $\leq$ 33%
	By CMR: regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: • Ratio of RV end-diastolic volume to BSA $\geq$ 110 mL/m^2 (male) or $\geq$100 mL/m^2 (female) • Or RV ejection fraction $\leq$ 40%
Minor	By RV angiography: regional RV akinesia, dyskinesia, or aneurysm By 2D-TTE: regional RV akinesia or dyskinesia and 1 of the following (end-diastole): • PLAX RVOT $\geq$ 29 to <32 mm (corrected for body size [PLAX/BSA] $\geq$ 16 to <19 mm/m^2) • PSAX RVOT $\geq$ 32 to <36 mm (corrected for body size [PSAX/BSA] $\geq$ 18 to <21 mm/m^2) • Or fractional area change >33% to $\leq$40%
	By CMR: regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following • Ratio of RV end-diastolic volume to BSA $\geq$100 to <110 mL/m^2 (male) or $\geq$90 to <100 mL/m^2 (female) • Or RV ejection fraction >40% to $\leq$45%

LV involvement is identified in more than half of patients with ACM, and biventricular as well as predominant LV ACM forms may occur [94], which are associated with a worse prognosis [95]. Specific diagnostic criteria for LV ACM were recently proposed: global LV systolic dysfunction (either LVEF or GLS) with or without LV dilatation, or regional LV hypokinesia/akinesia of the LV free wall or septum are considered minor criteria [93].

Emerging TTE parameters in the evaluation of patients with suspected or established ACM include the measurement of tricuspid annular plane systolic excursion (TAPSE), RV basal diameter, GLS (RV and LV), mechanical dispersion (RV and LV), and the use of 3D

TTE. In particular, RV GLS is affected in early ACM phases [96], TAPSE (as well as fractional area change) are associated with worse outcomes [97], and RV mechanical dispersion correlates with ventricular arrhythmias risk [98]. Besides, LVEF has an incremental prognostic role over RV systolic function [99]. Altogether, an international consensus proposed that prophylactic ICD implantation should be indicated in case of severe RV/LV systolic dysfunction and should be considered if there is moderate RV or LV impairment [100].

Due to the limitations of TTE in RV evaluation, CMR has become an integral part of the diagnostic evaluation in ACM. Beyond determining the presence of morpho-functional ventricular abnormalities, CMR provides information on the presence, morphology, and wall distribution of myocardial fibrofatty scar by LGE or fat-saturation T1 sequences. The same criteria previously described for TTE apply to CMR with corresponding cut-off points and nomograms (Table 7) [92,93]. RVEF by CMR has been incorporated into the risk prediction model of ventricular arrhythmias [101]. The presence of transmural LGE of $\geq$1 RV region or LV LGE of the free wall (subepicardial or intramyocardial) or septum are considered major criteria [93]. Typically, the LGE pattern shows large amounts of contrast uptake in the LV with a non-ischaemic pattern, predominantly involving the subepicardial layers of the inferior and the inferolateral regions (Figure 22). The presence of a subepicardial annular (ring-like pattern) is also suggestive of ACM.

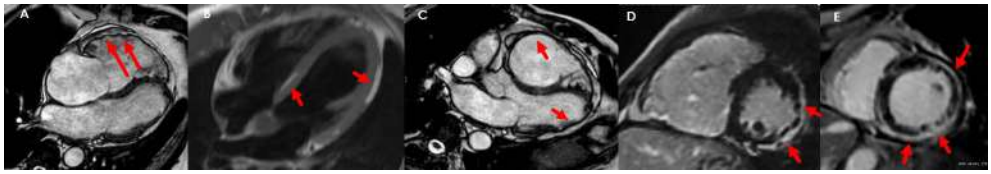

Figure 22. CMR findings in a patient with ACM. (**A**) RV aneurysms (arrows) in cine images. (**B**) Fibrofatty infiltration in T1-weighted turbo spin-echo sequences (arrow). (**C**) Right ventricular enlargement and left ventricular wall thinning (subepicardial fatty infiltration) (arrows) in a 3-chamber view cine. (**D**) Subepicardial LGE (arrows) and (**E**) subepicardial annular (arrows) patterns.

In cases where CMR is contraindicated, CT can be an alternative for the evaluation of RV and LV volumes and EF, aneurysms, fibrofatty infiltration, and wall motion abnormalities. Although generally not used in clinical practice for this purpose, angiography may be an alternative in the evaluation of these patients.

6. Left Ventricular Noncompaction

Left ventricular noncompaction (LVNC) is a heterogeneous entity characterized by prominent LV trabeculae, deep intertrabecular recesses, and a thin compacted (C) myocardial layer [102] (Figure 23). Hypertrabeculation may occur associated with LV dilatation (DCM) or hypertrophy (HCM), and both acquired and genetic LVNC forms may occur.

Different diagnostic criteria have been described for LVNC (Figures 24 and 25). By TTE, the distance from the epicardial surface to the trough of the trabeculae (X) and the distance from the epicardial surface to the peak of the trabeculae (Y) can be measured on short-axis views. A ratio of X/Y $\leq$0.5 at end-diastole is diagnostic of LVNC [103]. Alternatively, a ratio of NC/C layers >2 measured on the short-axis at end-systole is also suggestive of LVNC [104]. By CMR, a ratio of NC/C layers >2.3 measured on long-axis views [105], a trabeculated mass >20% of the total LV mass [106], or a fractal dimension >1.30 [107] are diagnostic of LVNC (all measured at end-diastole). Fulfillment of LVNC morphologic criteria per se has not been associated with LV remodeling [108] or clinical events [109] throughout follow-up. However, the extension of the trabeculae has been recently related to outcomes: patients presenting hypertrabeculation from the apex to the base have been found to have higher mortality [110].

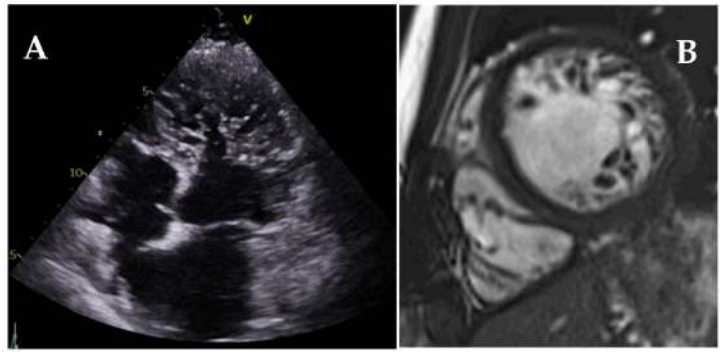

Figure 23. TTE (**A**) and CMR (**B**) images of patients with left ventricular noncompaction showing marked hypertrabeculation and deep intertrabecular recesses.

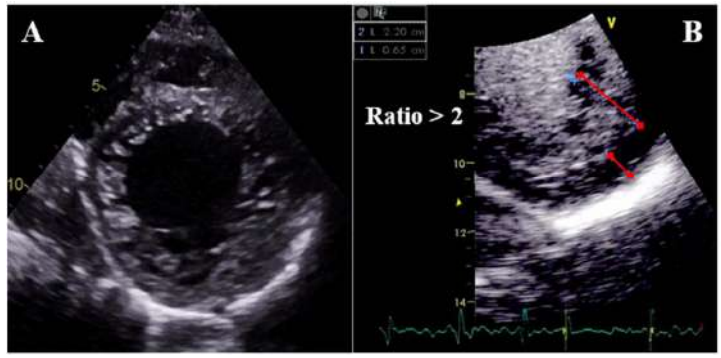

Figure 24. TTE parasternal short-axis mid-ventricular view of a patient with LVNC (**A**). Measurement of the compacted and non-compacted layers at end-diastole after echocontrast administration, fulfilling LVNC diagnostic criteria (**B**).

TTE is the first-line imaging technique for both quantification and localization of the trabeculae: the apex and lateral segments are the most frequently involved. Contrast echocardiography may be used to enhance trabeculation measurement and exclude the presence of intertrabecular thrombi (Figure 24B). Assessment of LVEF is mandatory since it is one of the strongest predictors of outcomes [110–112]. Strain analysis by TTE may detect subclinical myocardial dysfunction [113] and different studies have shown the diagnostic value of strain to differentiate LVNC from healthy controls [113] and DCM [114]. However, no consistent data is available on its prognostic implications.

CMR should be performed in all LVNC patients. The presence of LV dilatation [111,115] and a thinned compacted myocardial layer [115] has been associated with negative outcomes. Although LGE seems to be less frequent in LVNC compared to DCM or HCM [111], and not always related to the most hypertrabeculated segments, it is a powerful and independent predictor of outcomes, with added prognostic implications over LVEF [111,112,116]. Of note, patients with preserved LVEF and negative LGE have an excellent prognosis, while those with positive LGE are at increased risk irrespective of LVEF [116]. LGE has also been associated with SCD risk, even in the absence of severe systolic dysfunction [112]. Mapping techniques have been studied in LVNC; a small report has described worse outcomes with higher ECV values [117]. In addition, feature-tracking strain analysis may be used

to differentiate LVNC from the general population [118] and DCM [119]. However, it is not recommended in routine practice due to lack of standardization and unvalidated association with clinical events.

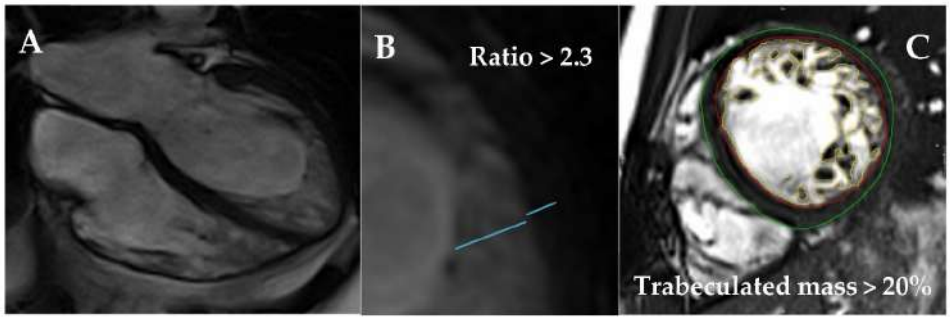

Figure 25. CMR 4-chambers view of a patient with LVNC (**A**). Measurement of the compacted and non-compacted layers at end-diastole on a long-axis view (Petersen criteria, **B**). Measurement of the trabeculated mass on a short-axis view (Jacquier criteria, **C**).

Finally, cardiac CT is rarely used in LVNC, with its main objective being to exclude coronary artery disease. However, a large population study has demonstrated that the degree of hypertrabeculation measured by CT was independently related to outcomes [120]. Therefore, cardiac CT may be considered in patients with contraindications for CMR.

7. Conclusions

Cardiac imaging techniques are an essential tool in the study of cardiomyopathies, and they provide both diagnostic and prognostic relevant information. Transthoracic echocardiography should always be the first technique used due to its availability and cost, as well as the possibility of periodic testing. Cardiovascular magnetic resonance should also be performed in all patients due to its additional anatomical and functional information as well as thorough tissue characterization, with important prognostic implications. Other techniques (e.g., CT, PET-CT, scintigraphy, among others) may be applied in selected entities while more advanced imaging analysis (e.g., strain, myocardial work, mapping, etc.) offer promising but still preliminary results. Altogether, multimodality cardiac imaging plays an important role in clinical decision-making and helps to improve patients' management and outcomes.

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Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ACM	arrhythmogenic cardiomyopathy
AL	primary amyloidosis
ATTR	transthyretin amyloidosis
C/CL	cardiac compared to the contralateral chest
CA	cardiac amyloidosis
CMR	cardiovascular magnetic resonance
CRT	cardiac resynchronization therapy
CS	cardiac sarcoidosis
CT	computed tomography
DCM	dilated cardiomyopathy
ECG	electrocardiogram
ECV	extracellular volume
EMF	endomyocardial fibrosis
ESC	European Society of Cardiology
FD	Anderson–Fabry disease
FDG	18F-fluorodeoxyglucose
GCS	global circumferential strain
GLS	global longitudinal strain
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter-defibrillator
IOC	iron overload cardiomyopathy
LGE	late gadolinium enhancement
LV	left ventricle
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVNC	left ventricular noncompaction
LVOTO	left ventricular outflow tract obstruction
MIBG	123I-meta-iodobenzylguanidine
MW	myocardial work
PET	positron emission tomography
RCM	restrictive cardiomyopathies
RV	right ventricle
RVEF	right ventricle ejection fraction
SAM	systolic anterior motion
SCD	sudden cardiac death
TAPSE	tricuspid annular plane systolic excursion
TTE	transthoracic echocardiography

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10.2. COMUNICACIONES EN CONGRESOS

10.2.1. Comunicación 1

Guillem Casas, Eduard Rodenas-Alesina, Javier Limeres, Roberto Barriales-Villa, Pablo García-Pavía, Eduardo Villacorta, Esther Zorio, Juan Jimenez-Jaimez, Albert Teis, Tomas Ripoll, Juan-Ramon Gimeno, Andrea Guala, Ignacio Ferreira-Gonzalez, José-Fernando Rodríguez-Palomares, Kiosk 8R-FA-01 - Cardiovascular Magnetic Resonance for Precise Prognostic Assessment in Patients with Excessive Trabeculation of the Left Ventricle, Journal of Cardiovascular Magnetic Resonance, Volume 26, Supplement 1, 2024, 100872, ISSN 1097-6647, https://doi.org/10.1016/j.jocmr.2024.100872.

Kiosk 8R-FA-01
Cardiovascular Magnetic Resonance for Precise Prognostic Assessment in Patients with Excessive Trabeculation of the Left Ventricle

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Background: Excessive trabeculation of the left ventricle (ETLV) is a heterogeneous entity. Risk assessment by cardiovascular magnetic resonance (CMR) remains poorly defined. Our aim was to develop a CMR prediction model of major adverse cardiovascular events (MACE) in ETLV.

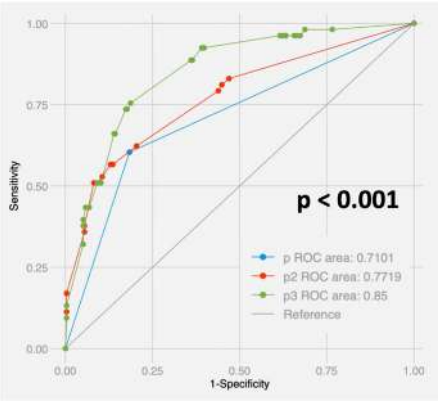
Methods: We conducted a retrospective longitudinal multicentre cohort study of ETLV patients with corelab CMR analysis. The endpoint was a composite of MACE: heart failure, ventricular arrhythmias, systemic embolisms and all-cause death. Cox regression analysis was performed. Three sequential prediction models were developed: a "traditional model" based on LV ejection fraction (LVEF); a "clinical model" based on daily-practice CMR variables (e.g.: LVEF, right ventricular (RV) EF, and late gadolinium enhancement (LGE)); and a "research model" including advanced parameters (e.g.: global longitudinal strain (GLS) and hemodynamic forces (HDF)). The best prediction models were chosen based on C-statistic and Akaike information criterion. Finally, a risk score was developed based on the third model.

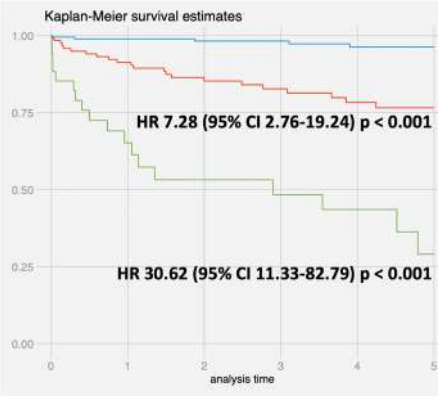
Results: A total of 348 patients from 11 centers were included: age was 46±19 years and 150 (43%) were female. LVEF was 48 ±14% and 32 (10%) had LGE. During a median follow-up of 3.9 (1.8-6.1) years, 54 (16%) patients developed MACE: 27 (8%) heart failure, 32 (9%) ventricular arrhythmias, 2 (1%) systemic embolisms and 6 (2%) deaths. Table 1 shows the association of the main CMR variables with the endpoint.

The "traditional model" (LVEF) had an AUC of 0.71 (95% CI: 0.64- 0.78). The best "clinical model" was a combination of LVEF, RVEF, left atrium (LA) volume index, and percentage of LGE mass (LGE%), with an AUC of 0.77 (95% CI: 0.70-0.85; p=0.006 compared to the first model). The best "research model" included LVEF, RVEF, LGE%, LA GLS, and lateral-septal HDF, with an AUC of 0.85 (95% CI: 0.80-0.90; p=0.007 compared to the second model) (Figure 1).

Subsequently, a risk score was developed: 1 point was assigned to LVEF<40%, RVEF<35%, LGE% >5% and LA-GLS <28%, 2 points to LA-GLS <17% and 4 points to HDF<3%. The score was accurate at identifying both low- (0-4 points), intermediate- (5-7 points) and high-risk (8-9 points) patients (Figure 2).

Conclusion: A comprehensive CMR evaluation in patients with excessive trabeculation of the left ventricle allows for precise risk stratification. Our proposed prediction model could be used to individualise patients' management, which might improve long-term outcomes.





Baseline CMR characteristics according to the occurrence of MACE

	TOTAL (n = 348)	MACE (n = 54)	NO MACE (n = 294)	p-value
LVEDV, mL	179.0 (68.3)	230.6 (97.3)	169.5 (56.9)	<0.001
LVESV, mL	84.9 (39.4)	94.2 (52.3)	83.1 (36.4)	0.059
LVEF, %	47.6 (14.4)	35.9 (17.4)	49.8 (12.7)	<0.001
RVEDV, mL	158.9 (51.2)	153.3 (53.0)	160.0 (50.9)	0.38
RVESV, mL	84.9 (39.4)	94.2 (52.3)	83.1 (36.4)	0.05
RVEF, %	47.5 (12.4)	40.4 (16.3)	48.8 (11.0)	<0.001
LAVi, mL/m²	52.9 (22.5)	68.8 (30.7)	49.8 (19.1)	<0.001

LGE, n	32 (10.4%)	15 (31.2%)	17 (6.6%)	<0.001
LGE, % of mass	1.0 (3.7)	3.6 (7.3)	0.5 (2.4)	<0.001
LV GLS, %	-10.4 (4.0)	-8.0 (3.8)	-10.9 (3.8)	<0.001
LV GCS, %	-13.7 (4.4)	-9.8 (5.0)	-14.4 (3.9)	<0.001
LV GRS, %	20.9 (8.5)	14.3 (9.1)	22.1 (7.9)	<0.001
LA GLS, %	28.9 (18.1)	18.5 (19.1)	30.8 (17.3)	<0.001
HDFIs, %	2.8 (1.2)	1.9 (0.8)	2.9 (1.2)	<0.001

Author Disclosure: G Casas: Nothing to disclose; **E Rodenas-Alesina**: N/A; **J Limeres**: N/A; **R Barriales-Villa**: N/A; **P García-Pavía**: N/A; **E Villacorta**: N/A; **E Zorio**: N/A; **J Jimenez-Jaimez**: N/A; **A Teis**: N/A; **T Ripoll**: N/A; **J Gimeno**: N/A; **A Guala**: N/A; **I Ferreira-Gonzalez**: N/A; **J Rodríguez-Palomares**: N/A

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Kiosk 8R-FA-02

Predictive Value of Left Atrial Fast Long-axis Strain for Thrombotic Events in Hypertrophic Cardiomyopathy

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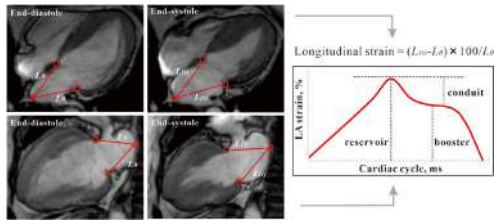
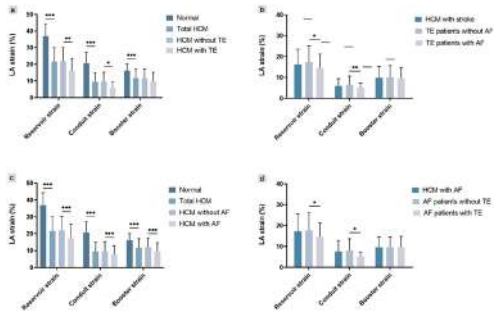
Background: Patients with hypertrophic cardiomyopathy (HCM) are at a significantly increased risk of thrombotic events (TEs) with pre-existing atrial fibrillation (AF) or not. The CHA_2DS_2-VASc score is commonly used for stroke risk stratification in AF, however, it does not effectively predict stroke risk in patients with HCM. The aim of this study was to clarify the predictive value of left atrial (LA) rapid long-axis strain (LAS) based on standardized cardiac magnetic resonance (CMR) imaging for TEs in patients with HCM.

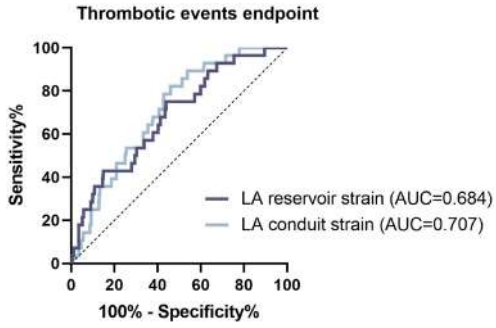
Methods: This study prospectively enrolled consecutive HCM patients without atrial fibrillation (AF) who underwent standardized CMR from January 2012 to December 2020. The rapid LA-LAS (reservoir, conduit, and booster) was obtained by semi-automatically tracking the distance between the atrioventricular junction and mid-posterior LA wall (the intersection point of the LA posterior wall and the LA long-axis). The primary endpoint was defined as TEs, including ischemic stroke, transient ischemic attack, and systemic thromboembolism. The predictive value of LA-LAS for TE was determined by Cox regression analysis.

Results: A total of 714 HCM patients (61.8% male, 40.5% obstructive HCM, 20.2% apical HCM) were included with a median follow-up of 51 months. 28 (3.9%) HCM patients developed TE, while 60% of TEs occurred without new-onset AF documented. HCM Patients with TE had significantly lower LA rapid long-axis strains (LA reservoir strain 16.2 ± 7.3 % vs. 21.8 ± 8.3 %, LA conduit strain 5.9 ± 3.5% vs. 9.7 ± 5.5 %). LA strains were independent predictors of TE in HCM, even after correction for age, gender, LVEF, and AF: adjusted HR were 0.93 (95% CI: 0.88-0.99, P = 0.024) and 0.90(95% CI: 0.81-0.99, P = 0.038) in LA reservoir and conduit strain, respectively.

Conclusion: The LA strain measured using fast long-axis strain was independently associated with the endpoint of TE (independent of AF).







Author Disclosure: L Pu: Nothing to disclose; **J Wang**: N/A; **J Li**: N/A; **W Qi**: N/A; **Y Han**: N/A; **Y Chen**: N/A

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10.2.2. Comunicación 2

Guillem Casas, Eduard Rodenas-Alesina, Javier Limeres, Roberto Barriales-Villa, Pablo García-Pavía, Eduardo Villacorta, Esther Zorio, Juan Jimenez-Jaimez, Albert Teis, Tomas Ripoll, Juan-Ramon Gimeno, Andrea Guala, Ignacio Ferreira-Gonzalez, José-Fernando Rodríguez-Palomares, CMR 4-123 - Predicting Left Ventricular Ejection Fraction Decline in Patients with Excessive Trabeculation of the Left Ventricle and Risk of Future Major Cardiovascular Events, Journal of Cardiovascular Magnetic Resonance, Volume 26, Supplement 1, 2024, 100206, ISSN 1097-6647, https://doi.org/10.1016/j.jocmr.2024.100206.

CMR 4-123
Predicting Left Ventricular Ejection Fraction Decline in Patients with Excessive Trabeculation of the Left Ventricle and Risk of Future Major Cardiovascular Events

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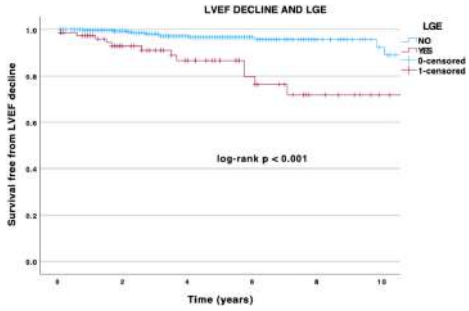
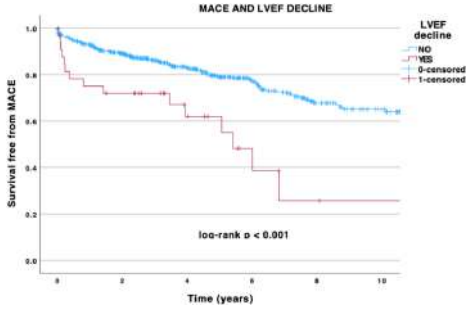
Background: Excessive trabeculation of the left ventricle (ETLV) is a controversial entity. The evolution of left ventricular ejection fraction (LVEF) over time could aid in the diagnostic and prognostic assessment. Our aim was to describe the incidence of and factors associated with LVEF decline, and to investigate its correlation with future major adverse cardiovascular events (MACE).

Methods: We conducted a retrospective, longitudinal, multicenter cohort study of ETLV patients. Two endpoints were analyzed: 1) LVEF decline (>10% absolute decrease in LVEF with LVEF< 50% at follow-up); and 2) MACE, a composite of heart failure, ventricular arrhythmias, systemic embolisms or all-cause mortality.

Results: A total of 577 patients from 12 centers were included: 45±20 years old, 42% women, with an LVEF of 48±17% and 18% with late gadolinium enhancement (LGE). Over a median 4.3-year echocardiographic follow-up, 34 (6%) patients developed a decline in LVEF. LGE (HR 4.78, 95% CI 2.12-10.78, p< 0.001) and sinus rhythm (HR 0.23, 95% CI 0.09-0.59, p=0.002) were independently associated with LVEF decline. During an additional 3.8-year clinical follow-up, 136 (24%) patients experienced MACE: 65 (11%) heart failure, 70 (12%) ventricular arrhythmias, 14 (2%) systemic embolismsand 33 (6%) deaths. Baseline LVEF (HR 0.95, 95% CI 0.93-0.97, p< 0.001), LVEF decline (HR 2.68, 95% CI 1.11-6.45, p=0.028), sinus rhythm (HR 0.45, 95% CI 0.22-0.95, p=0.037) and QRS ≥ 120 ms (HR 2.10, 95% CI 1.15-3.84, p=0.016) remained associated with MACE after adjustment.

Conclusion: In patients with excessive trabeculation of the left ventricle, the incidence of LVEF decline is low and mainly associated with the presence of myocardial fibrosis. LVEF decline is an independent risk factor for future cardiovascular events. The evolution of LVEF could be used for the differential diagnosis and risk assessment in this population.





Baseline characteristics and left ventricular ejection fraction decline

	All (n = 577)	LVEF decline(n = 34)	No LVEF decline(n = 543)	p Value
Clinical characteristics				
Age at diagnosis, yrs (SD)	45 (20)	51 (21)	45 (20)	0.032
Female gender, n (%)	245 (43)	23 (43)	222 (42)	0.406
Cardiovascular risk factors				
Hypertension, n (%)	136 (24)	13 (24)	123 (24)	0.071
Dyslipidemia, n (%)	141 (25)	15 (28)	126 (25)	0.029
Diabetes mellitus, n (%)	50 (9)	7 (13)	43 (9)	0.023
Electrocardiogram				
Sinus rhythm, n (%)	495 (91)	46 (85)	449 (92)	0.007
QRS ≥ 120 ms, n (%)	155 (35)	15 (52)	140 (34)	0.128
Echocardiography				

LVEF, % (SD)	48 (17)	47 (15)	48 (17)	0.473
LVEDD, mm (SD)	54 (10)	56 (10)	54 (10)	0.360
LVESD, mm (SD)	38 (11)	42 (11)	37 (11)	0.030
TAPSE, mm (SD)	21 (5)	22 (5)	21 (5)	0.255
Cardiovascular magnetic resonance				
LVEF, % (SD)	51 (16)	44 (17)	51 (16)	0.005
LVEDV, ml (SD)	167 (74)	193 (100)	165 (72)	0.014
LVESV, ml (SD)	87 (64)	113 (89)	85 (62)	0.004
RVEF, % (SD)	54 (12)	53 (12)	54 (12)	0.323
RVEDV, ml (SD)	143 (49)	130 (37)	144 (50)	0.394
RVESV, ml (SD)	68 (34)	62 (24)	69 (35)	0.733
LGE, n (%)	79 (18)	12 (30)	67 (17)	< 0.0

Author Disclosure: G Casas: Nothing to disclose; **E Rodenas-Alesina**: N/A; **J Limeres**: N/A; **R Barriales-Villa**: N/A; **P García-Pavía**: N/A; **E Villacorta**: N/A; **E Zorio**: N/A; **J Jimenez-Jaimez**: N/A; **A Teis**: N/A; **T Ripoll**: N/A; **J Gimeno**: N/A; **A Guala**: N/A; **I Ferreira-Gonzalez**: N/A; **J Rodríguez-Palomares**: N/A

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CMR 4-124
The Predictive Power of Cardiovascular Magnetic Resonance Feature Tracking Global Longitudinal Strain Is Independent of Loading Condition

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Background: Cardiac magnetic resonance based feature tracking (CMR-FT) left ventricular (LV) strain has been shown to reflect early functional impairment, when visual estimation of LV ejection fraction is still normal and to confer prognosis.

However there is conflicting evidence to the afterload dependance of strain and to what extent afterload hampers CMR-FT strains ability to predict prognosis. The non-geometric left ventricular end-systolic afterload index (NGI) and the effective arterial elastance (Ea) are well-established metrics to estimate afterload non invasively.

The effective ventricular elastance index (Ees) has emerged as a reliable estimator of left ventricular elastance, which reflects contractility.

To correlate CMR-FT LV global longitudinal strain (GLS) and strain rate (GLSR) with afterload and contractility indices and to determine if the prognostic value of GLS and GLSR is independent of loading conditions.

Methods: Between April 2017 and December 2022, we enrolled consecutive patients with clinically indicated CMR over a wide range of indications and diagnoses into our BioCVI imaging registry. The combined endpoint was defined as all-cause mortality and heart failure hospitalisations.

The hemodynamic indices were defined as follows:

Ea = End-systolic pressure (ESP) / Stroke volume (SV)

NGI = ESP x Left ventricular end-systolic volume (LVESV) / Left-ventricular mass

Ees = ESP / LVESV

Univariate regression analysis was used to examine the relationship between afterload/contractility and GLS/GLSR. Uni- and multivariate Cox Regression Analysis were used to examine the predictive power of GLS and GLSR. ANOVA was used to test differences between tertiles of Ea, Ees and NGI.

Results: A total of 927 patients (333 females [35.92%], median age 61 years) were included in the follow-up analysis, with 40 patients (4.31%) experiencing the combined endpoint over a median follow-up period of 14 months. 225 (24.2%) of the patients were considered healthy while 337 (36.4%) had ischemic heart disease and 365 (39.3%) had non-ischemic heart disease. Ea exhibited a significant and modest negative correlation with GLS (β=-0.507, $p < 0.001$) and GLSR (β=-0.551, $p < 0.001$, Figure 1). Similarly, Ees displayed a modest negative correlation with GLS (β=-0.497, $p < 0.001$) and GLSR (β=-0.537, $p < 0.001$, Figure 2). NGI also exhibited a significant and modest positive correlation with GLS (β=0.497, $p < 0.001$) and GLSR (β=0.460, $p < 0.001$, Figure 3). GLS, GLSR, Ea, Ees and NGI were alle significantly predictive of the combined endpoint. In multivariate analysis only GLS (HR 1.14 [95% CI 1.05 – 1.22]) and GLSR (HR 12.22 [95% CI 2.18 – 68.53]) remained predictive of the combined endpoint.

Conclusion: Our study demonstrates that GLS and GLSR reflect contractility but are both dependent on afterload, however both GLS and GLSR are independently predictive of all-cause mortality and heart failure hospitalisations.

10.2.3. Comunicación 3

G Casas, E Rodenas, M Gonzalez-Del-Hoyo, R Barriales, P Garcia-Pavia, E Villacorta, E Zorio, J Jimenez-Jaimez, A Bayes, T Ripoll, J R Gimeno, A Guala, J Limeres, I Ferreira-Gonzalez, J F Rodriguez-Palomares, A comprehensive CMR analysis improves risk stratification in left ventricular noncompaction, European Heart Journal, Volume 44, Issue Supplement_2, November 2023, ehad655.200, https://doi.org/10.1093/eurheartj/ehad655.200

European Heart Journal (2023) 44 (Suppl 2)

Imaging – Cardiac Magnetic Resonance (CMR), Myocardial Disease

A comprehensive CMR analysis improves risk stratification in left ventricular noncompaction

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Funding Acknowledgements: None.

Background: Left ventricular noncompaction (LVNC) is a heterogeneous and controversial entity. Risk assessment by cardiovascular magnetic resonance (CMR) remains poorly defined.

Purpose: To develop a CMR prediction model of major adverse cardiovascular events (MACE) in LVNC.

Methods: We conducted a retrospective longitudinal multicentre cohort study of LVNC patients with core-lab CMR analysis. The endpoint was a composite of MACE: heart failure, ventricular arrhythmias, systemic embolisms and all-cause death. The effect of variables on the endpoint was analysed by Cox regression and variables were dichotomized according to their association with the outcome. Three sequential prediction models were developed: a "traditional model" based on LV ejection fraction (LVEF); a "clinical model" based on daily-practice CMR variables (e.g.: LVEF, right ventricular (RV) EF, and late gadolinium enhancement (LGE)); and a "research model" including advanced parameters (e.g.: global longitudinal strain (GLS) and hemodynamic forces (HDF)). The best prediction models were chosen based on C-statistic and Akaike information criterion (AIC). A risk score was developed based on the third model, and according to proportional hazard ratios.

Results: A total of 348 patients were included, age was 46 (19) years and 150 (43%) were female. LVEF was 48 (14) % and 32 (10%) had LGE. During a median follow-up of 3.9 (1.8-6.1) years, 54 (16%) patients developed MACE: 27 (8%) heart failure, 32 (9%) ventricular arrhythmias, 2 (1%) systemic embolisms and 6 (2%) deaths. Figure 1 shows the association of the main CMR variables with the endpoint.

The "traditional model" (dichotomic LVEF with cut-off point at 40%) had an AUC of 0.71 (95% CI: 0.64-0.78). The best "clinical model" was a combination of LVEF, RVEF (cut-off point 35%), left atrium (LA) volume index (cut-off point 53 mL/m2) and percentage of LGE mass (LGE%, cut-off point 5%), with an AUC of 0.77 (95% CI: 0.70-0.85; p=0.006 compared to the first model). The best "research model" included LVEF, RVEF, LGE%, LA GLS (two cut-off points 17% and 28%), and lateral-septal HDF (cut-off point 3%), with an AUC of 0.85 (95% CI: 0.80-0.90; p=0.007 compared to the second model) (Figure 2a).

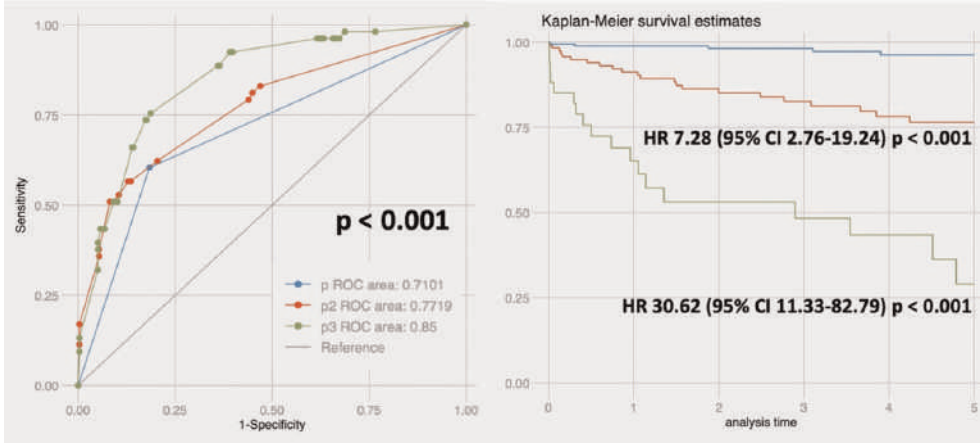
Subsequently, a risk score was developed: 1 point was assigned to LVEF<40%, RVEF<35%, LGE% >5% and LA-GLS <28%, 2 points to LA-GLS <17% and 4 points to HDF<3%. The score was accurate at identifying both low- (0-4 points), intermediate- (5-7 points) and high-risk (8-9 points) patients (Figure 2b).

Conclusions: A comprehensive CMR evaluation in LVNC allows for precise risk stratification. Our proposed prediction model could be used to individualise patients' management, which might improve long-term outcomes.

European Heart Journal (2023) 44 (Suppl 2)

	TOTAL (n = 348)	MACE (n = 54)	NO MACE (n = 294)	p-value
LVEDV, mL	179.0 (68.3)	230.6 (97.3)	169.5 (56.9)	<0.001
LVESV, mL	84.9 (39.4)	94.2 (52.3)	83.1 (36.4)	0.059
LVEF, %	47.6 (14.4)	35.9 (17.4)	49.8 (12.7)	<0.001
RVEDV, mL	158.9 (51.2)	153.3 (53.0)	160.0 (50.9)	0.38
RVESV, mL	84.9 (39.4)	94.2 (52.3)	83.1 (36.4)	0.05
RVEF, %	47.5 (12.4)	40.4 (16.3)	48.8 (11.0)	<0.001
LAVi, mL/m²	52.9 (22.5)	68.8 (30.7)	49.8 (19.1)	<0.001
LGE, n	32 (10.4%)	15 (31.2%)	17 (6.6%)	<0.001
LGE, % of mass	1.0 (3.7)	3.6 (7.3)	0.5 (2.4)	<0.001
LV GLS, %	-10.4 (4.0)	-8.0 (3.8)	-10.9 (3.8)	<0.001
LV GCS, %	-13.7 (4.4)	-9.8 (5.0)	-14.4 (3.9)	<0.001
LV GRS, %	20.9 (8.5)	14.3 (9.1)	22.1 (7.9)	<0.001
LA GLS, %	28.9 (18.1)	18.5 (19.1)	30.8 (17.3)	<0.001
HDFIs, %	2.8 (1.2)	1.9 (0.8)	2.9 (1.2)	<0.001

CMR characteristics according to MACE



Prediction models of MACE and risk score

10.2.4. Comunicación 4

G Casas, J Limeres, L Gutierrez-Garcia, L La Mura, A Guala, G Teixido, R Escalona, M Gonzalez-Del-Hoyo, J R Gimeno, E Zorio, P Garcia-Pavia, R Barriales, A Evangelista, I Ferreira-Gonzalez, J F Rodriguez-Palomares, Prognosis of left ventricular noncompaction with preserved ejection fraction, European Heart Journal, Volume 42, Issue Supplement_1, October 2021, ehab724.1758, https://doi.org/10.1093/eurheartj/ehab724.1758

1758

Valvular, Myocardial, Pericardial, Pulmonary, Congenital Heart Disease – Myocardial Disease, Clinical, Ventricular Noncompaction

Prognosis of left ventricular noncompaction with preserved ejection fraction

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Funding Acknowledgement: Type of funding sources: None.

Introduction: Left ventricular noncompaction (LVNC) is a poorly defined entity with heterogeneous prognosis. LV ejection fraction (LVEF) is one of the main predictors of major adverse cardiovascular events (MACE). However, outcomes of LVNC patients with preserved LVEF (pEF) remain uncertain.

Purpose: The aim of our study was to determine the incidence and predictors of MACE in LVNC patients with pEF as well as to assess the evolution of LVEF throughout follow-up.

Methods: We conducted a retrospective, longitudinal, multicentre cohort study. Consecutive patients with transthoracic echocardiography (TTE) and/or cardiac magnetic resonance (CMR) diagnostic criteria for LVNC and initially pEF (LVEF≥50%) were recruited. MACE were defined as a composite of heart failure (HF), ventricular arrhythmias (VA), systemic embolisms (SE) and/or all-cause mortality. Progressive systolic dysfunction was defined as an LVEF<50% at last TTE and/or an absolute ≥10-point decrease in LVEF from first to last TTE. Lower limit of LVEF values were considered 50–53% for TTE and 50–57% for CMR, according to current recommendations.

Results: A total of 305 patients from 12 centres were included from 2000 to 2018. Age was 38±19 years, 165 (54%) were men and 185 (61%) were probands. LVEF was 62±8% and 8% had late gadolinium enhancement (LGE). During a median follow-up of 4.7 (IQR 2.1–7.4) years, MACE occurred in 40 (13%) patients with an incidence rate of 2.96 (95% CI 2.17–4.04) events per 100 person-years: 8 HF, 27 VA, 3 SE and 5 deaths. LVEF by TTE (HR 0.95, 95% CI 0.90–0.99, p=0.035) and age (HR 1.02, 95% CI 1.01–1-04, p=0.04) were the only variables independently associated with the endpoint. Patients with lower limit LVEF values showed an increased risk of MACE (Figure 1). Among probands, those with family aggregation presented a higher incidence of MACE compared to nonfamilial cases (HR 2.74, p=0.043). A positive genotype was not associated.

Sixty-one (21%) patients experienced progressive systolic dysfunction: 31 (11%) had an LVEF<50% and 48 (17%) an absolute ≥10-point decrease in LVEF at last follow-up. On multivariate analysis, LVEF by CMR was the only independent predictor (HR 0.96, 95% CI 0.92–0.99, p=0.031). Patients with lower limit LVEF values had an increased risk (Figure 2). In this subgroup, LGE was also associated with the endpoint (HR 3.52, p=0.011). Family aggregation was not associated, while a positive genotype correlated with lower risk (HR 0.52, p=0.029).

Conclusions: Patients with left ventricular noncompaction and preserved ejection fraction carry a moderate risk of major adverse cardiovascular events and progressive systolic dysfunction. LVEF remains the main predictor of outcomes in this subgroup. Patients with lower limit LVEF values are at increased risk, probably suggesting subclinical systolic dysfunction. Therefore, they should be carefully monitored.

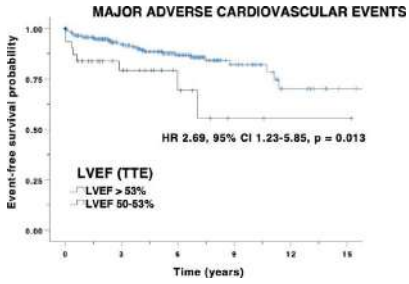

Figure 1

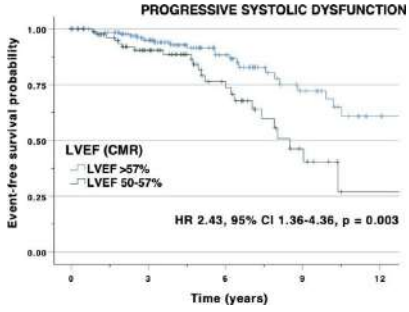

Figure 2

10.2.5. Comunicación 5

G Casas, J Limeres, R Barriales-Villa, P Garcia-Pavia, E Zorio, JR Gimeno-Blanes, J Palomino-Doza, JM Garcia-Pinilla, A Bayes-Genis, T Ripoll-Vera, J Jimenez-Jaimez, E Villacorta, A Evangelista, I Ferreira-Gonzales, JF Rodriguez-Palomares, Prognostic role of cardiac magnetic resonance in left ventricular noncompaction, European Heart Journal - Cardiovascular Imaging, Volume 22, Issue Supplement_2, June 2021, jeab090.111, https://doi.org/10.1093/ehjci/jeab090.111

European Heart Journal - Cardiovascular Imaging 2021 Volume 22, Supplement 2 ii161

Epidemiology, Prognosis, Outcome

Prognostic role of cardiac magnetic resonance in left ventricular noncompaction

Casas G.[1]; Limeres J.[1]; Barriales-Villa R.[2]; Garcia-Pavia P.[3]; Zorio E.[4]; Gimeno-Blanes JR.[5]; Palomino-Doza J.[6]; Garcia-Pinilla JM.[7]; Bayes-Genis A.[8]; Ripoll-Vera T.[9]; Jimenez-Jaimez J.[10]; Villacorta E.[11]; Evangelista A.[1]; Ferreira-Gonzales I.[1]; Rodriguez-Palomares JF.[1]

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Funding Acknowledgements: Type of funding sources: None.

Background: Left ventricular noncompaction (LVNC) is a heterogeneous entity with a wide phenotypic expression. Risk factors have not been well established and prognostic stratification remains challenging.

Purpose: Describe prognostic role of CMR on long term outcomes of LVNC patients.

Methods:

Retrospective multicentric longitudinal cohort study of consecutive patients fulfilling imaging diagnostic criteria for LVNC (Jenni echo criteria and Petersen and Jacquier CMR criteria). Demographic, ECG, genetic, family and treatment variables were recorded. Baseline CMR was used for the analysis. LV ejection fraction (LVEF) was categorized according to heart failure (HF) guidelines and late gadolinium enhancement (LGE) was visually assessed in a binary way. End points were HF, ventricular arrhythmias (VA), systemic embolisms (SE) and all-cause death. Major adverse cardiovascular events (MACE) were the combination of the four previous end points. In patients with initially preserved LVEF (≥ 50%), LV adverse remodelling (LVAR) was defined as an LVEF < 50% and/or absolute decrease of ≥10% in LVEF at last follow-up.

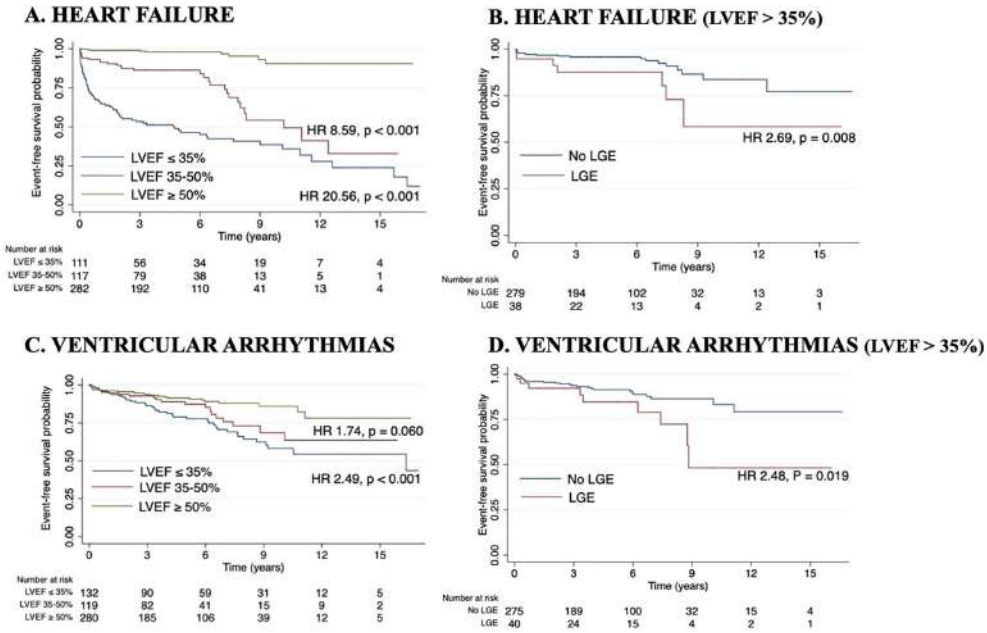
Results: 585 patients from 12 referral centres were included from 2000 to 2018. Age at diagnosis was 45 ± 20 years, 334 (57%) were male, baseline LVEF was 48 ± 17% and 18% presented LGE. During a median follow-up of 5.1 years (IQR 2.3-8.1), 110 (19%) patients presented HF, 87 (15%) VA, 18 (3%) SE and 34 (6%) died. MACE occurred in 223 (38%) patients.

LVEF was independently associated with HF, VA, SE and MACE: HR were 1.08, 1.02, 1.04 and 1.02 respectively (all $p < 0.05$). LGE was more frequent in patients with reduced LVEF (39 Vs 53%, $p < 0.001$) and was associated with higher HF and VA risk in patients with an LVEF > 35% (HR 2.69 and 2.48 respectively, $p < 0.05$) (Figure 1). No MACE (0%) occurred during long-term follow-up in patients with preserved LVEF, no LGE as well as no ECG abnormalities and no family aggregation.

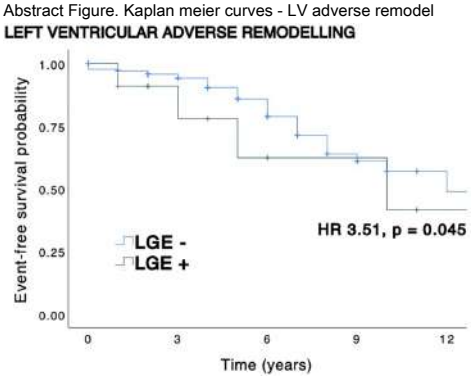
305 (52%) patients presented with initially preserved LVEF, and 230 (75%) of those had LVEF available at last follow-up. LVAR occurred in 50 (22%) patients: 22 (10%) had an LVEF < 50% and 41 (18%) an absolute ≥ 10% decrease in LVEF. LGE was independently associated with LVAR (HR 3.51, $p = 0.045$) (Figure 2).

Conclusions: Cardiac magnetic resonance has an important prognostic role in LVNC. LVEF is the most powerful predictor of events. Myocardial fibrosis is associated with worse outcomes in patients without severe systolic dysfunction, as well as with left ventricular adverse remodelling in those with initially preserved LVEF. Besides, CMR may identify a low-risk subgroup of LVNC patients. Therefore, CMR should be used in risk stratification in LVNC.

Abstract Figure. Kaplan meier curves - clinical outcomes



Abstract Figure. Kaplan meier curves - LV adverse remodel



10.2.6. Comunicación 6

G Casas, J Limeres, G Oristrell, L Gutierrez, R Barriales, P Garcia-Pavia, E Zorio, JR Gimeno, E Villacorta, J Jimenez-Jaimez, T Ripoll, A Bayes, I Ferreira, JF Rodriguez-Palomares, Long term outcomes in left ventricular noncompaction, European Heart Journal - Cardiovascular Imaging, Volume 22, Issue Supplement_1, January 2021, jeaa356.305, https://doi.org/10.1093/ehjci/jeaa356.305

i356

Late Gadolinium Enhancement and Viability

Long term outcomes in left ventricular noncompaction

Casas G.[1]; Limeres J.[1]; Oristrell G.[1]; Gutierrez L.[1]; Barriales R.[2]; Garcia-Pavia P.[3]; Zorio E.[4]; Gimeno JR.[5]; Villacorta E.[6]; Jimenez-Jaimez J.[7]; Ripoll T.[8]; Bayes A.[9]; Ferreira I.[1]; Rodriguez-Palomares JF.[10]

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[2]University Hospital Complex A Coru??a, A Coruna, Spain
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[4]Hospital Universitario y Politecnico La Fe, Valencia, Spain
[5]Hospital Universitario Virgen Arrixaca, Murcia, Spain
[6]Complejo Asistencial Universitario de Salamanca, Salamanca, Spain
[7]University Hospital Virgen de las Nieves, Granada, Spain
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Funding Acknowledgements: Type of funding sources: None.

Background: Left ventricular noncompaction (LVNC) is a heterogeneous entity with a wide phenotypic expression. Risk factors have not been well established and prognostic stratification remains challenging.

Objectives: Describe long term outcomes of LVNC patients and determine predictors of cardiovascular events.

Methods:

Prospective multicentric study of consecutive patients fulfilling imaging diangostic criteria for LVNC (Jenni echo criteria and Petersen CMR criteria). Demographic, ECG, imaging and genetic variables were collected. End points were heart failure (HF), ventricular arrhythmias (VA), systemic embolisms (SE) and all-cause death. Major adverse cardiovascular events (MACE) was the combination of the four previous end points.

Results: 585 patients from 12 referral centres were included from 2000 to 2018. Age at diagnosis was 45 ± 20 years, 334 (57%) were male, baseline LVEF was 48 ± 17% and 18% presented late gadolinium enhancement (LGE). During a median follow-up of 5.1 years (IQR 2.3-8.1), 110 (19%) patients presented HF, 87 (15%) VA, 18 (3%) SE and 34 (6%) died. MACE occurred in 223 (38%) patients.

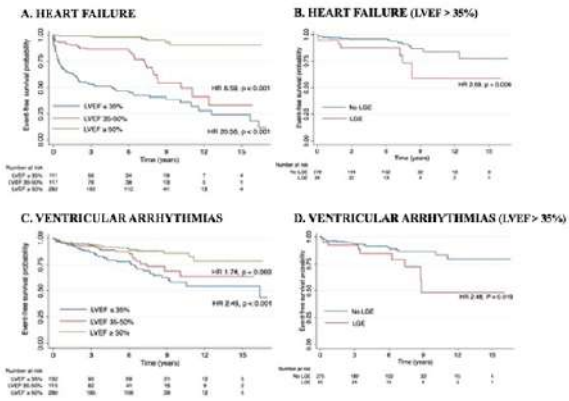
LVEF was independently associated with HF, VA, SE and MACE: HR were 1.08, 1.02, 1.04 and 1.02 respectively (all $p < 0.05$). LGE was more frequent in patients with reduced LVEF (39 Vs 53%, $p < 0.001$) and was associated with higher HF and VA risk in patients with LVEF > 35% (HR 2.69 and 2.48 respectively, $p < 0.05$) (Figure 1). Patients with a normal ECG, LVEF≥50%, no LGE and no family aggregation presented no MACE (0%) at long term follow-up.

Among patients who underwent genetic testing (354, 61%), TTN variants and complex genotype (more than one variant) presented lower LVEF and higher HF risk. ACTC1 variants were associated with VA.

Conclusions: LVNC carries a high long term risk of heart faliure and ventricular arrhythmias. LVEF is the most important predictor and myocardial fibrosis is associated with increased risk in patients without severe systolic dysfunction. Genotype is a modifier of outcomes. These factors might be used to risk stratify LVNC patients.

Abstract Figure. Kaplan Meier survival curves

i357


A. HEART FAILURE
B. HEART FAILURE (LVEF > 35%)
C. VENTRICULAR ARRHYTHMIAS
D. VENTRICULAR ARRHYTHMIAS (LVEF > 35%)

10.2.7. Comunicación 7

G Casas, G Oristrell, J Limeres, L Gutierrez Garcia-Moreno, R Barriales, P Garcia-Pavia, E Zorio, J.R Gimeno, E Villacorta, J Jimenez-Jaimez, T Ripoll, A Bayes, C Diez, I Ferreira, J.F Rodriguez-Palomares, Long term outcomes in left ventricular non-compaction, European Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.2070, https://doi.org/10.1093/ehjci/ehaa946.2070

2070 *Valvular, Myocardial, Pericardial, Pulmonary, Congenital Heart Disease – Ventricular Non-compaction*

Long term outcomes in left ventricular non-compaction

G. Casas[1], G. Oristrell[1], J. Limeres[1], L. Gutierrez Garcia-Moreno[1], R. Barriales[2], P. Garcia-Pavia[3], E. Zorio[4], J.R. Gimeno[5], E. Villacorta[6], J. Jimenez-Jaimez[7], T. Ripoll[8], A. Bayes[9], C. Diez[10], I. Ferreira[1], J.F. Rodriguez-Palomares[11]

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Funding Acknowledgement: Type of funding source: None

Background: Left ventricular non-compaction (LVNC) is a highly heterogeneous entity with a wide phenotypic expression. Risk factors have not been well established and prognostic stratification remains challenging.
Objectives: Describe long term outcomes of LVNC patients and determine predictors of cardiovascular events.
Methods: Prospective multicentric study of consecutive patients fulfilling imaging criteria for LVNC. Demographic, ECG, imaging and genetic variables were collected. End points were heart failure (HF), ventricular arrhythmias (VA), systemic embolisms (SE) and all-cause death. Major adverse cardiovascular event (MACE) was described as the combination of the four previous end points.
Results: 592 patients from 13 referral centres were included from 2000 to 2018. Mean age at diagnosis was 45 years, 252 (43%) were female and mean LVEF was 48% (Table 1). During a median follow-up of 55 months (IQR 24–90), 144 (25%) patients presented HF, 101 (18%) VA, 27 (5%) SE and 33 (6%) died. MACE occurred in 223 (39%) patients.
In multivariate analysis, independent predictors of HF were LVEF (OR 0.9), PSAP (OR 1.17) and late gadolinium enhancement (LGE) (OR 1.3). VA were independently associated with LVEF (OR 0.97) and LGE (OR 2.51). Independent predictors of SE were LVEF (OR 0.96) and LA diameter (OR 1.07). No independent predictors of all-cause death could be described. MACE were independently associated with LVEF (OR 1.04) and PSAP (OR 1.08) (Table 1).
Among patients who underwent genetic testing (340, 57%), genotype was associated with outcomes: MYH7 and ACTC1 variants were protective while multiple mutations, TTN and MYBPC3 variants exhibited worse prognosis.
Conclusions: In a large prospective multicentric cohort of LVNC patients, there was a moderate long term incidence of cardiovascular events. LVEF and fibrosis were the main predictors and genotype was a modifier of outcomes. These factors might be used to risk stratify LVNC patients.

	GLOBAL (n=592)	MACE (n=223)	No MACE (n=369)	p
Women, n (%)	244 (43)	86 (39)	158 (46)	0.095
Age at diagnosis (SD), yr	45 (20)	54 (17)	39 (19)	0.000
Follow-up (IQR), months	55 (24–90)	59 (26–97)	51 (24–84)	0.267
Hypertension, n (%)	140 (25)	86 (39)	54 (16)	0.000
LBBB, n (%)	80 (18)	48 (27)	32 (12)	0.000
LVEF (SD), %	48 (17)	37 (15)	56 (13)	0.000
PSAP (SD), mmHg	34 (13)	39 (14)	28 (8)	0.000
LGE, n (%)	75 (18)	44 (29)	31 (11)	0.000

10.2.8. Comunicación 8

G Casas, G Oristrell, J Limeres, R Barriales, J R Gimeno, P Garcia Pavia, E Zorio, E Villacorta, J Jimenez Jaimez, A Bayes, J M Garcia Pinilla, A J Palomino, A Evangelista, I Ferreira, J F Rodriguez-Palomares, P1442 Outcomes of patients with left ventricular noncompaction and preserved ejection fraction, European Heart Journal - Cardiovascular Imaging, Volume 21, Issue Supplement_1, January 2020, jez319.870, https://doi.org/10.1093/ehjci/jez319.870

P1442

Outcomes of patients with left ventricular noncompaction and preserved ejection fraction

Casas G.[1]; Oristrell G.[1]; Limeres J.[1]; Barriales R.[2]; Gimeno JR.[3]; Garcia Pavia P.[4]; Zorio E.[5]; Villacorta E.[6]; Jimenez Jaimez J.[7]; Bayes A.[8]; Garcia Pinilla JM.[9]; Palomino AJ.[10]; Evangelista A.[1]; Ferreira I.[1]; Rodriguez-Palomares JF.[11]

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BACKGROUND

Left ventricular noncompaction (LVNC) has a wide phenotypic expression. Prognosis of patients with preserved ejection fraction (pEF) remains uncertain.

PURPOSE

To describe the characteristics and natural history of this subgroup of patients.

METHODS

LVNC patients were included in a multicentric registry. Those with pEF (LVEF > 50%) were considered for the analysis.

RESULTS

491 LVNC pts from 10 Spanish centres were recruited from 2000 to 2018. 239 (49%) had baseline pEF. Compared to those with reduced EF (rEF), they were younger, with no differences in gender and had less comorbilities (Table 1). Mean LVEF was 62% (SD 8). 18 pts (9% of the available CMR) had fibrosis even though LV volumes and LVEF were normal.

Family screening was completed in 199 pts, being positive in 113 (57%). Genetic testing was performed in 146 index cases, being positive in 80 (55%): ACTC1 (40), MYH7 (17), TTN (8), HCN4 (6) and other individual variants.

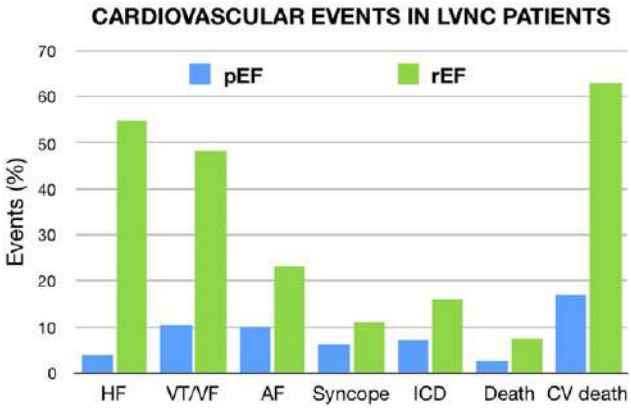
During a median follow-up of 4.9 years (IQR 2.1-7.3), there was a significant decrease in LVEF: last LVEF was 30- 40% in 5 pts (2%) and 40-50% in 21 (9%) (p = 0.01 compared to baseline LVEF). 6 pts (2.5%) died during follow-up, only 1 of cardiovascular cause. 9 patients (4%) presented heart failure (HF) and 25 (10.5%) ventricular tachycardia or fibrillation (VT/VF). All cardiovascular outcomes were less frequent compared to rEF (Image 1, all p < 0.05). In multivariate analysis (including demographic, imaging, genetic and family aggregation parameters) the only predictor for HF was change in LVEF (OR 0.89, mean LVEF at the event 47%, p = 0.01 compared to no HF). Fibrosis was not associated with VT/VF.

CONCLUSIONS: Patients with LVNC and pEF have an overall excellent prognosis, which is markedly better than those with rEF. However, there is progressive decrease in LVEF, associated with heart failure, and moderate risk of life threatening arrhythmias. Therefore, periodic follow-up should be promoted.

Table 1

	LVNC pEF (n = 239)	LVNC rEF (n = 252)	p
Men, n (%)	131 (55)	146 (58)	0.65
Median age at diagnosis (IQR) - yr	38 (23-54)	58 (42-72)	0.01
Median follow up (IQR) - yr	4.9 (2.1-7.3)	3.9 (1.4-7.9)	0.04
QRS (SD) - ms	93 (18)	117 (32)	0.01
LGE, n (%)	18 (9)	52 (30)	0.01

Abstract P1442 Figure. Image 1


CARDIOVASCULAR EVENTS IN LVNC PATIENTS
pEF
rEF
Events (%)
70
60
50
40
30
20
10
0
HF
VT/VF
AF
Syncope
ICD
Death
CV death

10.2.9. Comunicación 9

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Abstracts i917

Poster Session

P1441

Predictors of systemic embolisms in a large cohort of left ventricular noncompaction patients

Casas G.[1]; Oristrell G.[1]; Limeres J.[1]; Barriales R.[2]; Gimeno JR.[3]; Garcia Pavia P.[4]; Zorio E.[5]; Villacorta E.[6]; Jimenez Jaimez J.[7]; Bayes A.[8]; Garcia Pinilla JM.[9]; Palomino AJ.[10]; Evangelista A.[1]; Ferreira I.[1]; Rodriguez-Palomares JF.[11]

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BACKGROUND

Left ventricular noncompaction (LVNC) is associated with an increased risk of systemic embolisms (SE). However, incidence and risk factors are not well established.

PURPOSE

To evaluate the rate of SE in LVNC and describe risk factors.

METHODS

LNVC patients were included in a multicentric registry. Those with SE were considered for the analysis.

RESULTS

514 patients with LVNC from 10 Spanish centres were recruited from 2000 to 2018. During a median follow-up of 4.2 years (IQR 1.9-7.1), 23 patients (4.5%) had a SE. Patients with SE (Table 1) were older at diagnosis, with no differences in gender and had similar cardiovascular risk factors. They were more frequently under oral anticoagulation (OAC). Besides, they had a more reduced LVEF, and more dilated LV and left atrium (LA). Late gadolinium enhancement (LGE) was more frequent, altogether suggesting a more severe phenotype.

Patients with SE had non-significantly higher rates of hospitalization for heart failure (33% Vs 24%, p = 0.31) and atrial fibrillation (35% Vs 19%, p = 0.10). In multivariate analysis, only LA diameter was an independent predictor of SE (OR 1.04, p = 0.04). A LA diameter > 45 mm had an independent 3 fold increased risk of SE (OR 3.04, p = 0.02) (Image 1).

CONCLUSIONS

LVNC carries a moderate mid-term risk of SE, which appears to be irrespective of atrial fibrillation and associated with age, LV dilatation and systolic dysfunction and mainly LA dilatation. This subgroup of patients should be considered for oral anticoagulation in primary prevention.

Table 1

	Systemic embolisms (n = 23)	No systemic embolisms (n = 491)	p
Men, n (%)	15 (65)	289 (56)	0.52
Median age at diagnosis (IQR) - yr	60 (48-76)	48 (30-64)	0.02
Median follow up (IQR) - yr	5.9 (3.1-7.8)	4.2 (1.8-7.1)	0.18
OAC, n (%)	19 (83)	118 (24)	0.01
LVEF (SD) - %	37 (15)	48 (17)	0.01
LVEDD (SD) - mm	58 (11)	54 (10)	0.04
LA diameter (SD) - mm	46 (9)	39 (9)	0.01

Characteristics of patients with and without systemic embolisms

Abstract P1441 Figure. Image 1

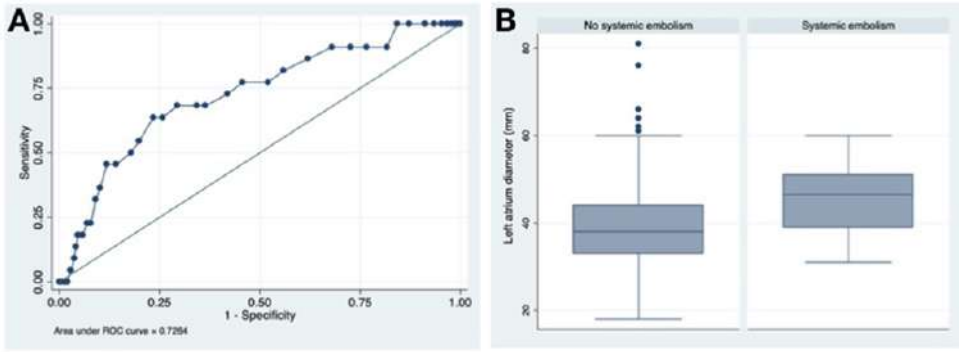

Image 1. A) Receiver operator curve for the predictive value of left atrium diameter for systemic embolisms (AUC 0.73). B) Box plot demonstrates different left atrium diameter values in patients with and without systemic embolisms.

10.2.10. Comunicación 10

G Casas, G Oristrell, F Valente, J Limeres, L Gutierrez, G Teixido, L Galian, C H Granato, V Pineda, M T Gonzalez-Alujas, A Evangelista, I Ferreira, J F Rodriguez-Palomares, 552 Imaging predictors of systemic embolisms in left ventricular noncompaction, European Heart Journal - Cardiovascular Imaging, Volume 20, Issue Supplement_2, June 2019, jez125.003, https://doi.org/10.1093/ehjci/jez125.003

Rapid Fire Abstracts -- Rapid Fire Abstract 7: cardiomyopathy

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Imaging predictors of systemic embolisms in left ventricular noncompaction

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BACKGROUND: Left ventricular noncompaction (LVNC) is associated with an increased incidence of systemic embolisms (SE). However, the embolic risk factors, as well as indications for oral anticoagulation (OAC) in primary prevention, are not well established.

PURPOSE: The aim of this study is to evaluate the incidence of SE in a cohort of patients with imaging criteria for LVNC and to establish risk factors for such events.

METHODS: Patients who fulfilled both echocardiographic and CMR criteria for LVNC (Chin and Petersen criteria respectively) were included. Those with baseline indication for OAC were not considered for the analysis. Annual check-ups were performed with ECG, echocardiography and 24-hour holter monitoring. Fractal analysis was performed in CMR short axis sequences in order to assess LV trabeculae geometric complexity.

RESULTS: From 2007 to 2017, 128 patients were included. 68 (53%) were men, mean age at diagnosis was 37.2 ± 18.5 years and mean follow-up was 36 ± 25 months. Mean CMR-LVEF at diagnosis was 53.2 ± 14.2%.

5 patients (4%) presented 6 SE during follow-up: 4 embolic strokes, 1 embolic myocardial infarction and 1 peripheral artery embolism. One patient had two events and stroke was the first clinical manifestation of LVNC in 2 of them. They were all men and mean age at the event was 57 years. None of them had previous history of atrial fibrillation and all their subsequent annual ECG and 24h holter monitoring showed sinus rhythm.

Patients with SE had a mean LVEF at diagnosis of 23.3 ± 8.1% (range 16-32%) whereas for those without SE it was 53.5 ± 13.2% ($p < 0.0001$). LV dimensions were significantly larger in patients with SE: LVEDV was 275 ± 106 mL (Vs 155 ± 67 mL) and LVESV was 207 ± 58 mL (Vs 81 ± 59 mL) (both $p < 0.0001$). LGE was significantly more frequent in patients with SE (40% Vs 7%, $p < 0.0001$), in consonance with the more severe systolic dysfunction. Left atrium was also significantly larger in them: 46.6 ± 4.6 mm Vs 38.9 ± 7.9 mm for anteroposterior diameter ($p = 0.039$).

17% of the patients with LVEF ≤ 35% presented SE, whereas no patients with LVEF > 35% had such outcomes. Fractal analysis showed no differences among groups: fractal dimension was 1.294 ± 0.066 for patients with SE and 1.388 ± 0.067 for those without events ($p = 0.059$). This might suggest that the actual trabeculae are not associated with thrombogenicity in LVNC. None of these patients had LV thrombus noted either on echo or CMR.

CONCLUSIONS: LVNC carries a moderate risk of systemic embolisms. This risk seems to be irrespective of atrial fibrillation and mainly associated with severe systolic impairment rather than the actual LV trabeculae. Our data suggest that oral anticoagulation should be considered in LVNC patients with LVEF ≤ 35% for primary prevention.

10.3. MATERIAL SUPLEMENTARIO

10.3.1. Tabla Suplementaria 1

Tabla Suplementaria 1: Listado completo de los 213 genes relacionados con enfermedades cardíacas hereditarias incluidos en el panel *next-generation sequencing*. Adaptado de Casas *et al* [67].

Gen	Proteína codificada
AARS2	Alanine--tRNA ligase, mitochondrial
ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9
ACAD9	Acyl-CoA dehydrogenase family member 9, mitochondrial
ACADM	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial
ACADVL	Very long-chain specific acyl-CoA dehydrogenase, mitochondrial
ACTA1	Actin, alfa 1, skeletal muscle
ACTA2	Actin, aortic smooth muscle
ACTC1	Actin, alpha cardiac muscle 1
ACTN2	Alpha-actinin-2
ACVRL1	Serine/threonine-protein kinase receptor R3
ADAMTSL4	ADAMTS-like protein 4
AGK	Acylglycerol kinase, mitochondrial
AGL	Glycogen debranching enzyme
AGPAT2	1-acyl-sn-glycerol-3-phosphate acyltransferase beta
AKAP9	A-kinase anchor protein 9
ALMS1	Alstrom syndrome protein 1
ANK2	Ankyrin 2
ANK3	Ankyrin-3
ANKRD1	Ankyrin repeat domain-containing protein 1
APOA5	Apolipoprotein A-V
APOB	Apolipoprotein B-100
APOC3	Apolipoprotein C-III
ATPAF2	ATP synthase mitochondrial F1 complex assembly factor 2
BAG3	BAG family molecular chaperone regulator 3
BMPR1B	Bone morphogenetic protein receptor type-1B
BMPR2	Bone morphogenetic protein receptor type II
BRAF	Serine/threonine-protein kinase B-raf
BSCL2	Seipin
CACNA1C	Voltage-dependent L-type calcium channel subunit alpha-1C
CACNA1D	Voltage-dependent L-type calcium channel subunit alpha-1D
CACNA2D1	Voltage-dependent calcium channel subunit alpha-2/delta-1
CACNB2	Voltage-dependent L-type calcium channel subunit beta-2
CALM1	Calmodulin
CALM2	Calmodulin
CALR3	Calreticulin 3
CAPN3	Calpain-3
CASQ2	Calsequestrin-2
CAV1	Caveolin-1
CAV3	Caveolin-3
CBL	E3 ubiquitin-protein ligase CBL
CBS	Cystathionine beta-synthase
CETP	Cholesteryl ester transfer protein
COL1A1	Collagen alpha-1(I) chain
COL1A2	Collagen alpha-2(I) chain
COL3A1	Collagen alpha-1(III) chain
COL5A1	Collagen alpha-1(V) chain
COL5A2	Collagen alpha-2(V) chain
COQ2	4-hydroxybenzoate polyprenyltransferase, mitochondrial
COX15	Cytochrome c oxidase assembly protein COX15 homolog
COX6B1	Cytochrome c oxidase subunit 6B1

Gen	Proteína codificada
CRELD1	Cysteine-rich with EGF-like domain protein 1
CRYAB	Alpha-crystallin B chain
CSRP3	Cysteine and glycine-rich protein 3
CTF1	Cardiotrophin 1
CTNNA3	Catenin alpha-3
DES	Desmin
DLD	Dihydrolipoyl dehydrogenase, mitochondrial
DMD	Dystrophin
DNAJC19	Mitochondrial import inner membrane translocase subunit TIM14
DOLK	Dolichol kinase
DSC2	Desmocollin 2
DSG2	Desmoglein 2
DSP	Desmoplakin
DTNA	Dystrobrevin alpha
ELN	Elastin
EMD	Emerin
ENG	Endoglin
EYA4	Eyes absent homolog 4
FAH	Fumarylacetoacetase
FBN1	Fibrillin 1
FBN2	Fibrillin 2
FHL1	Four and a half LIM domains protein 1
FHL2	Four and a half LIM domains 2
FHOD3	FH1/FH2 domain-containing protein 3
FKRP	Fukutin-related protein
FKTN	Fukutin
FLNA	Filamin-A
FLNC	Filamin-C
FOXD4	Forkhead box protein D4
GAA	Lysosomal alpha-glucosidase
GATA4	Transcription factor GATA-4
GATA6	Transcription factor GATA-6
GATAD1	GATA zinc finger domain-containing protein 1
GDF2	Growth/differentiation factor 2
GFM1	Elongation factor G, mitochondrial
GJA1	Gap junction alpha-1 protein
GJA5	Gap junction alpha-5 protein
GLA	Alpha-galactosidase A
GLB1	Beta-galactosidase
GNPTAB	N-acetylglucosamine-1-phosphotransferase subunits alpha/beta
GPD1L	Glycerol-3-phospate dehydrogenase 1-like protein
GUSB	Beta-glucuronidase
HCN4	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4
HFE	Hereditary hemochromatosis protein
HRAS	GTPase HRas
JAG1	Jagged-1
JPH2	Junctophilin 2
JUP	Junction plakoglobin
KCNA5	Potassium voltage-gated channel subfamily A member 5
KCND3	Potassium voltage-gated channel subfamily D member 3
KCNE1	Potassium voltage-gated channel subfamily E member 1
KCNE1L	Potassium voltage-gated channel subfamily E member 1-like protein
KCNE2	Potassium voltage-gated channel subfamily E member 2
KCNE3	Potassium voltage-gated channel subfamily E member 3
KCNH2	Potassium voltage-gated channel subfamily H member 2
KCNJ2	Inward rectifier potassium channel 2
KCNJ5	G protein-activated inward rectifier potassium channel 4
KCNJ8	ATP-sensitive inward rectifier potassium channel 8
KCNK3	Potassium channel subfamily K member 3

Gen	Proteína codificada
KCNQ1	Potassium voltage-gated channel subfamily KQT member 1
KLF10	Krueppel-like factor 10
KRAS	GTPase KRas
LAMA2	Laminin subunit alpha-2
LAMA4	Laminin subunit alpha-4
LAMP2	Lysosome-associated membrane glycoprotein 2
LDB3	LIM domain-binding protein 3
LDLR	Low density lipoprotein receptor
LIAS	Lipoyl synthase, mitochondrial
LMNA	Prelamin-A/C
LRP6	Low-density lipoprotein receptor-related protein 6
MAP2K1	Dual specificity mitogen-activated protein kinase kinase 1
MAP2K2	Dual specificity mitogen-activated protein kinase kinase 2
MIB1	E3 ubiquitin-protein ligase MIB1
MLYCD	Malonyl-CoA decarboxylase, mitochondrial
MRPL3	39S ribosomal protein L3, mitochondrial
MRPS22	28S ribosomal protein S22, mitochondrial
MTO1	Protein MTO1 homolog, mitochondrial
MURC	Muscle-related coiled-coil protein
MYBPC3	Myosin-binding protein C, cardiac-type
MYH11	Myosin-11
MYH6	Myosin-6
MYH7	Myosin-7
MYL2	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform
MYL3	Myosin light chain 3
MYLK	Myosin light chain kinase, smooth muscle
MYLK2	Myosin light chain kinase 2, skeletal/cardiac muscle
MYOT	Myotilin
MYOZ2	Myozenin 2
MYPN	Myopalladin
NEBL	Nebulette
NEXN	Nexilin
NKX2-5	Homeobox protein Nkx-2.5
NOTCH1	Neurogenic locus notch homolog protein 1
NOTCH3	Neurogenic locus notch homolog protein 3
NPPA	Atrial natriuretic factor
NRAS	GTPase NRas
OBSL1	Obscurin-like protein 1
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDHA1	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial
PDLIM3	PDZ and LIM domain protein 3
PHKA1	Phosphorylase b kinase regulatory subunit alpha, skeletal muscle isoform
PITX2	Pituitary homeobox 2
PKP2	Plakophilin 2
PLN	Cardiac phospholamban
PLOD1	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1
PMM2	Phosphomannomutase 2
PRDM16	PR domain zinc finger protein 16
PRKAG2	5'-AMP-activated protein kinase subunit gamma-2
PRKG1	cGMP-dependent protein kinase 1
PSEN1	Presenilin-1
PSEN2	Presenilin 2
PTPN11	Tyrosine-protein phosphatase non-receptor type 11
RAF1	RAF proto-oncogene serine/threonine-protein kinase
RANGRF	Ran guanine nucleotide release factor
RBM20	Probable RNA-binding protein 20
RYR2	Ryanodine receptor 2
SCN10A	Sodium channel protein type 10 subunit alpha
SCN1B	Sodium channel subunit beta-1

Gen	Proteína codificada
SCN2B	Sodium channel subunit beta-2
SCN3B	Sodium channel subunit beta-3
SCN4B	Sodium channel subunit beta-4
SCN5A	Sodium channel protein type 5 subunit alpha
SGCA	Alpha-sarcoglycan
SGCB	Beta-sarcoglycan
SGCD	Delta-sarcoglycan
SHOC2	Leucine-rich repeat protein SHOC-2
SKI	Ski oncogene
SLC22A5	Solute carrier family 22 member 5
SLC25A4	ADP/ATP translocase 1
SLC2A10	Solute carrier family 2, facilitated glucose transporter member 10
SLMAP	Sarcolemmal membrane-associated protein
SMAD1	Mothers against decapentaplegic homolog 1
SMAD3	Mothers against decapentaplegic homolog 3
SMAD4	Mothers against decapentaplegic homolog 4
SMAD9	Mothers against decapentaplegic homolog 9
SNTA1	Alpha-1-syntrophin
SOS1	Son of sevenless homolog 1
SPRED1	Sprouty-related, EVH1 domain-containing protein 1
SURF1	Surfeit locus protein 1
TAZ	Tafazzin
TBX1	T-box transcription factor TBX1
TBX20	T-box transcription factor TBX20
TBX5	T-box transcription factor TBX5
TCAP	Telethonin
TGFB2	Transforming growth factor beta-2
TGFB3	Transforming growth factor, beta 3
TGFBR1	TGF-beta receptor type-1
TGFBR2	TGF-beta receptor type-2
TMEM43	Transmembrane protein 43
TMEM70	Transmembrane protein 70, mitochondrial
TMPO	Thymopoietin
TNNC1	Troponin C, slow skeletal and cardiac muscles
TNNI3	Troponin I, cardiac muscle
TNNT2	Troponin T, cardiac muscle
TPM1	Tropomyosin alpha-1 chain
TRDN	Triadin
TRIM63	E3 ubiquitin-protein ligase TRIM63
TRPM4	Transient receptor potential cation channel subfamily M member 4
TSFM	Elongation factor Ts, mitochondria
TTN	Titin
TTR	Transthyretin
TXNRD2	Thioredoxin reductase 2, mitochondrial
VCL	Vinculin

10.3.2. Tabla Suplementaria 2

Tabla Suplementaria 2: Listado completo de las variantes genéticas descritas en nuestra cohorte de no compactación del ventrículo izquierdo. Adaptado de Casas *et al* [67].

	Variantes (posiblemente) patogénicas en probandos (n = 99)	Variantes (posiblemente) patogénicas en probandos y familiares (n = 192)	Todas las variantes genéticas descritas (n = 269)
Genotipo complejo	21	25	41
MYH7	19	42	52
TTN	13	17	25
ACTC1	10	50	50
MYBPC3	10	18	20
DSP	3	3	5
LDB3	3	3	4
BAG3	3	3	4
Notch1	2	2	3
ACTN2	2	2	2
DMD	2	2	2
HCN4	1	6	8
TBX20	1	5	5
FHOD3	0	2	3
MIB1	0	2	3
FLNC	1	1	3
JPH2	0	1	1
TNNT2	1	1	2
NKX2-5	1	1	2
FHL1	1	1	1
JUP	1	1	1
RBM20	1	1	1
TNNC1	1	1	1
TNNI3	1	1	1
TPM1	1	1	1
RYR2	0	0	6
PLEC	0	0	3
MYH6	0	0	2
CASQ2	0	0	2
JAG1	0	0	2
NKX2-6	0	0	1
DMN1L	0	0	1
KCNJ2	0	0	1
KRAS	0	0	1
MYOT	0	0	1
MYPN	0	0	1
PDLIM3	0	0	1
PMM2	0	0	1
SCN5A	0	0	1
TGFBR2	0	0	1
TMEM43	0	0	1
TXNRD2	0	0	1
MAP2K1	0	0	1

10.3.3. Tabla Suplementaria 3

Tabla Suplementaria 3: Características basales de los pacientes con no compactación del ventrículo izquierdo de acuerdo al resultado del estudio genético. Adaptado de Casas *et al* [67].

	Todos los pacientes con estudio genético (n = 354)	Genotipo positivo (n = 192)	Genotipo negativo (n = 162)	p valor
Características clínicas				
Edad al diagnóstico, años (DE)	43 (20)	42 (21)	44 (18)	0,328
Sexo masculino, n (%)	193 (55)	101 (53)	92 (57)	0,431
Probando, n (%)	236 (67)	99 (52)	137 (85)	<0,001
CF NYHA III-IV basal, n (%)	28 (8)	20 (11)	8 (5)	0,040
Historia familiar de MC, n (% de probandos)	77 (35)	40 (43)	37 (29)	0,019
Historia familiar de MSC, n (% de probandos)	43 (19)	21 (21)	22 (17)	0,256
Screening familiar positivo, n (% de probandos)	87 (39)	42 (46)	45 (35)	0,070
Factores de riesgo cardiovascular				
Hipertensión arterial, n (%)	69 (20)	34 (18)	35 (22)	0,354
Dislipidemia, n (%)	79 (23)	38 (20)	41 (26)	0,198
Diabetes mellitus, n (%)	22 (6)	12 (6)	10 (6)	0,235
Tabaquismo, n (%)	46 (18)	21 (15)	25 (22)	0,093
IMC, kg/m² (DE)	25,1 (4,8)	24,6 (4,5)	25,7 (5,0)	0,032
Factores de riesgo cardiovascular, n (%)	118 (33)	60 (31)	58 (36)	0,214
Electrocardiograma				
Ritmo sinusal, n (%)	326 (93)	175 (92)	151 (94)	0,541
QRS, ms (DE)	105 (28)	99 (26)	111 (30)	0,001
BRIHH, n (%)	48 (18)	19 (14)	29 (23)	0,072
Alteraciones de la repolarización, n (%)	126 (37)	71 (38)	55 (35)	0,371
ECG anormal, n (%)	171 (63)	90 (64)	81 (62)	0,416
Ecocardiografía				
FEVI, % (DE)	50 (17)	50 (18)	49 (15)	0,422
DTDVI, mm (DE)	53 (10)	52 (10)	54 (9)	0,127
DTSVI, mm (DE)	37 (12)	37 (12)	38 (12)	0,502
TAPSE, mm (DE)	21 (5)	21 (5)	22 (4)	0,210
PAPS, mmHg (DE)	32 (11)	33 (12)	31 (10)	0,315
Diámetro AI, mm (DE)	38 (9)	38 (9)	37 (8)	0,197
IM grado ≥ 3, n (%)	13 (6)	9 (7)	4 (4)	0,178
Disfunción diastólica grado ≥ 2, n (%)	41 (23)	25 (30)	16 (17)	0,039
Resonancia magnética cardiovascular				
FEVI, % (DE)	51 (16)	50 (16)	51 (15)	0,780
VTDVI, ml (DE)	167 (73)	162 (74)	172 (73)	0,284
VTSVI, ml (DE)	86 (62)	84 (66)	87 (57)	0,699
FEVD, % (DE)	54 (12)	54 (13)	54 (12)	0,943
RTG, n (%)	39 (15)	23 (16)	16 (13)	0,447

***AI**: aurícula izquierda. **BRIHH**: bloqueo de rama izquierda del haz de hiss. **CF NYHA**: clase funcional de la New York Heart Association. **DE**: desviación estándar. **DTDVI**: diámetro telediastólico del ventrículo izquierdo. **DTSVI**: diámetro telesistólico del ventrículo izquierdo. **ECG**: electrocardiograma. **FEVD**: fracción de eyección del ventrículo derecho. **FEVI**: fracción de eyección del ventrículo izquierdo. **IM**: insuficiencia mitral. **IMC**: índice de masa corporal. **MC**: miocardiopatía. **MSC**: muerte súbita cardíaca. **PAPS**: presión de la arteria pulmonar sistólica. **RTG**: realce tardío de gadolinio. **TAPSE**: excursión sistólica del anillo tricúspide. **VTDVI**: volumen telediastólico del ventrículo izquierdo. **VTSVI**: volumen telesistólico del ventrículo izquierdo.*

10.3.4. Tabla Suplementaria 4

Tabla Suplementaria 4: Características basales de los pacientes con no compactación del ventrículo izquierdo de acuerdo a la ocurrencia de embolismos sistémicos y mortalidad global. Adaptado de Casas *et al* [67].

	Todos (n = 585)	Embolismos sistémicos (n = 18)				Mortalidad global (n = 34)			
		Sí	No	HR Crudo (IC 95%)	p	Sí	No	HR Crudo (IC 95%)	p
Características clínicas									
Edad al diagnóstico, años (DE)	45 (20)	56 (16)	45 (20)	1,04 (1,01-1,06)	0,007	64 (16)	44 (19)	1,08 (1,05-1,10)	0,000
Sexo masculino, n (%)	334 (57)	12 (67)	322 (57)	1,58 (0,59-4,25)	0,361	27 (79)	307 (56)	3,00 (1,30-6,91)	0,010
Factores de riesgo cardiovascular									
Hipertensión arterial, n (%)	139 (25)	11 (61)	128 (23)	7,09 (2,46-20,4)	0,000	17 (55)	122 (23)	4,10 (1,09-8,47)	0,000
Dislipidemia, n (%)	142 (25)	10 (59)	132 (24)	4,20 (1,58-11,12)	0,004	16 (53)	126 (24)	2,85 (1,39-5,84)	0,004
Diabetes mellitus, n (%)	52 (9)	4 (24)	48 (9)	1,95 (0,79-4,78)	0,145	11 (37)	41 (8)	3,64 (2,10 – 6,32)	0,000
Electrocardiograma									
Ritmo sinusal, n (%)	503 (91)	9 (60)	494 (92)	0,17 (0,06-0,48)	0,001	14 (52)	489 (94)	0,19 (0,09-0,42)	0,000
QRS, ms (DE)	105 (29)	122 (34)	105 (28)	1,02 (1,00-1,03)	0,073	141 (34)	104 (27)	1,03 (1,01 – 1,04)	0,000
BRIHH, n (%)	81 (18)	4 (27)	77 (18)	1,62 (0,51-5,09)	0,413	7 (28)	74 (18)	1,57 (0,65-3,75)	0,315
Alteraciones de la repolarización, n (%)	187 (35)	6 (50)	181 (35)	1,46 (0,47-4,58)	0,517	10 (46)	177 (35)	1,22 (0,52-2,82)	0,651
Ecocardiografía									
FEVI, % (DE)	48 (17)	35 (14)	48 (17)	0,96 (0,93-0,99)	0,004	37 (16)	49 (17)	0,97 (0,95 – 0,99)	0,011
DTDVI, mm (DE)	54 (10)	59 (8)	54 (10)	1,04 (0,99-1,08)	0,089	61 (10)	53 (10)	1,04 (1,01 – 1,07)	0,005
DTSVI, mm (DE)	38 (11)	47 (11)	38 (11)	1,05 (1,00-1,09)	0,033	46 (14)	37 (11)	1,04 (1,01 – 1,07)	0,018
TAPSE, mm (DE)	21 (5)	20 (6)	21 (5)	0,95 (0,84-1,07)	0,389	19 (5)	21 (5)	0,95 (0,86 – 1,05)	0,350
PAPS, mmHg (DE)	34 (13)	38 (18)	34 (13)	1,01 (0,97-1,05)	0,697	47 (17)	33 (12)	1,04 (1,01 – 1,07)	0,003
Diámetro AI, mm (DE)	39 (9)	48 (6)	39 (9)	1,08 (1,04-1,12)	0,000	48 (11)	38 (8)	1,06 (1,03 – 1,09)	0,000
Resonancia magnética cardiovascular									
FEVI, % (DE)	51 (16)	45 (21)	51 (16)	0,98 (0,94-1,02)	0,267	45 (20)	51 (16)	0,98 (0,94 – 1,02)	0,241
VTDVI, ml (DE)	167 (74)	210 (53)	166 (74)	1,01 (1,00-1,01)	0,089	228 (118)	166 (72)	1,01 (1,00-1,01)	0,009
VTSVI, ml (DE)	87 (64)	130 (55)	86 (64)	1,01 (1,00-1,01)	0,044	121 (87)	86 (64)	1,01 (1,00-1,01)	0,037
FEVD, % (DE)	54 (12)	53 (12)	54 (12)	0,99 (0,92-1,07)	0,819	40 (-)	54 (12)	0,90 (0,76-1,07)	0,242
RTG, n (%)	79 (18)	5 (50)	74 (17)	4,74 (1,37-16,4)	0,014	5 (36)	74 (18)	1,61 (0,53-4,93)	0,405

***HR**: Hazard ratio. **IC**: intervalo de confianza. Otras abreviaciones como en **Tabla Suplementaria 3**.*

10.3.5. Tabla Suplementaria 5

Tabla Suplementaria 5: Características basales de los pacientes con no compactación del ventrículo izquierdo de acuerdo a la ocurrencia de eventos cardiovasculares adversos mayores.

	Cohorte global (n = 577)	MACE (n = 136)	No MACE (n = 441)	HR crudo (IC 95%)	p Valor
Características clínicas					
Edad al diagnóstico, años (DE)	45 (20)	53 (17)	43 (20)	1,03 (1,02-1,04)	<0,001
Sexo femenino, n (%)	245 (43)	46 (34)	199 (45)	0,68 (0,48-0,98)	0,037
Probando, n (%)	433 (75)	118 (87)	315 (71)	2,71 (1,64-4,45)	<0,001
Screening familiar positivo, n (% de probandos)	106 (42)	24 (43)	82 (42)	0,90* (0,53-1,54)	0,704
Genotipo positivo, n (% de probandos con estudio genético)	99 (42)	32 (51)	67 (39)	1,14† (0,73-1,80)	0,569
Factores de riesgo cardiovascular					
Hipertensión arterial, n (%)	136 (24)	52 (40)	84 (20)	2,45 (1,72-3,49)	<0,001
Dislipidemia, n (%)	141 (25)	51 (40)	90 (21)	2,09 (1,47-2,99)	<0,001
Diabetes mellitus, n (%)	50 (9)	24 (19)	26 (6)	2,33 (1,49-3,64)	<0,001
Tabaquismo, n (%)	76 (19)	23 (23)	53 (18)	1,58 (0,99-2,52)	0,056
IMC, kg/m² (DE)	25 (5)	27 (5)	25 (5)	1,05 (1,01-1,08)	0,006
Electrocardiograma					
Ritmo sinusal, n (%)	495 (91)	89 (74)	406 (96)	0,26 (0,17-0,39)	<0,001
QRS, ms (DE)	105 (28)	124 (31)	100 (25)	1,02 (1,01-1,03)	<0,001
QRS ≥120 ms, n (%)	155 (35)	62 (59)	93 (28)	2,47 (1,67-3,65)	<0,001
BRIHH, n (%)	80 (18)	28 (26)	52 (16)	1,45 (0,93-2,26)	0,099
Ecocardiografía (n = 577, 100%)					
FEVI, % (DE)	48 (17)	37 (15)	51 (16)	0,96 (0,95-0,97)	<0,001
iDTDVI, mm/m² (DE)	29,6 (5,4)	32,5 (5,7)	28,7 (4,9)	1,10 (1,07-1,13)	<0,001
iDTSVI, mm/m² (DE)	20,7 (6,3)	24,9 (7,4)	19,8 (5,6)	1,11 (1,08-1,15)	<0,001
TAPSE, mm (DE)	21 (5)	19 (5)	22 (5)	0,92 (0,88-0,96)	<0,001
PAPS, mmHg (DE)	34 (12)	39 (13)	31 (11)	1,03 (1,01-1,05)	<0,001
Diámetro AI, mm (DE)	39 (9)	44 (10)	37 (8)	1,05 (1,04-1,07)	<0,001
FEVI final seguimiento, % (DE)	49 (15)	38 (15)	52 (13)	-	-
Deterioro de la FEVI, n (%)	34 (6)	16 (12)	18 (4)	2,99 (1,77 – 5,06)	<0,001
Resonancia magnética cardiovascular (n = 435, 75%)					
FEVI, % (DE)	51 (16)	41 (18)	53 (14)	0,95 (0,94-0,96)	<0,001
iVTDVI, ml/m² (DE)	92 (41)	110 (49)	88 (37)	1,01 (1,01-1,02)	<0,001
iVTSVI, ml/m² (DE)	48 (35)	66 (44)	44 (32)	1,02 (1,01-1,02)	<0,001
iVEVI, ml/m² (DE)	43 (15)	41 (16)	44 (15)	0,99 (0,97-1,01)	0,187
FEVD, % (DE)	54 (12)	52 (15)	54 (12)	0,98 (0,95-1,01)	0,218
iVTDVD, ml/m² (DE)	78 (27)	75 (25)	79 (27)	1,00 (0,98-1,01)	0,726
iVTSVD, ml/m² (DE)	38 (19)	40 (21)	37 (18)	1,02 (0,99-1,04)	0,175
RTG, n (%)	79 (18)	28 (32)	51 (15)	2,59 (1,65-4,07)	<0,001
Tratamiento médico ‡					
Beta-bloqueantes, n (%)	319 (56)	116 (85)	203 (46)	-	-
IECA / ARAII, n (%)	286 (50)	92 (68)	194 (44)	-	-
Sacubitril-valsartan, n (%)	30 (5)	19 (14)	11 (3)	-	-
ARM, n (%)	162 (28)	75 (55)	87 (20)	-	-
Ivabradina, n (%)	42 (8)	15 (13)	27 (6)	-	-
Diuréticos, n (%)	147 (26)	76 (56)	71 (16)	-	-
Anticoagulación oral, n (%)	155 (27)	76 (57)	79 (18)	-	-

Abreviaturas como en ***Tabla 4*** y ***10.***

10.4. FINANCIACIÓN

Esta tesis doctoral fue financiada parcialmente por una beca de la Societat Catalana de Cardiologia (2019).