

# Natural History of *MYH7*-Related Dilated Cardiomyopathy



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## ABSTRACT

**BACKGROUND** Variants in myosin heavy chain 7 (*MYH7*) are responsible for disease in 1% to 5% of patients with dilated cardiomyopathy (DCM); however, the clinical characteristics and natural history of *MYH7*-related DCM are poorly described.

**OBJECTIVES** We sought to determine the phenotype and prognosis of *MYH7*-related DCM. We also evaluated the influence of variant location on phenotypic expression.

**METHODS** We studied clinical data from 147 individuals with DCM-causing *MYH7* variants (47.6% female; 35.6 ± 19.2 years) recruited from 29 international centers.

**RESULTS** At initial evaluation, 106 (72.1%) patients had DCM (left ventricular ejection fraction: 34.5% ± 11.7%). Median follow-up was 4.5 years (IQR: 1.7-8.0 years), and 23.7% of carriers who were initially phenotype-negative developed DCM. Phenotypic expression by 40 and 60 years was 46% and 88%, respectively, with 18 patients (16%) first diagnosed at <18 years of age. Thirty-six percent of patients with DCM met imaging criteria for LV noncompaction. During follow-up, 28% showed left ventricular reverse remodeling. Incidence of adverse cardiac events among patients with DCM at 5 years was 11.6%, with 5 (4.6%) deaths caused by end-stage heart failure (ESHF) and 5 patients (4.6%) requiring heart transplantation. The major ventricular arrhythmia rate was low (1.0% and 2.1% at 5 years in patients with DCM and in those with LVEF of ≤35%, respectively). ESHF and major ventricular arrhythmia were significantly lower compared with *LMNA*-related DCM and similar to DCM caused by *TTN* truncating variants.

**CONCLUSIONS** *MYH7*-related DCM is characterized by early age of onset, high phenotypic expression, low left ventricular reverse remodeling, and frequent progression to ESHF. Heart failure complications predominate over ventricular arrhythmias, which are rare. (J Am Coll Cardiol 2022;80:1447-1461) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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## ABBREVIATIONS AND ACRONYMS

<b>DCM</b>	= dilated cardiomyopathy
<b>ESHF</b>	= end-stage heart failure
<b>HCM</b>	= hypertrophic cardiomyopathy
<b>HF</b>	= heart failure
<b>LGE</b>	= late gadolinium enhancement
<b>LV</b>	= left ventricle
<b>LVEF</b>	= left ventricular ejection fraction
<b>LVRR</b>	= left ventricular reverse remodeling
<b>MVA</b>	= malignant ventricular arrhythmias
<b>MYH7</b>	= myosin heavy chain 7

**D**ilated cardiomyopathy (DCM), defined as left ventricular (LV) or biventricular dilatation and systolic dysfunction unexplained by abnormal loading conditions or coronary artery disease,<sup>1</sup> is the leading cause of heart failure (HF) in the young and the most frequent indication for heart transplantation worldwide.<sup>2</sup> Recent reports suggest that 30% to 40% of DCM cases are caused by pathogenic or likely pathogenic gene variants,<sup>3-5</sup> and >50 genes have been associated with the disease.<sup>6</sup>

Pathogenic variants in myosin heavy chain 7 (*MYH7*) are described in 1% to 5.3% of DCM cases, making it one of the most common genes implicated in contemporary DCM cohorts.<sup>4,5,7</sup> *MYH7* encodes for  $\beta$ -myosin heavy

chain, a key component of the cardiac sarcomere, and DCM-related *MYH7* variants affect myocardial contractile function by impairing the formation of myosin-actin cross bridges responsible for myocyte contraction.<sup>8</sup> Of note, specific small-molecule therapies that rescue the impaired force production associated with *MYH7* variants are under development and have the potential to improve the management of these patients beyond standard treatment for DCM.<sup>9</sup>

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Despite its clinical relevance, data on the clinical characteristics and natural history of *MYH7*-associated DCM are scarce and based on limited case series.<sup>10,11</sup> The objective of the present study was to describe the clinical profile and long-term cardiac outcomes of patients with DCM and asymptomatic

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relatives with *MYH7* DCM-causing variants recruited from an international multicenter collaboration. Additionally, we sought to determine the relationship between the location of variants across the gene and phenotypic expression and clinical outcomes.

## METHODS

**STUDY POPULATION.** Inherited cardiac disease units and cardiomyopathy clinics from Europe, Argentina, and Australia were contacted and invited to participate in this longitudinal retrospective cohort study. The cohort comprised patients with DCM defined as LV ejection fraction (LVEF) of <50% not explained by abnormal loading conditions or ischemic heart disease<sup>1</sup> who carried a pathogenic or likely pathogenic variant in *MYH7*. Relatives of index cases were identified through clinical and genetic cascade screening, and those harboring the same genetic variant were also included irrespective of phenotype expression. Patients with DCM and their relatives with variants of unknown significance (VUSs) were also identified for central interpretation and reclassification. Exclusion criteria included severe valvular heart disease or significant coronary artery disease. Patients with LV wall thickness of  $\geq 13$  mm or with any relative with hypertrophic cardiomyopathy (HCM) were excluded to avoid the inclusion of patients with end-stage HCM. In addition, patients with *MYH7* variants predominantly associated with the HCM phenotype in the Health in Code (A Coruña) database were also excluded (Supplemental Appendix 2). Finally, patients with concomitant pathogenic or likely pathogenic variants in other genes related to cardiomyopathies were excluded.

The study was approved by the Hospital Universitario Puerta de Hierro ethics committee and conformed to the principles of the Declaration of Helsinki. The authors from each participating center guarantee the integrity of data.

**GENETIC TESTING AND INTERPRETATION.** Genetic testing was performed at participating centers or at accredited genetic laboratories. Genetic variant interpretation was centrally curated following American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines adapted for *MYH7*.<sup>12</sup>

Pathogenic and likely pathogenic variants were grouped according to the 3 main domains of  $\beta$ -myosin heavy chain: globular head (S1) containing adenosine triphosphate and actin binding sites and a lever domain (amino acids 1-847); neck region (S2) (amino acids 848-1216); and an alpha helical tail also known as light meromyosin (LMM) (amino acids 1217-1936).<sup>13</sup>

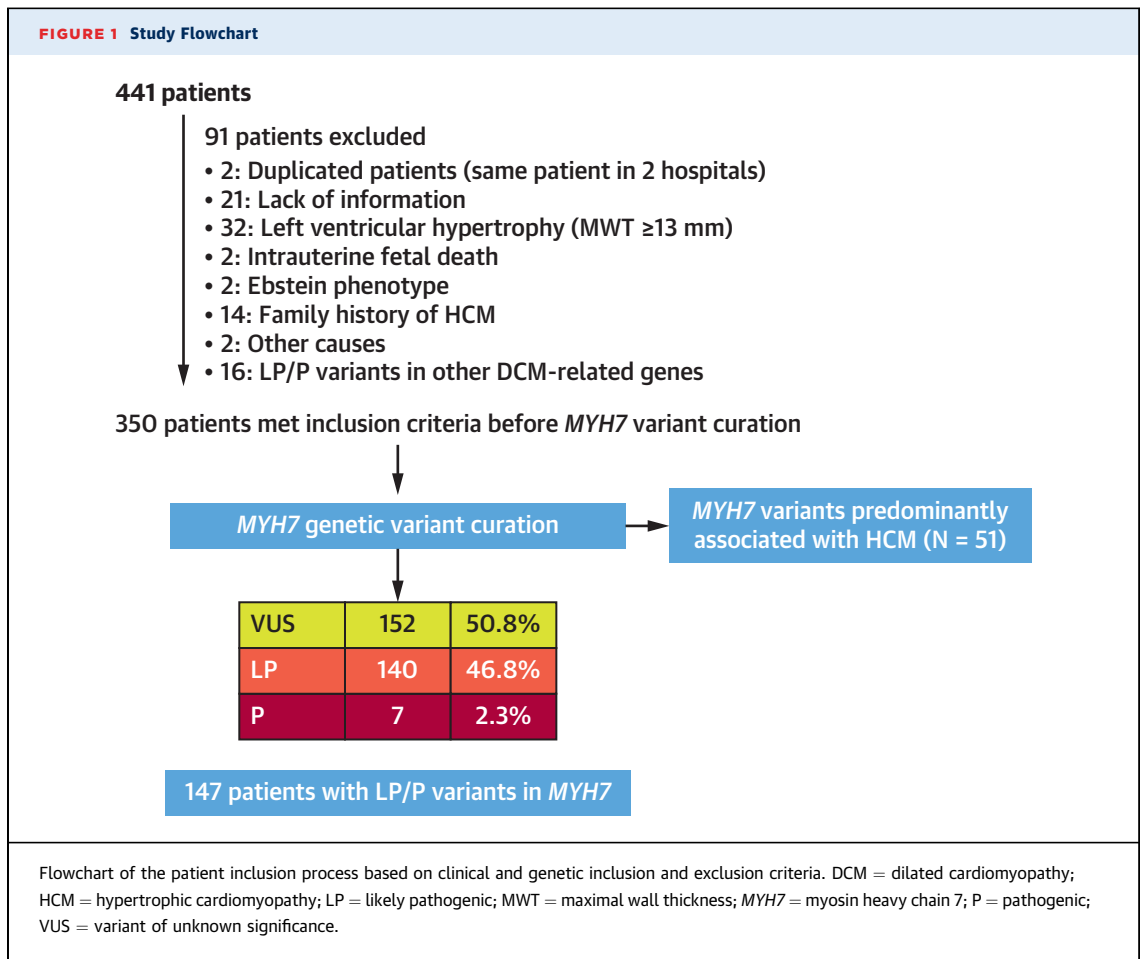
Additionally, a subanalysis of patients with VUS was performed in terms of distribution across the gene, phenotypic characteristics, and events during follow-up.

**DATA ACQUISITION.** Data were retrieved and anonymized by each center from medical records. The data set included demographics, family history, signs, symptoms, and treatment at first evaluation. Complementary tests including electrocardiogram, Holter electrocardiogram, echocardiography, as well as cardiac magnetic resonance (CMR) and endomyocardial biopsy results (when performed), both at first and last evaluation, were also included. LV noncompaction was defined according to Jenni criteria for echocardiography<sup>14</sup> and Petersen criteria for CMR.<sup>15</sup>

Events during follow-up including device implantation, atrial fibrillation (AF), ventricular arrhythmias, implantable cardioverter-defibrillator (ICD) therapies for ventricular arrhythmias, HF admission, LV assist device implantation, heart transplantation, or death were collected.

**STUDY ENDPOINTS.** To determine the natural history of the disease, a series of clinical events were evaluated. DCM onset, defined as a reduction of LVEF to <50%, was assessed in patients who did not meet DCM criteria at first evaluation. Phenotypic expression, in terms of DCM expression, was estimated using date of birth as the baseline for all carriers and date of DCM diagnosis. Changes in LVEF were assessed in patients with DCM; LV reverse remodeling (LVRR) was defined as either LV normalization (LVEF improvement to  $\geq 50\%$  with a  $\geq 5\%$  LVEF increment at the last follow-up) or an absolute increase in LVEF by  $\geq 10\%$  at the last follow-up from baseline, as previously described.<sup>16,17</sup> Malignant ventricular arrhythmia (MVA) was defined as a composite of sudden cardiac death (SCD), sustained ventricular tachycardia (VT), or appropriate ICD therapy. End-stage HF (ESHF) was defined as LV assist device implantation, heart transplantation, or HF-related death. MVA, ESHF, and LVRR rates in DCM patients aged  $\geq 15$  years were compared with those observed in 182 patients  $\geq 15$  years with *TTN*-related DCM and 50 patients with *LMNA*-related DCM included in a recently published Spanish cohort of nonischemic DCM.<sup>5</sup>

**STATISTICAL ANALYSIS.** Results are presented as mean  $\pm$  SD for continuous variables and as number (%) for categorical variables. Student's *t*-test and analysis of variance tests were used to compare continuous variables with normal distribution assessed by the Shapiro-Wilk test, whereas nonparametric Wilcoxon rank sum or Kruskal-Wallis tests were applied for those not meeting normal

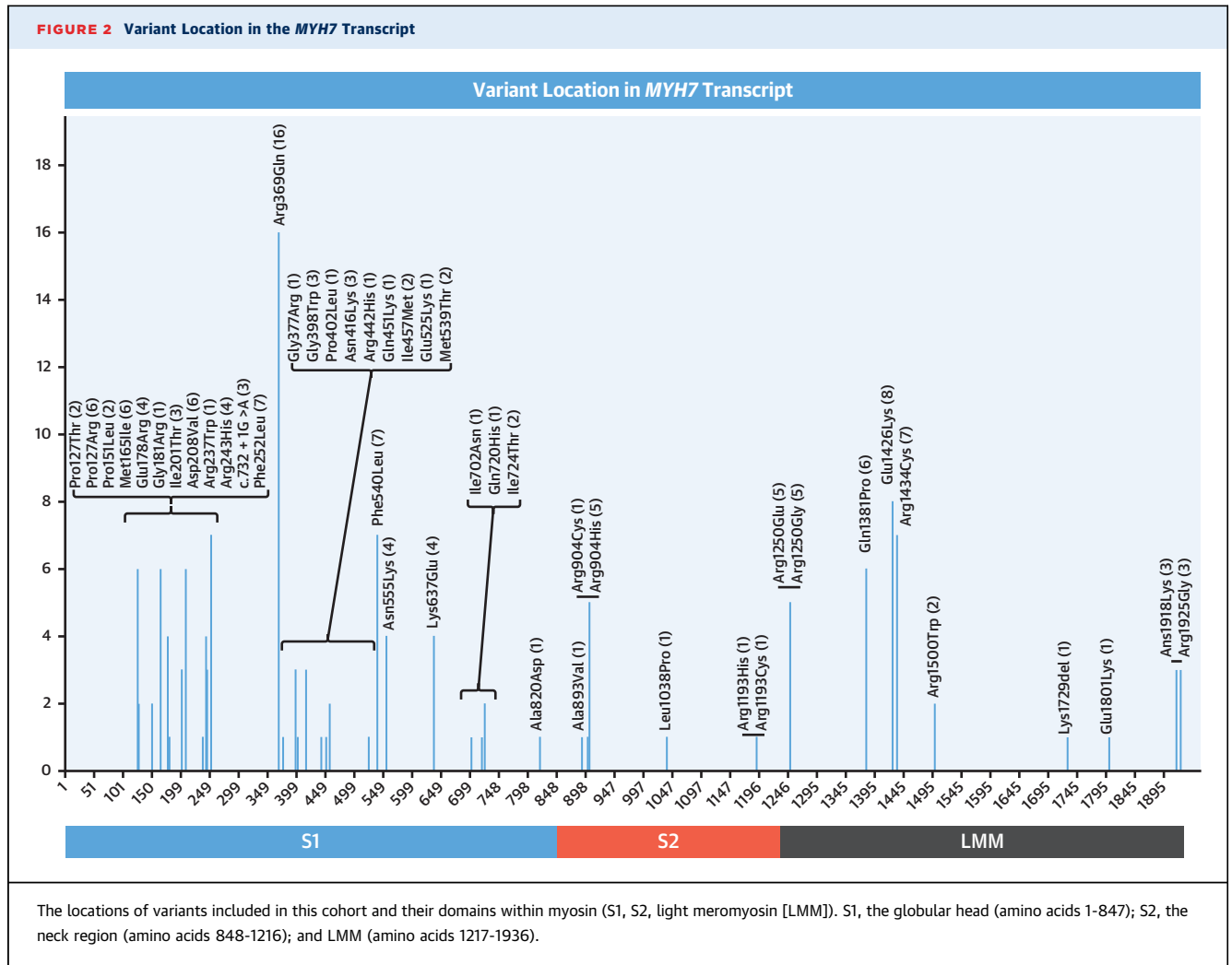


distribution. Categorical variables were compared between groups with the parametric chi-square test or nonparametric Fisher exact test. Survival analyses with Kaplan-Meier curves were used to describe phenotypic expression as well as MVA and ESHF events. Cox proportional hazards regression or log-rank tests were performed to assess the association between baseline characteristics and DCM onset and to analyze the impact of sex, LVEF ( $\leq 35\%$ ,  $>35\%$ ), late gadolinium enhancement (LGE) presence, and mutation location on clinical events. STATA software version 15.1 (StataCorp) was used for statistical analysis. A 2-tailed *P* value of  $<0.05$  was considered statistically significant.

## RESULTS

Information on 441 patients was submitted from 40 centers. The flowchart for patient selection is displayed in [Figure 1](#). A total of 91 patients were excluded for various reasons: 2 patients were included by 2 centers simultaneously; 21 patients

lacked information considered essential for accurate phenotypic description; 32 patients had LV wall thickness of  $\geq 13$  mm; 14 patients had family history of HCM; 16 patients had concomitant pathogenic or likely pathogenic variants in other genes related to cardiomyopathies; 2 patients were stillborn, and the diagnosis of DCM was established postmortem; 2 patients had Ebstein's anomaly; and 2 patients were excluded for other reasons (1 had severe aortic regurgitation, and the other did not meet DCM criteria). In addition, 51 patients were excluded because they carried *MYH7* variants that were predominantly associated with HCM. Variant classification of the remaining 299 patients resulted in 147 patients with pathogenic or likely pathogenic variants (43 missense variants, 1 splice donor variant, and 1 in-frame deletion) and 152 patients with VUSs. Patients with pathogenic or likely pathogenic variants were distributed in 67 different families provided by 29 centers. The variant locations across *MYH7* from the patients included in the study are shown in [Figure 2](#). Criteria applied for the classification of variants and



variants included in the study are provided in [Supplemental Appendices 3 and 4](#).

**BASELINE CHARACTERISTICS.** Characteristics of the 147 patients with pathogenic or likely pathogenic variants at first evaluation are presented in [Table 1](#). Sixty (40.8%) were probands, and the remaining 87 (59.2%) were relatives. Overall, 106 patients had a diagnosis of DCM at first evaluation, and 41 patients did not meet criteria for DCM at baseline.

Of the 106 patients with DCM at first evaluation, the mean age was  $38.7 \pm 18.7$  years, and 42.5% were female. Exposure to acquired modifiers such as excessive alcohol intake (2.9%), cardiotoxic chemotherapy (1.0%), or peripartum cardiomyopathy (1.9%) was low. Almost one-half of the patients were in New York Heart Association functional class  $\geq$ II at first evaluation. Only 1 (0.8%) patient had skeletal muscle disease described as Laing distal myopathy. Six (6.5%) patients had previous history of AF at first

evaluation. Twenty-three (22.8%) patients had intra-ventricular conduction disturbances, and 13 (20.6%) had nonsustained VT (NSVT) at first Holter, whereas 3 (5.8%) patients had frequent premature ventricular beats ( $>500/24$  h). Mean LVEF was  $39.8\% \pm 12.3\%$ , and LV noncompaction by echocardiographic criteria was observed in 35.6% of patients; this proportion increased to 58.5% in patients who were assessed with CMR. Overall, 26.5% of patients had LGE at first CMR, with midwall as the most frequent pattern of LGE distribution.

Pharmacologic treatment at baseline evaluation in patients with DCM included beta blockers in 60 (57.1%) patients, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors in 86 (81.9%), and mineralocorticoid receptor antagonists in 26 (24.8%). Two (1.9%) patients had a pacemaker implanted, and 3 (2.9%) had an ICD.

**TABLE 1** Baseline Characteristics

	Overall (N = 147)	No DCM at First Evaluation (n = 41)	DCM at First Evaluation (n = 106)	P Value
Age, y	35.6 ± 19.2	27.5 ± 18.4	38.7 ± 18.7	0.002
Female	70 (47.6)	25 (61.0)	45 (42.5)	0.04
<b>Modifiers</b>				
Alcohol abuse	3 (2.1)	0 (0.0)	3 (2.9)	0.27
Cardiotoxic chemotherapy	1 (0.7)	0 (0.0)	1 (1.0)	0.53
PPCM	2 (1.4)	0 (0.0)	2 (1.9)	0.38
<b>Baseline treatment</b>				
Beta blockers	63 (43.2)	3 (7.3)	60 (57.1)	<0.001
ACE inhibitors/ARBs/ARN inhibitors	91 (62.3)	5 (12.2)	86 (81.9)	<0.001
MRA	27 (18.5)	1 (2.4)	26 (24.8)	0.002
<b>Devices</b>				
Pacemaker	2 (1.4)	0 (0.0)	2 (1.9)	0.36
ICD	3 (2.1)	0 (0.0)	3 (2.9)	
CRT/CRT-D	0 (0.0)	0 (0.0)	0 (0.0)	
<b>Clinical status</b>				
NYHA functional class				<0.001
I	95 (64.6)	40 (97.6)	55 (51.9)	
II	28 (19.1)	0 (0.0)	28 (26.4)	
III	18 (12.2)	1 (2.4)	17 (16.0)	
IV	6 (4.1)	0 (0.0)	6 (5.7)	
Skeletal muscle disease	2 (1.4)	1 (2.4)	1 (0.9)	0.48
Prior AF	6 (4.8)	0 (0.0)	6 (6.5)	0.14
Prior stroke/TIA	1 (0.7)	0 (0.0)	1 (1.0)	0.53
<b>ECG</b>				
AF	6 (4.1)	0 (0.0)	6 (5.7)	0.12
QRS morphology				0.44
RBBB	3 (2.1)	0 (0.0)	3 (2.9)	
LB	10 (7.1)	1 (2.6)	9 (8.8)	
NIVCD	14 (10.0)	3 (7.9)	14 (10.8)	
Paced	1 (0.7)	0 (0.0)	1 (1.0)	
Abnormal TWI	28 (20.4)	5 (12.8)	23 (23.5)	0.16
Q waves	13 (9.6)	1 (2.6)	12 (12.4)	0.08
<b>Holter ECG (n = 82)</b>				
PVB (>500/24 h)	4 (6.0)	1 (6.7)	3 (5.8)	0.89
NSVT	14 (17.1)	1 (5.3)	13 (20.6)	0.12
<b>Echocardiography</b>				
MWT, mm <sup>3</sup>	9.1 ± 1.5	8.6 ± 1.2	9.3 ± 1.6	0.08
LVEF, %	41.4 ± 15.1	58.4 ± 4.5	34.8 ± 12.3	<0.001
LVEDD, mm <sup>3</sup>	58.9 ± 9.9	49.5 ± 5.8	61.3 ± 9.4	<0.001
Noncompaction	49 (33.8)	12 (29.3)	37 (35.6)	0.47
TAPSE <7 mm <sup>3</sup>	7 (10.8)	0 (0.0)	7 (13.7)	0.14
<b>CMR (n = 68)</b>				
LVEF, %	43.0 ± 13.4	54.9 ± 8.7	39.8 ± 12.7	<0.001
Noncompaction	41 (61.2)	10 (71.4)	31 (58.5)	0.38
LGE	13 (20.6)	0 (0.0)	13 (26.5)	0.03
<b>LGE pattern</b>				
Midwall	8 (12.7)	0 (0.0)	8 (16.3)	
Subepicardial	1 (1.6)	0 (0.0)	1 (2.0)	
RV-LV junction	1 (1.6)	0 (0.0)	1 (2.0)	
Multiple	3 (4.8)	0 (0.0)	3 (6.1)	

Values are mean ± SD or n (%). <sup>a</sup>Obtained only from adults.  
ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARN = angiotensin receptor-neprilysin inhibitor; CMR = cardiac magnetic resonance; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy-defibrillator; DCM = dilated cardiomyopathy; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LB = left bundle branch block; LGE = late gadolinium enhancement; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; MWT = maximal wall thickness; NIVCD = nonspecific intraventricular conduction delay; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PPCM = peripartum cardiomyopathy; PVB = premature ventricular beats; RBBB = right bundle branch block; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; TIA = transient ischemic attack; TWI = T-wave inversion.

The 41 patients without DCM at initial evaluation were significantly younger than their peers with DCM (mean age: 27.5 ± 18.4 years vs 38.7 ± 18.7 years; P = 0.002). None had a previous history of AF or pacemaker implantation. Premature ventricular beats and NSVT were uncommon before DCM expression, and 29.3% of patients fulfilled imaging criteria for LV noncompaction at initial echocardiogram, rising to 71.4% among those assessed with CMR. LGE was absent in the 14 MYH7 carriers without DCM who underwent CMR, and only 1 individual showed skeletal muscle disease (described as generalized hypotonia and psychomotor retardation in a 1-year-old infant).

**FOLLOW-UP.** Overall median follow-up was 4.5 years (IQR: 1.7-8.0 years). Six patients (3 with DCM and 3 without) were evaluated only once and were lost to follow-up.

**DCM PROGRESSION.** Nine (23.7%) patients developed DCM during follow-up. Table 2 compares baseline characteristics of individuals without DCM at baseline according to DCM onset during follow-up. The presence of intraventricular conduction disturbances was the strongest predictor for progression to DCM (HR: 15.5; 95% CI: 3.37-71.5; P < 0.001) in individuals without DCM at baseline. Older age and NSVT were also associated with progression to DCM. Of note, presence of LV noncompaction imaging criteria in individuals without DCM was not associated with DCM onset during follow-up (Table 2).

**AGE-RELATED PHENOTYPIC EXPRESSION.** The age of phenotypic expression of DCM from birth is shown in Figure 3A. Overall, mean age at DCM diagnosis was 36.9 ± 18.6 years. Male patients were significantly younger at DCM diagnosis than female patients (33.3 ± 18.0 years vs 41.7 ± 18.6 years; P = 0.02). The phenotypic expression rates at 40, 60, and 80 years were 45.9%, 88.1% and 98.8%, respectively. Although most patients were diagnosed with DCM between 20 and 60 years of age (Figure 3B), 18 (15.7%) patients were diagnosed before 18 years of age, and 9 (7.8%) were diagnosed during the first year of life.

**LV REVERSE REMODELING.** Changes in LVEF were assessed in 85 patients with DCM at baseline evaluation. Mean change in LVEF was +4.5% ± 11.1%, with 24 (28.2%) patients fulfilling LVRR definition after a median follow-up of 5.4 years (IQR: 2.0-8.7 years). Characteristics of patients based on LVRR are shown in Supplemental Appendix 5. Patients with LVRR had a lower LVEF at baseline than patients without LVRR (27.2% vs 37.6%; P < 0.001), higher wall thickness (9.9 ± 1.6 mm vs 8.9 ± 1.3 mm; P = 0.01), and higher LV diameter (63.3 ± 11.2 mm vs 60.1 ± 7.8 mm; P = 0.04), and a higher proportion received beta



blockers (75.0% vs 47.5%;  $P = 0.02$ ) and mineralocorticoid receptor antagonists (41.7% vs 18.0%;  $P = 0.02$ ) at initial evaluation. The presence of LGE and noncompaction did not differ between both groups. When compared with the *TTN* and *LMNA* DCM cohorts, the percentage of patients exhibiting LVRR was lower in the *MYH7* DCM cohort than in the *TTN* cohort (24.7% vs 50.8%;  $P < 0.001$ ), and there was no significant difference with the *LMNA* cohort (24.7% vs 22.5%;  $P = 0.08$ ).

**MALIGNANT VENTRICULAR ARRHYTHMIAS.** Seven (6.5%) patients with DCM experienced MVA during follow-up: appropriate ICD therapies were delivered in 3 patients because of VT (2.8%), 2 (1.9%) patients had sustained VT (1 as the initial manifestation of DCM), and 2 (1.9%) patients had SCD. Overall incidence of MVA at 5 years was 1.0%. All patients with MVA had LVEF of  $\leq 35\%$  at initial evaluation (log-rank  $P = 0.03$ ), and the MVA event rate in this subgroup was 2.1% at 5 years (Figure 4A). The presence of LGE was associated with MVA in patients with LVEF of  $\leq 35\%$  (log-rank  $P = 0.046$ ). No sex differences were found. None of the individuals without DCM had MVA. Compared with other DCM genes, no significant differences were found when compared with patients with *TTN*-related DCM (HR: 1.56; 95% CI: 0.63-3.87;  $P = 0.34$ ), whereas patients with *LMNA*-related DCM showed higher risk for MVA (HR: 8.78; 95% CI: 3.45-22.4;  $P < 0.001$ ) (Figure 4B).

**END-STAGE HF.** Ten (9.3%) patients with DCM had an ESHF event during follow-up. A total of 5 (4.6%) patients received a heart transplant during follow-up, and 5 patients (4.6%) died of ESHF. Overall incidence of ESHF at 5 years was 11.6%. Patients with LVEF of  $\leq 35\%$  at baseline had an increased risk of ESHF events compared with those with LVEF of  $> 35\%$  (log-rank  $P = 0.001$ ). Again, no significant differences were found in comparison with the *TTN* DCM cohort (HR: 1.11; 95% CI: 0.46-2.66;  $P = 0.23$ ), whereas patients with *LMNA* DCM showed an increased risk for ESHF (HR: 5.98; 95% CI: 2.44-14.6;  $P < 0.001$ ) (Figure 5B).

**VARIANT LOCATION IN MYH7.** Table 3 shows the distribution and baseline characteristics of patients according to variant location domains. Overall, patients with variants in S1 were the most frequent (65.3%). Interestingly, noncompaction was more prevalent (44.2%) in this group than in patients with variants in the S2 (0.0%) or LMM (17.5%) domains ( $P < 0.001$ ).

Figure 6A shows age-related phenotypic expression according to variant location. We did not observe significant differences among groups despite a trend

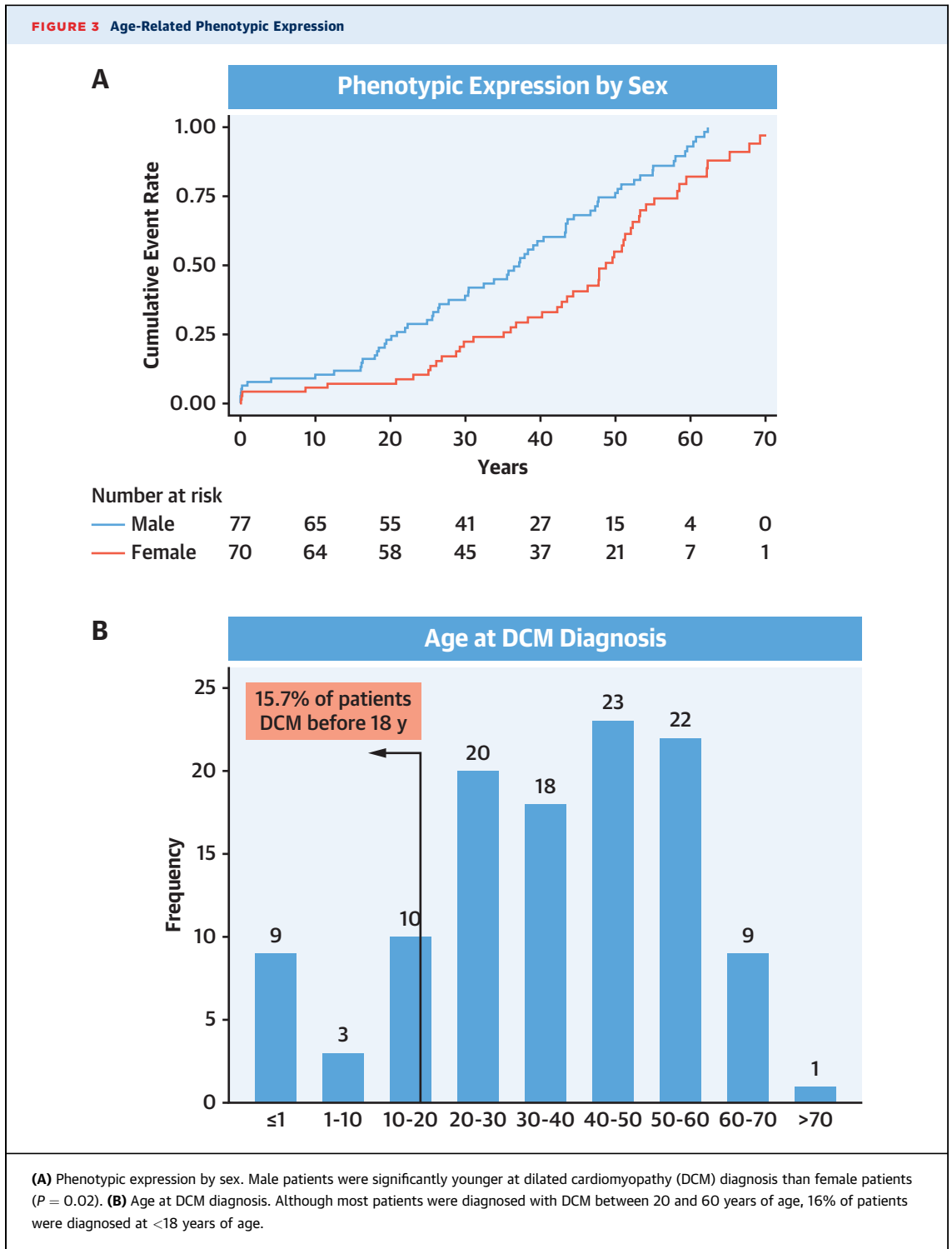
**TABLE 2 Clinical Characteristics of Individuals Without DCM at Initial Evaluation According to DCM Onset During Follow-Up**

	No DCM Progression (n = 29)	DCM Progression (n = 9)	HR <sup>b</sup> (95% CI)	P Value
Age, y	24.9 ± 17.4	39.2 ± 19.7	1.04 (1.00-1.08)	0.048
Female	19 (65.5)	4 (44.4)	0.52 (0.14-1.97)	0.34
<b>Modifiers</b>				
Alcohol	0 (0.0)	0 (0.0)	—	—
Cardiotoxic chemotherapy	0 (0.0)	0 (0.0)	—	—
<b>ECG</b>				
AF	0 (0.0)	0 (0.0)	—	—
IVCD	0 (0.0)	4 (44.4)	15.5 (3.37-71.5)	<0.001
Abnormal TWI	4 (14.3)	1 (11.1)	0.53 (0.07-4.28)	0.55
Q waves	1 (3.7)	0 (0.0)	—	0.67
<b>Holter ECG (n = 18)</b>				
PVB (>500/24 h)	1 (9.1)	0 (0.0)	—	0.78
NSVT	0 (0.0)	1 (25.0)	—	<0.001
<b>Echocardiography</b>				
MWT, mm <sup>3</sup>	8.5 ± 1.1	9.0 ± 1.7	1.11 (0.59-2.08)	0.75
LVEF, %	59.2 ± 4.7	56.8 ± 3.3	0.95 (0.82-1.10)	0.47
LVEDD, mm <sup>3</sup>	48.4 ± 5.9	51.6 ± 6.2	1.12 (0.97-1.30)	0.12
Noncompaction	8 (27.6)	2 (22.2)	0.94 (0.19-4.62)	0.94
TAPSE <17 mm <sup>3</sup>	0 (0.0)	0 (0.0)	—	—
<b>CMR (n = 14)</b>				
Noncompaction	8 (78.6)	2 (66.7)	0.81 (0.07-8.96)	0.87
LGE	0 (0.0)	0 (0.0)	—	—

Values are mean ± SD or n (%), unless noted otherwise. <sup>a</sup>Obtained only from adults. <sup>b</sup>HRs are estimated based on the incremental effect of 1 U of continuous variables (year, millimeter, and percentage point, as applicable).  
IVCD = intraventricular conduction delay; other abbreviations as in Table 1.

for later onset in patients with variants in the LMM domain (log-rank  $P = 0.20$ ). We also did not observe differences among groups by variant location in MVA, ESHF, or combined ESHF/MVA events (Figure 6B, Supplemental Appendix 7) or in LVRR (S1: 25.5%; S2: 44.4%; LMM: 28.0%;  $P = 0.53$ ).

**PATIENTS WITH VUSs.** Baseline characteristics were compared between patients with VUSs and patients with pathogenic or likely pathogenic variants (Supplemental Appendix 10), revealing older age at DCM diagnosis (41.2 ± 19.0 years vs 36.9 ± 18.6 years;  $P = 0.03$ ) and a higher prevalence of increased ventricular premature beats (>500/24 h) in Holter monitoring (21.3% vs 6.0%;  $P = 0.02$ ) in patients with VUSs. No significant differences were found in other baseline characteristics, including prevalence of noncompaction (29.3% vs 33.8%  $P = 0.45$ ). After a median follow-up of 4.2 years (IQR: 1.9-8.2 years), a higher proportion of patients with VUSs showed LVRR than those with pathogenic or likely pathogenic variants (44.4% vs 28.2%;  $P = 0.03$ ). No significant differences between groups were found for MVA, ESHF, or combined ESHF/MVA event rates (Supplemental Appendix 11).



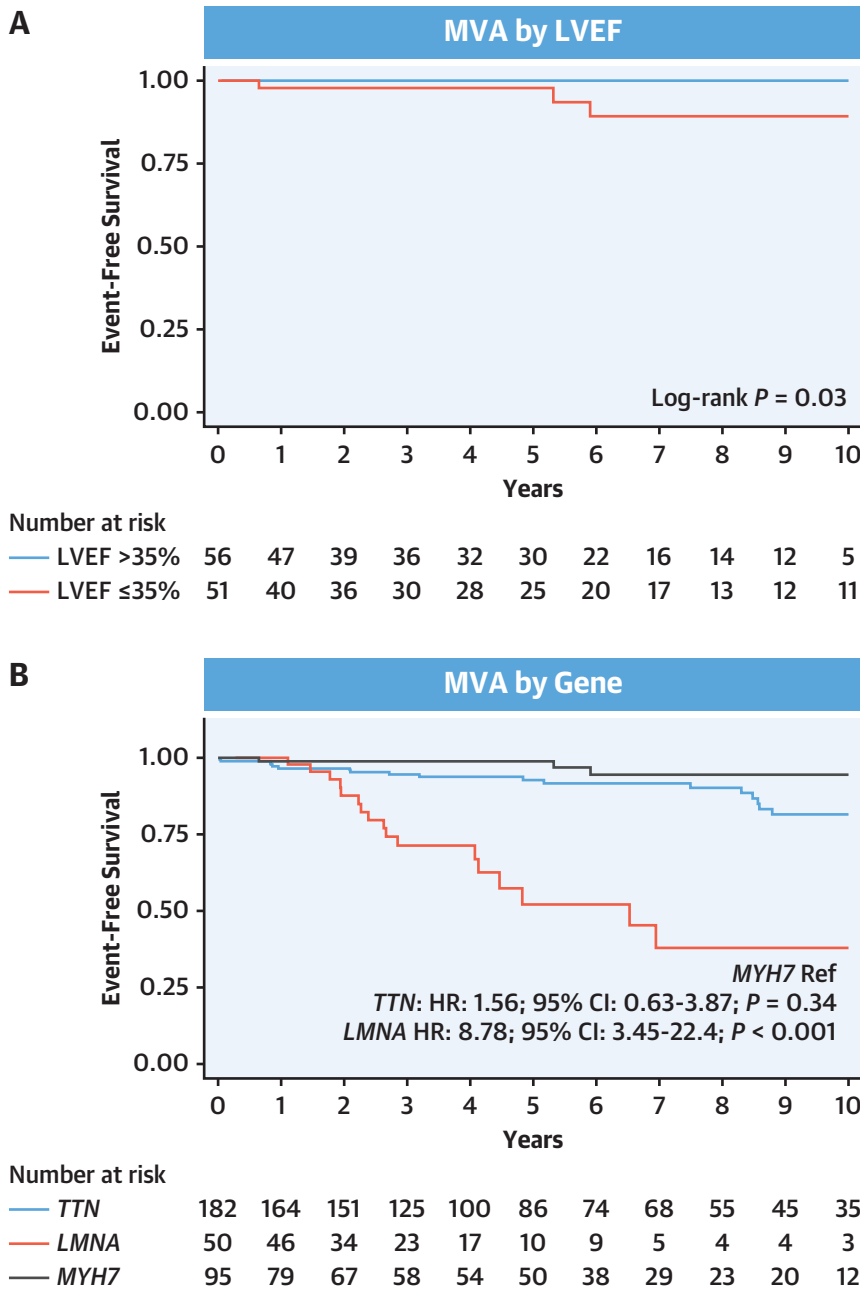
**DISCUSSION**

To our knowledge, the present study represents the largest cohort of DCM caused by *MYH7* variants described to date. Our findings reveal that DCM

caused by mutations in *MYH7* is characterized by a high rate of phenotypic expression, often with childhood presentation, and frequent association with LV noncompaction findings. During follow-up, HF complications predominate over MVA events,



**FIGURE 4** Malignant Ventricular Arrhythmias

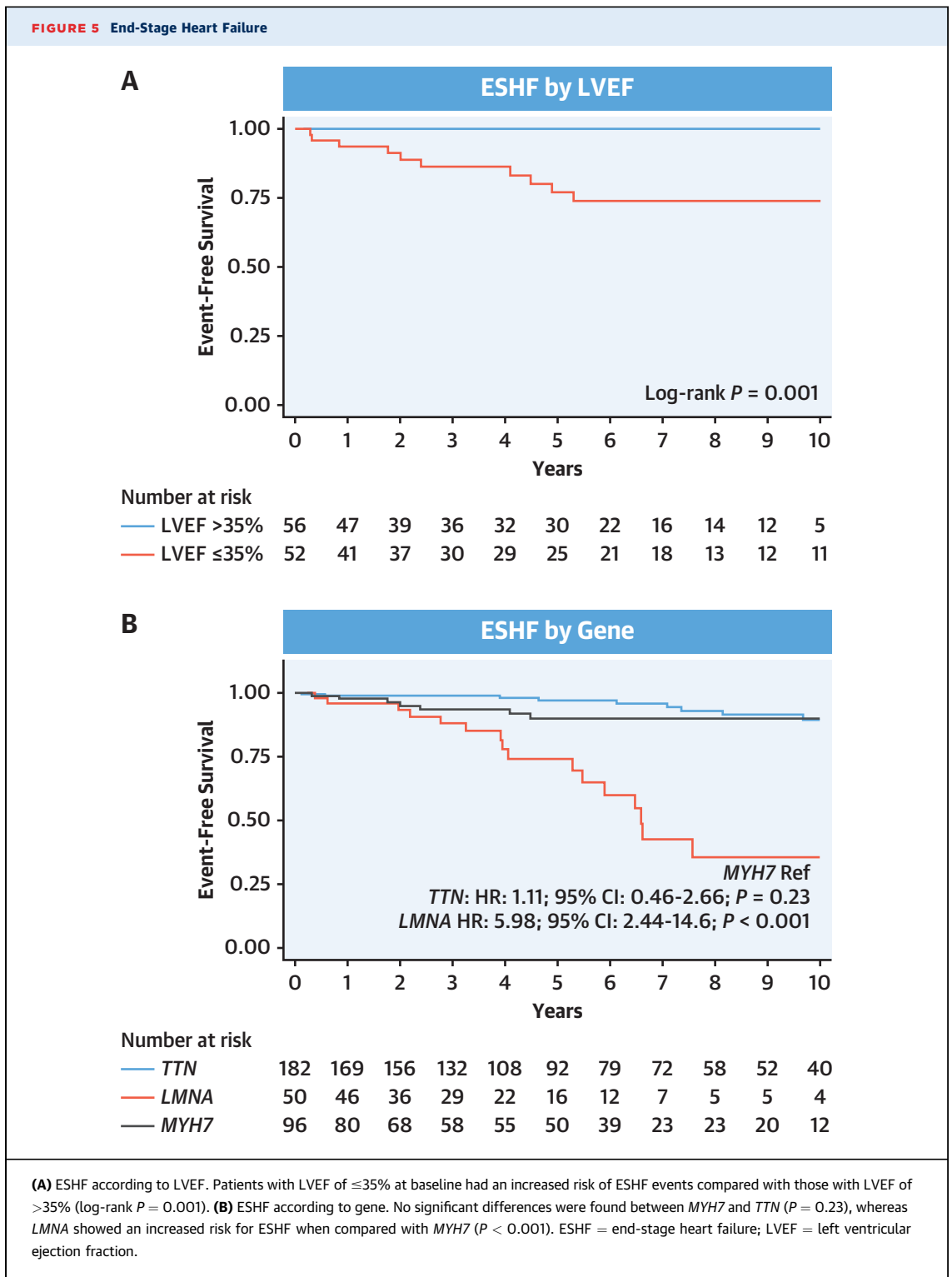


**(A)** MVA according to LVEF. All patients with MVA had an LVEF of  $\leq 35\%$  at initial evaluation (log-rank  $P = 0.03$ ). **(B)** MVA according to gene. No significant differences were found between *MYH7* and *TTN* ( $P = 0.34$ ), whereas *LMNA* showed an increased risk for MVA vs *MYH7* ( $P < 0.001$ ). LVEF = left ventricular ejection fraction; MVA = malignant ventricular arrhythmia.

which were rare even in patients with severe systolic dysfunction (**Central Illustration**).

Introduction of next-generation sequencing in clinical practice has revolutionized the classification of DCM and has enabled etiology-specific

management.<sup>5</sup> Mutations in *MYH7* were first described as a cause of HCM in the early 1990s and represent the second most frequent cause of this disease.<sup>18,19</sup> Later, variants in *MYH7* were reported in cases of DCM,<sup>10,11,20</sup> skeletal myopathy,<sup>21</sup> or mixed



phenotypes.<sup>22</sup> Contemporary studies have shown that *MYH7* missense variants are more frequent in patients with DCM than in healthy control individuals and have been described in up to 5% of DCM patients.<sup>5,23</sup>

To our knowledge, this is the first large-scale cohort describing the natural history of DCM related to *MYH7* gene variants and the first to provide data on age-related phenotypic expression of DCM. Similar to

other genetic forms of DCM, MYH7-related DCM has a high rate of phenotypic expression from middle age. We found, however, that a relevant proportion of carriers developed DCM during childhood, including the first year of life, which is consistent with previous work in pediatric DCM cohorts reporting MYH7 as one of the leading causes of genetic DCM in children.<sup>24</sup> In addition, 2 cases in our cohort were excluded from analysis because of stillbirth caused by DCM, a rare presentation that has been previously reported.<sup>25</sup>

Our findings suggest that skeletal myopathy is rare in MYH7-related DCM despite the known overlap of DCM and muscular phenotypes associated with specific variants in the LMM domain.<sup>21</sup> In contrast to what has been described in LMNA- and TTN-related DCM, AF and advanced atrioventricular conduction disturbances were uncommon and rarely appeared before DCM expression in MYH7 carriers.<sup>16,26-28</sup> However, intraventricular conduction disturbances were common in MYH7 carriers who developed DCM during follow-up in our study, and this finding might alert clinicians to the importance of identifying patients who would require closer follow-up.

LV noncompaction was a common echocardiographic finding of MYH7-related DCM in our series, in concordance with the high frequency of sarcomeric genetic variants described in LV noncompaction cohorts, although the mechanism for this association is not known.<sup>29,30</sup> By contrast, LGE was less prevalent in MYH7-related DCM compared with other genetic DCM forms such as LMNA (48%),<sup>26,27</sup> FLNC (74%),<sup>31</sup> and DSP (78%).<sup>32</sup>

LVRR in MYH7-related DCM also seems to be lower than that reported in TTN-related DCM but similar to that observed in other genetic causes of DCM, such as BAG3 and LMNA.<sup>5</sup> Overall MVA incidence was low, particularly when compared with other DCM-related genes such as LMNA, as demonstrated in our study, but likely when also compared with what has been described in other genes such as FLNC,<sup>31</sup> RBM20,<sup>33</sup> and DSP.<sup>32</sup> In addition, all patients who experienced MVA in our cohort had severe systolic LV dysfunction, and LGE (in those who underwent CMR) was a predictor of MVA in patients with LVEF of ≤35%. Progression to ESHF was observed in 9% of patients in our study, mostly in patients with severe systolic dysfunction at baseline.

DCM-causing MYH7 variants were most frequently located in the S1 domain. This could be explained by the different region sizes but could also have been influenced by American College of Medical Genetics and Genomics/Association for Molecular Pathology classification criteria adaptation for MYH7, which favors pathogenic classification of variants located in

**TABLE 3 Baseline Characteristics of Patients With DCM According to Location of MYH7 Variants**

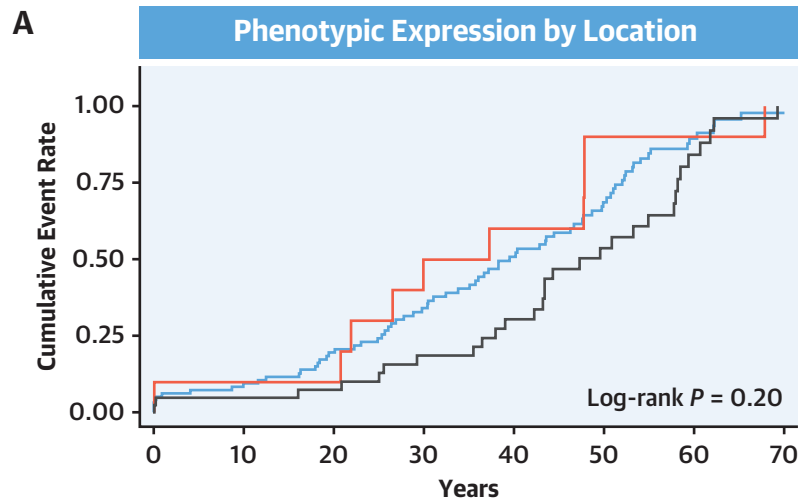
	S1 (n = 96)	S2 (n = 10)	LMM (n = 41)	P Value
Age DCM diagnosis, y	34.8 ± 18.7	34.7 ± 19.0	42.8 ± 19.7	0.10
DCM at first evaluation	69 (71.9)	9 (90.0)	28 (68.3)	0.41
Female	44 (45.8)	5 (50.0)	21 (51.2)	0.83
Clinical status				
NYHA functional class				0.04
I	63 (65.6)	4 (40.0)	28 (68.3)	
II	22 (22.9)	1 (10.0)	5 (12.2)	
III	9 (9.4)	3 (30.0)	6 (14.6)	
IV	2 (2.1)	2 (20.0)	2 (4.9)	
Skeletal muscle disease	1 (1.0)	0 (0.0)	1 (2.4)	0.58
Prior AF	3 (3.8)	1 (12.5)	2 (5.3)	0.35
Devices				0.34
Pacemaker	1 (1.1)	0 (0.0)	1 (2.4)	
ICD	2 (2.1)	1 (10.0)	0 (0.0)	
CRT/CRT-D	0 (0.0)	0 (0.0)	0 (0.0)	
ECG				
QRS morphology				0.03
RBBB	3 (3.4)	0 (0.0)	0 (0.0)	
LBBB	3 (3.4)	4 (40.0)	3 (7.3)	
NIVCD	8 (9.0)	1 (10.0)	5 (12.2)	
Paced	1 (1.1)	0 (0.0)	0 (0.0)	
Holter ECG (n = 82)				
PVB >500/24 h	2 (4.6)	0 (0.0)	2 (11.1)	0.69
NSVT	11 (21.2)	1 (16.7)	2 (8.3)	0.32
Echocardiography				
MWT, mm <sup>a</sup>	9.5 ± 1.5	8.9 ± 1.7	8.5 ± 1.4	0.04
LVEF, %	42.5 ± 14.6	29.9 ± 12.0	41.7 ± 15.9	0.04
LVEDD, mm <sup>a</sup>	58.3 ± 9.8	62.6 ± 11.7	59.5 ± 9.9	0.58
Noncompaction	42 (44.2)	0 (0.0)	7 (17.5)	<0.001
TAPSE < 17 mm <sup>a</sup>	6 (11.1)	1 (16.7)	2 (8.7)	0.73
CMR (n = 68)				
LGE	6 (16.2)	1 (25.0)	6 (27.3)	0.46

Values are mean ± SD or n (%). <sup>a</sup>Obtained only from adults.  
Abbreviations as in Table 1.

the hotspot area encompassing S1.<sup>12</sup> Interestingly, these patients had a higher prevalence of noncompaction, but this did not result in clinical differences with patients with variants located in the S2 or LMM domains, as illustrated by the absence of differences in LVRR, MVA, or ESHF across groups.

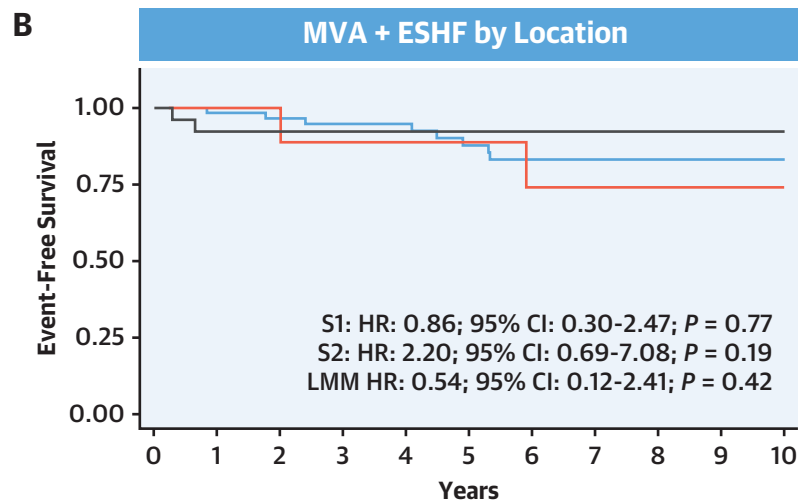
**CLINICAL IMPLICATIONS.** Results from this study have direct clinical implications for carriers of DCM-related MYH7 variants. First, relatives of these patients will benefit from very early clinical and genetic screening, in contrast to other genetic DCM causes that rarely present before adulthood. Early clinical screening should be extended to in utero surveillance of descendants of carriers in cases when transmission to the fetus has not been excluded. Also, carriers without a DCM phenotype who show intraventricular conduction disturbances should be closely followed,

**FIGURE 6** Prognosis According to Variant Location in *MYH7*



Number at risk

— S1	96	83	70	53	37	22	6	1
— S2	10	9	9	5	4	1	1	0
— LMM	41	37	34	28	23	13	4	0



Number at risk

— S1	70	58	52	48	43	38	29	20	16	13	7
— S2	10	9	9	8	8	7	5	5	4	4	4
— LMM	27	21	15	10	10	10	8	8	7	7	5

**(A)** Phenotypic expression by location. **(B)** Combined MVA and ESHF by location. LMM = light meromyosin; other abbreviations as in [Figures 4 and 5](#).

because intraventricular disturbances were associated with progression to DCM.

Regarding SCD prevention, our findings suggest that current recommendations based on LVEF might

perform well in *MYH7*-related DCM because no MVAs were observed in patients with baseline LVEF of >35%. MVA incidence was low even in patients with LVEF of ≤35%, but LGE was associated with MVA in

**CENTRAL ILLUSTRATION** Main Features of MYH7-Related Dilated Cardiomyopathy

**Natural History of MYH7-Related Dilated Cardiomyopathy**

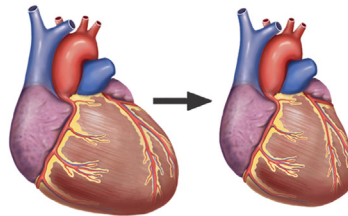
N = 147/29 centers, Median follow-up: 4.5 years (IQR: 1.7-8.0 years)

16% DCM Onset Under 18 Years



Noncompaction 36%

Low LVRR Rate 28%



Low MVA Rate 1% at 5 Years

de Frutos F, et al. J Am Coll Cardiol. 2022;80(15):1447-1461.

Clinical characteristics and evolution of 147 individuals with dilated cardiomyopathy (DCM)-causing MYH7 variants from 29 international centers were studied. MYH7-related DCM was characterized by early onset and high rate of phenotypic expression, with 16% of patients diagnosed at <18 years of age. Frequent presence of left ventricular noncompaction (36%) and low rate of left ventricular reverse remodeling (28%) were the main features. Heart failure complications predominated over ventricular arrhythmias in patients with DCM. ICD = implantable cardioverter-defibrillator; LVRR = left ventricular reverse remodeling; MVA = malignant ventricular arrhythmia.

these individuals, suggesting that LGE should be considered when predicting SCD in these individuals.<sup>34</sup> Finally, the results of the present study provide a rationale for clinical trials testing the efficacy of new myosin activators in this subtype of DCM.

**STUDY LIMITATIONS.** First, it was a retrospective longitudinal cohort study in which some patients might not have had all available current therapies at the time of diagnosis. Although it is the largest cohort of MYH7-related DCM described so far, the final number of patients included precludes generalization of our findings to other cohorts with other characteristics. Also, despite the very strict measures applied to exclude patients with end-stage HCM, we cannot fully exclude that some patients included in the study had this phenotype. Finally, current recommendations used to classify rare missense variants in MYH7 meant that we had to exclude more than one-half of our initial sample, highlighting a relevant gap in current knowledge that requires further study. Of note, patients with VUSs showed similar features and event rates as patients with pathogenic or likely pathogenic variants, suggesting that a good

proportion of patients with VUSs might be classified as patients with pathogenic or likely pathogenic variants in the future.

### CONCLUSIONS

MYH7-related DCM is characterized by early age at onset, high rate of phenotypic expression, low rate of LVRR, and frequent progression to ESHF despite optimal medical therapy. HF complications predominate over ventricular arrhythmias.

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## PERSPECTIVES

### COMPETENCY IN MEDICAL KNOWLEDGE:

MYH7-related DCM is characterized by early onset of clinical manifestations, high penetrance, infrequent LV reverse remodeling, and frequent progression to advanced HF.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to identify factors associated with the development of DCM and its complications in carriers of the MYH7 variant.

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**KEY WORDS** dilated cardiomyopathy, genetics, MYH7

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**APPENDIX** For supplemental materials, please see the online version of this paper.