

ORIGINAL RESEARCH

Clinical Implications of Transmural Late Gadolinium Enhancement in Genotype-Positive Arrhythmogenic and Dilated Cardiomyopathy

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ABSTRACT

BACKGROUND Midmyocardial and subepicardial late gadolinium enhancement (LGE) are typical in inherited arrhythmogenic cardiomyopathy (ACM) and dilated cardiomyopathy (DCM). Transmural LGE, usually considered ischemic and excluded from ACM criteria, may also occur, but its clinical relevance is unclear.

OBJECTIVES The objective of this study was to assess the prevalence, genetic associations, and prognostic significance of transmural LGE in patients with genotype-positive, nonischemic ACM/DCM.

METHODS We retrospectively analyzed 1,379 genotype-positive patients with ACM/DCM, identifying 711 with cardiac magnetic resonance imaging and no significant coronary artery disease. Patients were stratified by LGE pattern (transmural, nontransmural, or absent). Major ventricular arrhythmic (MVA) and advanced heart failure (AHF) events were evaluated using Kaplan-Meier and age-adjusted Cox regression analyses.

RESULTS Transmural LGE was present in 5% (33/711) of patients and was enriched in *LMNA* and *DSP* variant carriers. Compared with nontransmural or absent LGE, transmural LGE was associated with higher rates of thromboembolic events, atrial fibrillation, and implantable cardioverter-defibrillator implantation (all $P \leq 0.003$). It also conferred increased rates of MVA events (45% vs 27% vs 14%) and AHF therapies (18% vs 12% vs 6%) ($P < 0.05$). In age-adjusted models, transmural LGE independently predicted the composite endpoint of MVA/AHF compared with nontransmural LGE (HR: 1.9; $P = 0.03$) and no LGE (HR: 2.9; $P = 0.0005$).

CONCLUSIONS Transmural LGE identifies a small but high-risk subset of genotype-positive ACM/DCM, particularly among patients with *LMNA* and *DSP* variants, with significantly increased arrhythmic and heart failure risk (JACC Clin Electrophysiol. 2026;■:■-■) © 2026 by the American College of Cardiology Foundation.

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**ABBREVIATION
AND ACRONYMS****ACM** = arrhythmogenic
cardiomyopathy**AHF** = advanced heart failure**CAD** = coronary artery disease**CMR** = cardiac magnetic
resonance**DCM** = dilated cardiomyopathy**ICD** = implantable
cardioverter-defibrillator**LGE** = late gadolinium
enhancement**LVEDVI** = left ventricular end-
diastolic volume index**LVEF** = left ventricular
ejection fraction**MVA** = major ventricular
arrhythmias**P/LP** = pathogenic or likely
pathogenic**RVEF** = right ventricular
ejection fraction**SCD** = sudden cardiac death**VT** = ventricular tachycardia**INTRODUCTION**

Genetic arrhythmogenic cardiomyopathy (ACM) and dilated cardiomyopathy (DCM) are increasingly recognized as part of a phenotypic continuum characterized by overlapping structural and electrical abnormalities. Advances in cardiac magnetic resonance (CMR) imaging and next-generation sequencing have demonstrated that left ventricular involvement is common in ACM, challenging the distinction between DCM and the traditionally right-sided ACM.¹ This evolving paradigm has been incorporated into recent European Society of Cardiology guidelines, which introduced the entity of nondilated left ventricular cardiomyopathy to capture left-dominant arrhythmogenic phenotypes better.²

Within this framework, the Padua criteria for left-dominant ACM define subepicardial or midmyocardial fibrosis as a major structural criterion essential for diagnosis. In contrast, the presence of transmural late gadolinium enhancement (LGE), traditionally

interpreted as indicative of ischemic myocardial injury, does not fulfill imaging criteria for ACM.³ This creates diagnostic uncertainty in genotype-positive patients with nonischemic cardiomyopathy who exhibit transmural scar patterns.

In parallel, arrhythmic risk stratification remains a major challenge, with left ventricular ejection fraction (LVEF) alone providing only limited discriminatory value in genetic ACM/DCM. By contrast, the presence, extent, and distribution of LGE have consistently been associated with ventricular arrhythmias, heart failure progression, and mortality in nonischemic DCM, and genotype-specific LGE patterns have been described.⁴⁻⁷

However, little is known about the presence and prognostic implications of transmural LGE in patients with genotype-positive, nonischemic cardiomyopathy, and whether it represents a distinct arrhythmogenic substrate with specific prognostic implications remains unclear.

METHODS

STUDY GROUP. In this retrospective study, we analyzed 1,379 genotype-positive patients with ACM/DCM evaluated at our institution to identify individuals with available CMR. All patients had confirmed pathogenic or likely pathogenic (P/LP) variants in cardiomyopathy-associated genes. The study

was conducted in accordance with the Institutional Review Board approval, and all patients provided informed consent for the use of their clinical data.

Phenotypic classification followed contemporary definitions. DCM was defined by left ventricular systolic dysfunction (LVEF $\leq 50\%$) with left ventricular dilation by CMR (defined as an increased LV end-diastolic volume index [ie, left ventricular end-diastolic volume index [LVEDVI] >96 mL/m² for female patients and >105 mL/m² for male patients])⁸ in the absence of abnormal loading conditions or significant coronary artery disease (CAD).¹ Significant CAD (ie, stenosis $\geq 50\%$ in any major epicardial vessel) was systematically ruled out by coronary angiography or coronary computed tomography angiography. Alternative causes of systolic dysfunction, such as active viral or sarcoid myocarditis, were also excluded. ACM with left ventricular involvement was defined according to current international consensus criteria. Patients with hypertrophic cardiomyopathy, ischemic cardiomyopathy, and potentially clinically significant CAD were excluded.^{9,10}

CMR IMAGING AND LGE ASSESSMENT. CMR studies were performed using standard clinical protocols on 1.5-T scanners. LGE imaging was acquired 8-10 minutes after intravenous administration of gadolinium-based contrast using inversion-recovery sequences with an individualized inversion time to null normal myocardium. Left ventricular and right ventricular volumes and function were measured using a standard volumetric technique from the cine short-axis stack¹¹ and indexed to body surface area. Regional wall motion abnormalities were visually assessed and described using a 17-segment model for the left ventricle.¹² In postcontrast images, the presence of LGE was defined by the identification of areas of increased signal intensity confirmed in 2 orthogonal planes or after phase/frequency direction swapping. LGE pattern was visually classified as subepicardial, intramyocardial, subendocardial, or transmural.¹³ Transmural LGE was defined as gadolinium enhancement extending through the full thickness of the myocardium. The nontransmural LGE group included patients with LGE limited to a subepicardial pattern, a midmyocardial pattern, or a combined subepicardial/midmyocardial pattern. Patients without detectable LGE were classified as LGE negative. LGE patterns were additionally analyzed according to the underlying gene. Subtle areas of LGE confined to the right ventricular insertion points were considered physiological and excluded from both septal and nonseptal LGE.¹⁴ The CMR closest to the first cardiac evaluation was used for the study.

CLINICAL AND GENETIC DATA. Demographic, genetic, imaging, and clinical data were extracted from the electronic medical record. Family history of cardiomyopathy and sudden cardiac death (SCD) was recorded when available. Alternative causes of systolic dysfunction, including active viral myocarditis and cardiac sarcoidosis, were assessed through review of the electronic medical record, including clinical diagnoses, CMR reports, nuclear imaging when performed, extracardiac sarcoidosis history, endomyocardial biopsy results when available, and documentation from the treating cardiologist. Patients were excluded when an alternative inflammatory cardiomyopathy was considered the primary diagnosis. Myocarditis-like or inflammatory “hot-phase” presentations were not considered exclusionary when occurring in the setting of a disease-causative P/LP variant in an ACM/DCM-associated gene because these episodes may represent part of the natural history of genetic cardiomyopathy.

Patients were classified as harboring P/LP variants, variants of uncertain significance, or negative genetic test results according to the American College of Medical Genetics and Genomics criteria.¹⁵ Only those with P/LP variants were included in the study.

STUDY ENDPOINTS. The primary study endpoint was a composite of major ventricular arrhythmias (MVAs) and advanced heart failure (AHF) events. MVAs included SCD, sustained ventricular tachycardia (VT), or appropriate implantable cardioverter-defibrillator (ICD) therapy. AHF events were defined as ventricular assist device placement, extracorporeal membrane oxygenation, cardiac transplant, or cardiac death. SCD was defined as witnessed sudden death with or without documented ventricular fibrillation, death within 1 hour of acute symptoms, or nocturnal death with no antecedent history of immediate worsening symptoms.¹⁶ Sustained VT was defined as VT lasting >30 seconds or VT causing hemodynamic instability. Appropriate ICD therapy was defined as a shock for termination of rapid (>185 beats/min) sustained VT or ventricular fibrillation.¹⁷

The date of the first cardiac evaluation was considered the baseline date. The end of follow-up was defined as the date of event adjudication or the date of the last available contact with the patient. When multiple events occurred, patients were censored at the time of the first event. Separate analyses were performed for MVA, AHF, and composite events.

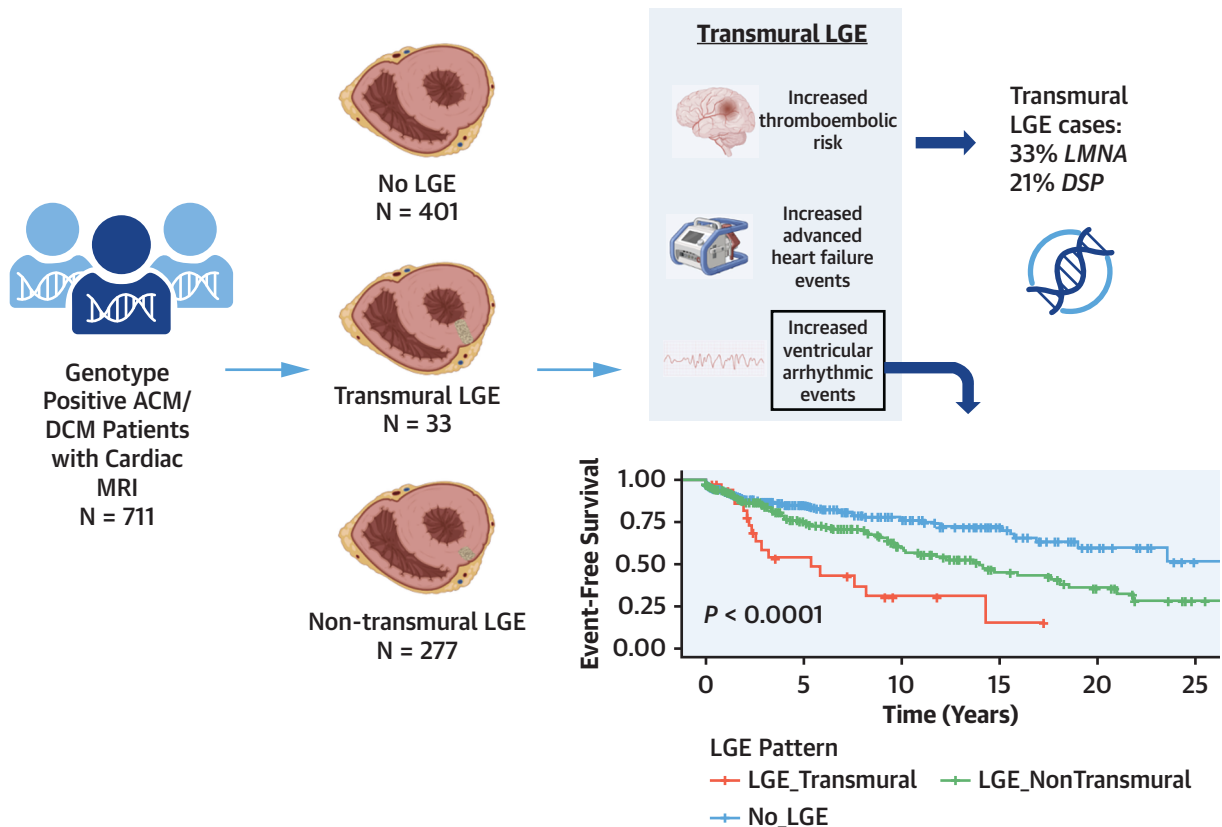
STATISTICAL ANALYSIS. Continuous variables are presented as mean $\pm$ SD and categorical variables as

counts and percentages. Baseline characteristics were compared across LGE pattern groups using appropriate parametric or nonparametric tests for continuous variables, with post hoc testing and chi-square or Fisher exact tests for categorical variables. Shapiro-Wilk tests were performed on the residuals of the analysis of variance, and if the residuals were non-normally distributed, Kruskal-Wallis tests were performed.

Time-to-event analyses were performed using Kaplan-Meier methods, with differences assessed by log-rank testing. Univariable Cox proportional hazards models were used to investigate the association of demographic variables, clinical parameters, and LGE pattern with the composite, MVA, and AHF endpoints. Additionally, multivariable Cox proportional hazards models were used to assess the independent association of LGE pattern with each endpoint, adjusting for age, sex, race, family history, other magnetic resonance imaging parameters, and atrial fibrillation. *DSP*- and *LMNA*-related cardiomyopathies were overrepresented among patients with transmural LGE. Adding genotype to the multivariable model was limited by the small sample sizes and the large number of different groups, which could lead to unstable estimates and overparameterization. To overcome these limitations and adjust for genotype as a confounding variable, a separate Cox proportional hazards regression model was generated in which *LMNA* and *DSP* were kept separate and compared with all the other genotypes combined, while also adjusting for the other covariates. Proportional hazards assumptions were assessed and met. A 2-sided *P* value <0.05 was considered statistically significant. Analyses were performed using RStudio (version 4.5.2), with visualization and plotting via ggplot2 (version 4.0.1) and survival analyses conducted using the survival package (version 3.8.3).

RESULTS

Of the 1,379 genotype-positive patients with ACM/DCM, 746 patients underwent CMR imaging, with 35 patients removed for having significant CAD or isolated subendocardial LGE, leaving a total of 711 patients (**Central Illustration**). Of the 711 patients, 33 (5%) transmural LGE, 277 (39%) had nontransmural LGE, and 401 (56%) had no LGE on their baseline CMR. Notably, of those with transmural LGE, the majority harbored a P/LP variant in *LMNA*-encoded lamin A/C (33%) or *DSP*-encoded desmoplakin (21%) (**Figure 1**). However, transmural LGE was observed in a minority of patients within each genotype group,

CENTRAL ILLUSTRATION Transmural Late Gadolinium Enhancement Identifies a High-Risk Phenotype in Genotype-Positive Arrhythmogenic and Dilated Cardiomyopathy

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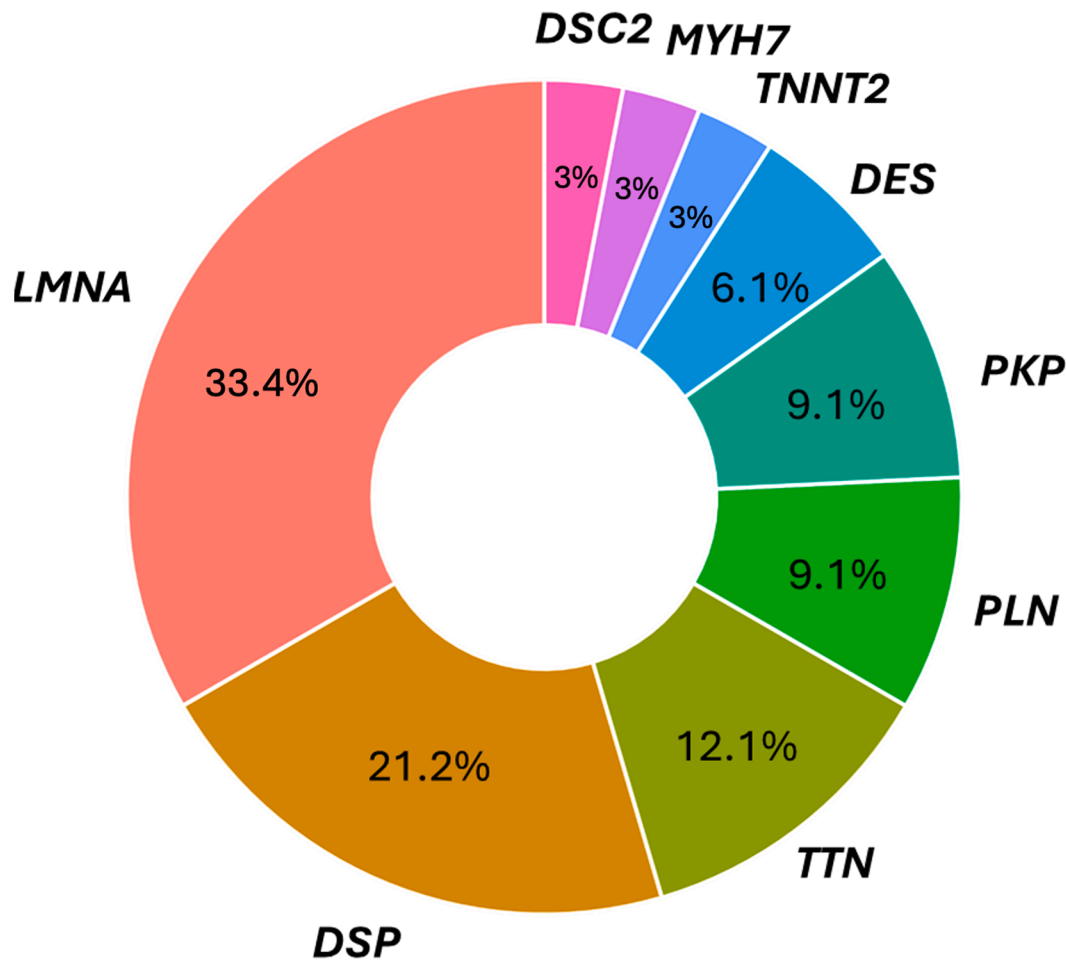
Comparison of 711 genotype-positive patients with ACM or DCM identified that 5% of patients have transmural LGE, which is associated with an increased risk of adverse events. ACM = arrhythmogenic cardiomyopathy; DCM = dilated cardiomyopathy; DSP = desmoplakin; LGE = late gadolinium enhancement; LMNA = lamin A/C; MRI = magnetic resonance imaging. Created with [BioRender.com](#).

specifically 11% of LMNA variant-positive patients and 7% of DSP variant-positive patients (Table 1).

Notably, the transmural LGE group had higher rates of thromboembolic events than the non-transmural and no-LGE groups (15% vs 11% vs 5%; $P = 0.003$; Table 2), ICD placement (82% vs 55% vs 32%; $P < 0.001$; Table 2), AHF events (18% vs 12% vs 6%; $P = 0.009$), and MVA events (45% vs 27% vs 14%; $P < 0.001$; Table 2). Interestingly, there were more male patients in the transmural LGE and non-transmural LGE groups compared to no-LGE group (64% vs 55% vs 45%; $P = 0.02$; Table 2). Additionally, LVEF ($P < 0.001$), right ventricular ejection fraction (RVEF) ($P < 0.001$), and LVEDVi ($P < 0.001$) differed across the 3 groups (Table 2). However, there were no differences in LVEF, RVEF, or LVEDVi between transmural the LGE and nontransmural LGE groups

with post hoc testing when directly compared. Age at baseline and follow-up time were not different across the groups. Kaplan-Meier analysis demonstrated significantly reduced event-free survival among patients with LGE compared with those without LGE (Figure 2A), with the poorest survival observed in patients with transmural LGE compared with those with non-transmural LGE or no LGE (Figure 2B).

Next, Cox proportional hazards regression was used to compare the risk of a composite endpoint of MVA or AHF events. Univariate analysis compared the no-LGE and nontransmural LGE groups with the transmural LGE group and demonstrated a lower risk in the no-LGE group (HR: 0.28; 95% CI: 0.16-0.49; $P < 0.00001$) and in the nontransmural LGE group (HR: 0.48; 95% CI: 0.28-0.82; $P = 0.007$) (Table 3). Multivariate analysis controlling for male sex, age at

FIGURE 1 Distribution of Transmural Late Gadolinium Enhancement According to Genotype

DES = desmin; DSC2 = desmocollin-2; DSP = desmoplakin; LMNA = lamin A/C; MYH7 = myosin heavy chain 7; PKP2 = plakophilin-2; PLN = phospholamban; TNNT2 = cardiac troponin T type 2; TTN = titin.

baseline, family history of SCD, family history of cardiomyopathy, atrial fibrillation, LVEF, RVEF, and left ventricular and right ventricular dilation demonstrated a lower risk in the nontransmural LGE group (HR: 0.53; 95% CI: 0.29-0.95; $P = 0.03$) and the no-LGE group (HR: 0.34; 95% CI: 0.18-0.62; $P = 0.0005$; [Table 3](#)) as compared with the transmural LGE group. Additionally, genotype was added to the multivariate model and demonstrated that, even when controlling for genotype and all other covariates, there was a lower risk for composite endpoint in the nonischemic LGE group compared with the transmural LGE group (HR: 0.54, 95% CI: 0.29-0.98; $P = 0.04$; [Supplemental Table 1](#)).

Univariate and multivariate analyses of MVA events continued to show an increased risk compared

with both the nontransmural LGE and no-LGE groups ([Table 4](#)). Multivariate analyses of LGE pattern for the risk of AHF events did not reach statistical significance for an increased risk in the transmural LGE group compared with the nontransmural LGE group. However, univariate analysis did show a decreased risk in the no-LGE group compared with the transmural LGE group (HR: 0.29; 95% CI: 0.12-0.71; $P = 0.007$) ([Table 5](#)).

DISCUSSION

In this large genotype-positive cohort of ACM/DCM, we demonstrate that a transmural LGE pattern is present in 5% of patients and identifies a distinct high-risk phenotype. Patients with transmural LGE

TABLE 1 Genotype Distribution Across CMR Groups

Genotype	No LGE	Transmural LGE	Nontransmural LGE	Total (N)
BAG3	4 (44.4%)	0 (0%)	5 (55.6%)	9
CDH2	5 (62.5%)	0 (0%)	3 (37.5%)	8
DES	1 (12.5%)	2 (25%)	5 (62.5%)	8
DMD	3 (25%)	0 (0%)	9 (75%)	12
DSC2	5 (62.5%)	1 (12.5%)	2 (25%)	8
DSG2	12 (70.6%)	0 (0%)	5 (29.4%)	17
DSP	38 (38.4%)	7 (7.1%)	54 (54.5%)	99
FLNC	22 (45.8%)	0 (0%)	26 (54.2%)	48
JUP	2 (100%)	0 (0%)	0 (0%)	2
LMNA	43 (43.4%)	11 (11.1%)	45 (45.5%)	99
MYBPC3	0 (0%)	0 (0%)	3 (100%)	3
MYH7	17 (89.5%)	1 (5.3%)	1 (5.3%)	19
PKP2	94 (75.2%)	3 (2.4%)	28 (22.4%)	125
PLN	9 (37.5%)	3 (12.5%)	12 (50%)	24
RBM20	29 (72.5%)	0 (0%)	11 (27.5%)	40
SCN5A	5 (83.3%)	0 (0%)	1 (16.7%)	6
TNNT2	5 (62.5%)	1 (12.5%)	2 (25%)	8
TTN	107 (60.8%)	4 (2.3%)	65 (36.9%)	176

LGE = late gadolinium enhancement.

exhibited substantially higher burdens of MVA events, AHF events, thromboembolic complications, and ICD implantation compared with patients with nontransmural LGE or no detectable LGE. Specifically, MVA occurred in 45.5% of patients with transmural LGE compared with 27.1% and 14.2% in those with nontransmural LGE and no LGE, respectively, whereas AHF events occurred in 18.2%, 11.6%, and 6.3% of patients in the 3 groups. Similarly,

thromboembolic events and atrial fibrillation were significantly more common in the transmural LGE group. Importantly, these adverse outcomes occurred despite similar ventricular functional parameters between the transmural and nontransmural LGE groups, suggesting that the transmural scar pattern reflects a particularly malignant myocardial substrate beyond conventional measures of ventricular dysfunction.

In patients with ACM/DCM, LGE positivity has been reported in approximately 35%-50% of patients in prior CMR studies,^{5,6,18-20} which is consistent with the 44% prevalence observed in our cohort. However, a transmural pattern remains uncommon. In our genetically characterized study group, transmural LGE was present in 5% of patients, underscoring that although rare, this phenomenon is observed in patients with nonischemic genetic cardiomyopathies. These findings extend the prognostic relevance of CMR tissue characterization beyond traditional non-transmural LGE patterns and challenge the assumption that transmural fibrosis is exclusive to CAD.

It is well known that the presence of LGE is associated with major arrhythmic events, providing incremental value over conventional risk stratifiers, such as LVEF, particularly in DCM.^{5,6,18,20} Prior studies have consistently shown that the presence and distribution of LGE confer important prognostic information in nonischemic cardiomyopathy. Halliday et al⁵ described a higher risk of SCD or aborted SCD in patients with DCM with septal LGE than those with nonseptal LGE locations. Di Marco et al⁶ found that

TABLE 2 Baseline Characteristics of the Cohort Comparing Those With Transmural LGE Pattern to Those With Nontransmural LGE Pattern and Those Without LGE

	Total (N = 711)	No LGE (n = 401)	Transmural LGE (n = 33)	Nontransmural LGE (n = 277)	P Value
Male, n (%)	354 (49.8)	182 (45.4)	21 (63.6)	151 (54.5)	0.02
Age at baseline, y, mean ± SD	40.29 ± 17.42	38.02 ± 17.92	40.81 ± 17.53	43.48 ± 16.20	0.0003
Caucasian, n (%)	655 (93.4)	367 (92.9)	30 (96.8)	258 (93.8)	0.8
Family history of SCD, n (%)	261 (36.7)	153 (38.2)	13 (39.4)	95 (34.3)	0.6
Family history of cardiomyopathy, n (%)	430 (60.5)	256 (63.8)	21 (63.6)	153 (55.2)	0.07
History of thromboembolic event, n (%)	55 (7.9)	20 (5.1)	5 (15.2)	30 (11.4)	0.003
AF, n (%)	216 (30.4)	94 (23.4)	15 (45.5)	107 (38.6)	<0.00001
ICD, n (%)	307 (43.2)	127 (31.7)	27 (81.8)	153 (55.2)	<0.00001
Advanced heart failure events, n (%)	62 (8.9)	25 (6.3)	6 (18.2)	31 (11.6)	0.009
Major ventricular arrhythmic events, n (%)	146 (20.7)	56 (14.2)	15 (45.5)	75 (27.1)	<0.00001
LVEDVi, mL/m ² , mean ± SD	89.74 ± 33.80	85.21 ± 29.63	103.05 ± 32.71	94.53 ± 38.21	0.0003
LVEF, %, mean ± SD	47.40 ± 15.09	51.20 ± 13.74	39.77 ± 15.14	42.87 ± 15.40	<0.00001
RVEDVi, mL/m ² , mean ± SD	83.56 ± 27.08	82.84 ± 25.41	90.14 ± 32.14	83.79 ± 28.71	0.3
RVEF, %, mean ± SD	46.94 ± 11.90	49.23 ± 10.89	42.13 ± 12.80	44.13 ± 12.46	<0.00001
Composite follow-up time, y, mean ± SD	5.47 ± 5.96	5.41 ± 6.08	4.11 ± 4.32	5.72 ± 5.95	0.3

P value comparing across all 3 groups.

AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death.

the combination of septal and free-wall LGE conferred a higher risk of MVA than both isolated septal and isolated free-wall LGE. de Frutos et al²¹ described the LGE distribution according to genotype and the risk of MVA in a large multicenter cohort of patients with DCM. Septal LGE was associated with a 3.4-fold unadjusted increased risk of MVA or SCD, compared with a 1.9-fold unadjusted increased risk for free-wall LGE. After adjusting for other clinical and instrumental significant features, septal LGE location remained an independent predictor of MVA or SCD.

However, there are no studies that have specifically focused on the presence and prognostic role of transmural LGE in a well-phenotyped ACM/DCM genetic cohort. Our findings therefore extend this literature by demonstrating that transmural LGE represents the most adverse imaging phenotype within genetically mediated cardiomyopathy.

The mechanisms underlying transmural LGE in genetic cardiomyopathy remain speculative. Although transmural LGE classically raises concern for ischemic injury, including the possibility of prior embolic myocardial infarction, this explanation appears unlikely in our cohort, given the absence of a consistent clinical substrate, and potential explanations include progressive replacement fibrosis driven by chronic mechanical stress and cumulative myocardial injury in advanced disease. Regardless of mechanism, the strong association between transmural LGE and MVA supports its role as a clinically meaningful arrhythmogenic substrate.

In our cohort, transmural LGE was observed across multiple cardiomyopathy-associated genes but appeared enriched in patients harboring P/LP variants in *LMNA* and *DSP*, which together accounted for more than half of transmural cases. Although the absolute prevalence of transmural LGE remained relatively low within individual genotypes (11% of the patients with *LMNA* variants and 7% of patients with *DSP* variants), these genes are well known to be associated with aggressive arrhythmogenic phenotypes characterized by myocardial fibrosis, ventricular arrhythmias, and progressive myocardial dysfunction. The presence of transmural scar in these patients may therefore reflect a particularly advanced stage of replacement fibrosis or a variant-specific pattern of myocardial fibrosis, such as the distinctive fibrosis phenotype recently described in *LMNA* missense variants involving the C-terminal immunoglobulin-like domain.²²

CLINICAL IMPLICATIONS. Our findings also have important implications for the interpretation of CMR within current diagnostic frameworks. According to

TABLE 3 Univariable and Multivariable Analysis for the Composite Primary Endpoint of Major Ventricular Arrhythmias and Advanced Heart Failure Events in the Overall Cohort

	Univariable		Multivariable	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Male	1.36 (1.00-1.85)	0.05	0.87 (0.60-1.3)	0.5
Family history of SCD	0.68 (0.48-0.95)	0.02	0.85 (0.55-1.32)	0.5
Family history of cardiomyopathy	0.61 (0.45-0.82)	0.001	0.70 (0.47-1.04)	0.08
AF	1.46 (1.08-1.98)	0.02	1.25 (0.87-1.80)	0.2
LVEF	0.97 (0.96-0.98)	<0.00001	0.99 (0.97-1.02)	0.6
LVEDVi	1.01 (1.00-1.01)	0.0006	0.99 (0.99-1.00)	0.3
RVEF	0.96 (0.94-0.97)	<0.00001	0.97 (0.95-0.99)	0.002
RVEDVi	1.01 (1.01-1.02)	<0.00001	1.01 (1.00-1.02)	0.02
Nontransmural LGE ^a	0.48 (0.28-0.82)	0.007	0.53 (0.29-0.95)	0.03
No LGE ^a	0.28 (0.16-0.49)	<0.00001	0.34 (0.18-0.62)	0.0005
Age at baseline	1.00 (0.99-1.01)	0.7	1.00 (0.98-1.01)	0.4

^aIn the same model, LGE pattern was compared to transmural LGE.

AF = atrial fibrillation; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death.

the Padua criteria, myocardial fibrosis with a sub-epicardial or midmyocardial LGE pattern is considered a major left ventricular structural criterion, whereas transmural LGE is not included among the diagnostic criteria. Consequently, genotype-positive patients presenting with isolated transmural LGE could be considered Padua negative and may not receive a formal diagnosis of ACM under the Padua criteria despite having an inherited ACM substrate.

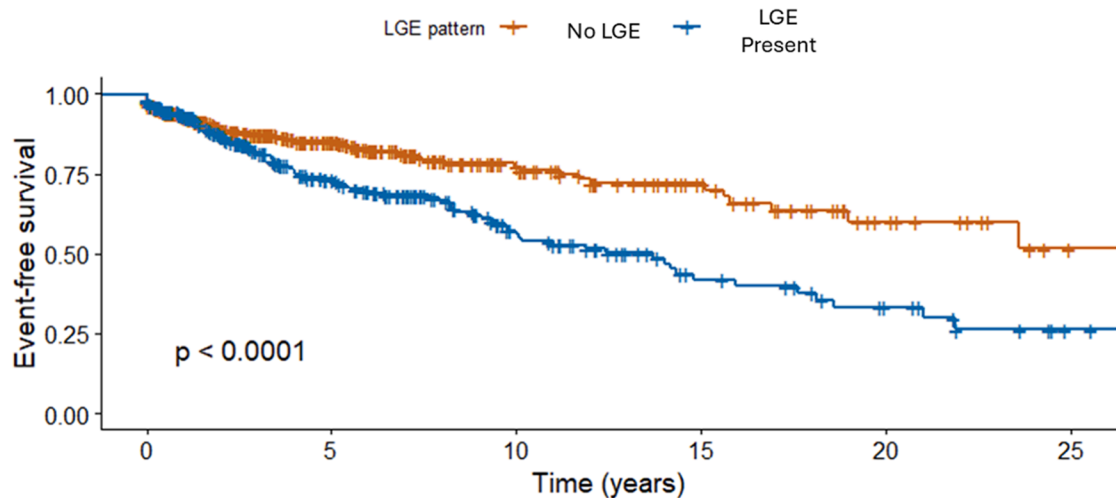
Our data suggest that transmural LGE may represent a severe fibrosis phenotype within genetic ACM/DCM, highlighting the limitations of considering only subepicardial and midmyocardial LGE patterns in the diagnostic framework. Importantly, patients with

TABLE 4 Univariable and Multivariable Analysis for the Primary Endpoint of Major Ventricular Arrhythmias in the Overall Study Group

	Univariable		Multivariable	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Male	1.36 (0.98-1.89)	0.06	0.93 (0.62-1.39)	0.9
Family history of SCD	0.66 (0.46-0.95)	0.03	0.76 (0.47-1.22)	0.3
Family history of cardiomyopathy	0.59 (0.43-0.82)	0.001	0.68 (0.44-1.04)	0.08
AF	1.49 (1.07-2.06)	0.02	1.25 (0.84-1.85)	0.3
LVEF	0.98 (0.96-0.99)	<0.00001	1.00 (1.00-1.02)	0.8
LVEDVi	1.01 (1.00-1.01)	0.003	1.00 (0.99-1.01)	0.6
RVEF	0.96 (0.94-0.97)	<0.00001	0.96 (0.94-0.99)	0.001
RVEDVi	1.01 (1.01-1.02)	<0.00001	1.01 (0.99-1.02)	0.06
Nontransmural LGE ^a	0.46 (0.26-0.80)	0.006	0.47 (0.25-0.86)	0.02
No LGE ^a	0.25 (0.14-0.44)	<0.00001	0.28 (0.15-0.54)	0.0001
Age at baseline	1.00 (0.99-1.01)	0.5	1.00 (0.99-1.01)	0.7

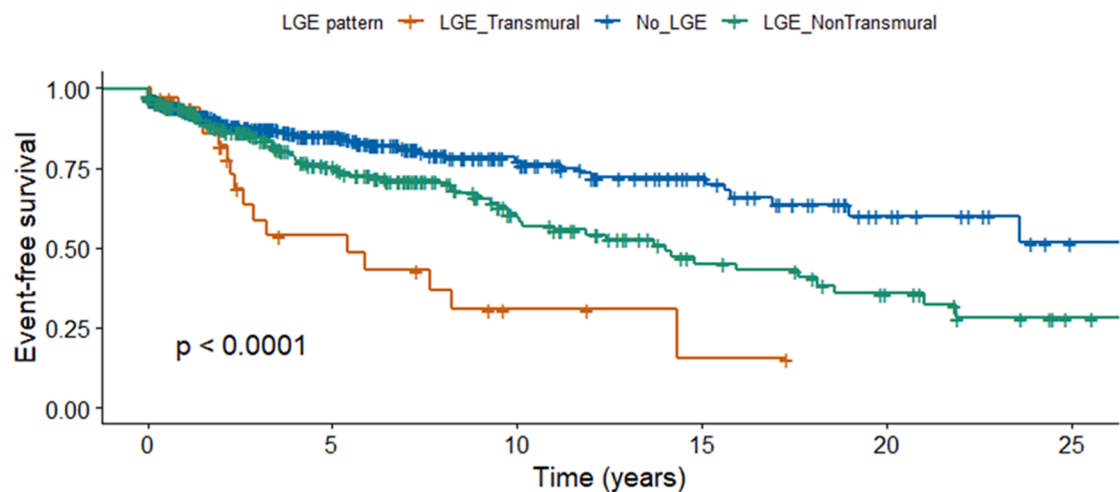
^aIn the same model, LGE pattern was compared to transmural LGE.

AF = atrial fibrillation; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death.

FIGURE 2 Kaplan-Meier Curves for the Composite Endpoint**A**

Number at risk

—	401	156	69	37	14	3
—	309	123	51	23	12	2

B

Number at risk

—	33	10	3	1	0	0
—	401	156	69	37	14	3
—	276	113	48	22	12	2

Kaplan-Meier curves for the occurrence of the composite endpoint (sudden cardiac death, major ventricular arrhythmias, or heart failure) according to the presence (A) and location (B) of LGE in the overall study group. LGE = late gadolinium enhancement.

TABLE 5 Univariable and Multivariable Analysis for the Primary Endpoint of Advanced Heart Failure in the Overall Study Group

	Univariable		Multivariable	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Male	1.00 (0.60-1.67)	0.9	0.55 (0.28-1.10)	0.09
Family history of SCD	1.19 (0.70-2.02)	0.5	2.16 (1.02-4.60)	0.05
Family history of cardiomyopathy	0.85 (0.51-1.41)	0.5	0.58 (0.28-1.22)	0.2
AF	1.64 (0.99-2.72)	0.06	1.13 (0.58-2.20)	0.7
LVEF	0.95 (0.93-0.97)	<0.00001	0.96 (0.93-0.99)	0.03
LVEDVi	1.01 (1.01-1.02)	<0.00001	1.00 (0.99-1.01)	0.5
RVEF	0.96 (0.94-0.98)	0.0005	1.00 (0.96-1.04)	0.8
RVEDVi	1.01 (1.00-1.02)	0.02	1.01 (0.99-1.02)	0.3
Nontransmural LGE ^a	0.42 (0.17-1.02)	0.06	0.47 (0.17-1.33)	0.2
No LGE ^a	0.29 (0.12-0.71)	0.007	0.34 (0.11-1.02)	0.06
Age at baseline, y	1.00 (0.99-1.02)	0.9	0.99 (0.97-1.01)	0.4

^aIn the same model, LGE pattern was compared to transmural LGE.

AF = atrial fibrillation; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death.

transmural LGE demonstrated markedly higher rates of MVA and AHF, suggesting that this imaging pattern may identify a particularly high-risk phenotype that could benefit from closer surveillance and consideration of primary prevention ICD therapy.

STUDY LIMITATIONS. As with all observational studies, our analysis is subject to limitations inherent to its retrospective design. Additionally, there is potential selection bias because only those with available CMR imaging were included in this study. Patients with LGE were more likely to have ICDs implanted and thus may have been more likely to have subclinical or asymptomatic arrhythmias detected, which would have been missed in patients without an ICD. LGE pattern classification was based on visual assessment and may therefore be subject to interobserver variability. In addition, although patients with significant CAD were excluded, unrecognized microvascular ischemia cannot be completely excluded. However, among the 5 patients with transmural LGE and thromboembolic events, none had atrial fibrillation before the event, and 4 of the 5 had LV thrombus adjacent to the apical transmural scar at the time of the event, supporting scar-associated thrombus formation rather than antecedent cardioembolism as the likely mechanism. Importantly, transmural LGE may reflect both a distinct scar pattern and a greater overall fibrosis burden; therefore, the increased event rate may be mediated in part by scar extent rather than transmural LGE alone. Finally, the relatively small number of patients with transmural LGE limits the power of gene-specific subgroup analyses and increases the risk of overfitting in the multivariable regression model.

CONCLUSIONS

In a large genotype-positive cohort of ACM and DCM, transmural LGE was present in 5% of patients and identified a distinct high-risk phenotype characterized by markedly increased ventricular arrhythmic events and adverse clinical outcomes. These findings challenge the traditional assumption that transmural fibrosis is exclusively ischemic and highlight the importance of careful interpretation of CMR tissue patterns in patients with genetically mediated cardiomyopathy. Prospective multicenter studies will be needed to validate these observations and determine whether transmural LGE should be incorporated into future diagnostic and risk stratification frameworks.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Transmural LGE, traditionally considered ischemic, can occur in genotype-positive ACM/DCM and identifies a high-risk phenotype with increased arrhythmic and heart failure events.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Recognition of transmural LGE in nonischemic ACM/DCM should prompt closer monitoring and consideration of earlier preventive strategies, particularly in patients with *LMNA* and *DSP* variants.

COMPETENCY IN PRACTICE-BASED LEARNING: This study highlights the need for clinicians to critically

re-evaluate conventional interpretations of LGE patterns, recognizing that transmural LGE in genotype-positive patients may represent a high-risk nonischemic substrate rather than prior infarction.

TRANSLATIONAL OUTLOOK: Prospective multicenter studies are needed to validate transmural LGE as an independent risk marker in nonischemic ACM/DCM and define its added value over existing models, particularly in *LMNA* and *DSP* cardiomyopathies. Mechanistic studies should clarify its basis, and integration into clinical frameworks may improve the timing of ICD implantation and heart failure therapies.

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KEYWORDS genetic cardiomyopathy, genotype-phenotype correlation, LGE

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