ESC European Heart Journal - Cardiovascular Imaging (2026) **00**, 1–11
https://doi.org/10.1093/ehjci/jeag150

ORIGINAL PAPER

Left atrial reservoir strain for predicting progression to end-stage in hypertrophic cardiomyopathy

Soongu Kwak[1,2], Min-Ha Jeong[1,2], Chan Soon Park[1,2], Hyun-Jung Lee[1,2], Jun-Bean Park [1,2], Seung-Pyo Lee [1,2], Yong-Jin Kim [1,2], Andrew Wang [3], and Hyung-Kwan Kim [1,2]*

[1]Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea; [2]Division of Cardiology, Cardiovascular Center, Seoul National University Hospital, Seoul, Republic of Korea; and [3]Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA

Received 13 March 2026; revised 26 May 2026; accepted 3 June 2026; online publish-ahead-of-print 16 June 2026

Aims End-stage hypertrophic cardiomyopathy (HCM), defined as a left ventricular (LV) ejection fraction (LVEF) < 50%, is associated with poor prognosis; however, predictors of progression remain unclear. We aimed to identify prognostic factors for progression to end-stage HCM.

Methods and results We analysed 925 patients with HCM between 2007 and 2023 who underwent ≥1 year of follow-up echocardiography. The primary outcome was progression to end-stage HCM, defined as an LVEF <50% without reversible causes. A cardiovascular magnetic resonance (CMR) subcohort included 491 patients with baseline CMR. During a median follow-up of 6.5 years (interquartile range: 3.3–10.7), 35 patients (3.8%) progressed to end-stage HCM [10-year cumulative incidence: 4.4%, 95% confidence interval (CI): 2.5–6.2%]. LVEF, LV apical aneurysm, and left atrial (LA) reservoir strain (LARS) were independent predictors of progression to end-stage HCM [per 1% decrease in LARS: adjusted hazard ratio (HR) 1.10, 95% CI 1.04–1.17, $P < 0.001$], and impaired LARS (<16.9%) was associated with a higher risk. In the CMR subcohort, LARS remained an independent predictor after adjusting for late gadolinium enhancement (LGE%) (adjusted HR 1.11, 95% CI 1.02–1.20, $P = 0.011$). Adding LARS to a model including LVEF, LV apical aneurysm, and LA size yielded significant incremental prognostic value (global χ^2 27.1 to 40.1; $P < 0.001$). Similar incremental value was observed in models including LGE % in the CMR subcohort. After progression to end-stage HCM, prognosis was poor, with 2-year cardiovascular event–free survival rate of 71.0%.

Conclusion Progression to end-stage HCM is infrequent but associated with poor prognosis. Impaired LARS independently predicts disease progression beyond conventional markers, supporting its role in risk stratification.

* Corresponding author. E-mail: cardiman73@gmail.com

Structured Graphical Abstract

Key Question

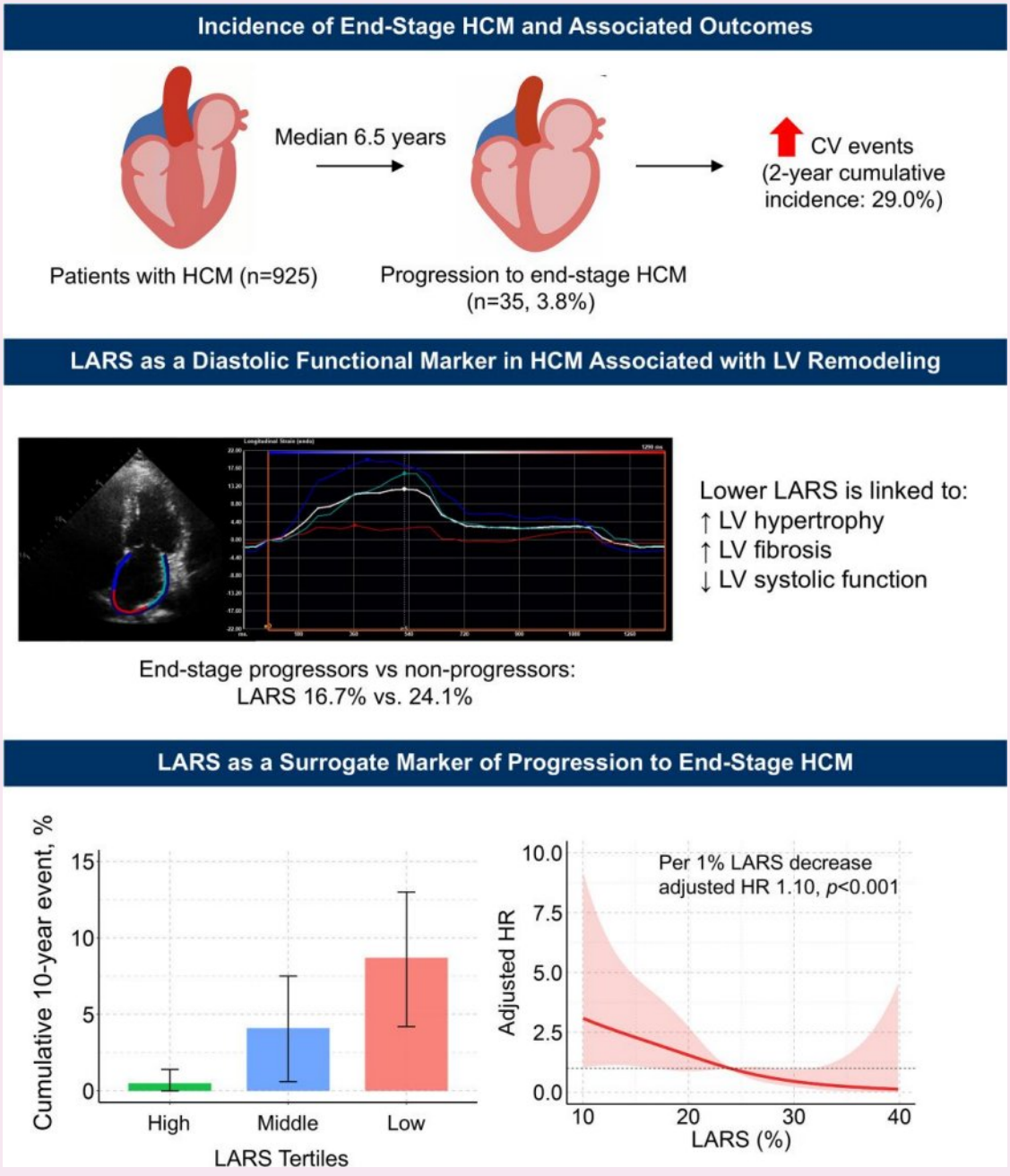
Which imaging markers, including left atrial reservoir strain (LARS), predict progression to end-stage hypertrophic cardiomyopathy (HCM)?

Key Finding

During a median follow-up of 6.5 years, progression to end-stage HCM occurred in 3.8% of patients. Impaired LARS independently predicted progression to end-stage HCM with incremental prognostic value beyond left ventricular (LV) ejection fraction (LVEF), LV apical aneurysm, and late gadolinium enhancement, supporting its role as an important prognostic marker.

Take-home Message

Impaired LARS identifies patients with HCM at higher risk of progression to end-stage HCM before LVEF declines. Incorporating LARS into routine imaging evaluation may enable improved risk stratification, closer surveillance, and more personalized management.



Keywords hypertrophic cardiomyopathy • echocardiography • myocardial contraction • heart failure

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy.[1,2] Although left ventricular (LV) systolic function is typically normal or even supranormal in the early phase of HCM,[3] adverse cardiac remodelling develops over time, ultimately leading to a decline in LV ejection fraction (LVEF).[4,5] A small but clinically important subset of patients progresses to an end-stage phase, defined by LVEF <50%, which confers a markedly increased risk of adverse outcomes, including sudden cardiac death (SCD).[6,7] Despite its grave prognoses, data on the incidence and risk factors for progression to end-stage HCM remain limited, partly because such events are relatively infrequent and require long-term follow-up to capture.[8–10]

Myocardial strain analysis has emerged as a valuable tool for risk stratification in HCM.[11–13] In particular, left atrial (LA) reservoir strain (LARS) reflects LA deformation and may provide a more sensitive measure of LV filling pressure than conventional assessments.[14,15] It has been shown to predict heart failure and SCD in HCM.[16,17] Therefore, LARS may serve as a novel surrogate marker to identify patients at risk of progression to end-stage HCM.

This study aimed to investigate the risk factors associated with the progression to end-stage HCM using a large echocardiographic database, with a particular focus on the predictive role of LARS in the identification of high-risk patients.

Methods

Study design

This study included consecutive patients diagnosed with HCM between 2007 and 2023 at a tertiary referral centre, Seoul National University Hospital (Seoul, Republic of Korea). The diagnosis of HCM was established by a comprehensive evaluation of imaging, clinical, and genetic/familial information, with a maximal LV wall thickness ≥15 mm on echocardiography or cardiovascular magnetic resonance (CMR). A more lenient criterion (e.g. ≥13 mm) was applied in patients with a family history of HCM or genetic confirmation. Other causes of LV hypertrophy, including hypertensive heart disease, cardiac amyloidosis, and Fabry disease, were excluded.

Among 1403 patients with HCM initially screened, those with baseline LVEF ≤50% were excluded (*Figure 1*). Patients were required to have follow-up echocardiography beyond 1 year, and those who experienced progression to end-stage HCM within the first year from baseline were excluded to ensure a wash-out period. Additional exclusion criteria included prior open-heart surgery (including myectomy) and end-stage kidney disease.

This study was approved by the Institutional Review Board of Seoul National University Hospital and conducted in accordance with the Declaration of Helsinki. The need for written informed consent was waived due to the retrospective design and use of anonymized data.

Clinical variables and CMR

Baseline echocardiography was defined as the first echocardiography performed to establish the diagnosis of HCM. The last follow-up echocardiography was defined as (i) the last available study in patients without progression to end-stage HCM or (ii) the first echocardiographic study that identified progression to end-stage HCM after exclusion of transient or reversible causes of LVEF reduction. The median number of echocardiographic examinations, including baseline and last follow-up studies, was 4 [interquartile range (IQR) 3–6], with a median interval of 1.5 years between examinations. The 5-year SCD risk was estimated using the HCM Risk-SCD score according to the European guidelines.[18] The maximal LV outflow tract gradient was assessed at rest or during the Valsalva manoeuvre. Obstructive HCM was defined as a maximal LV outflow tract gradient ≥30 mmHg.

Of the entire cohort, 491 patients underwent baseline CMR evaluation and constituted the CMR subcohort for analyses incorporating late gadolinium enhancement (LGE). CMR was performed using 1.5-T or 3.0-T scanners. LGE imaging was acquired in long- and short-axis views using a phase-sensitive inversion recovery sequence 10 to 15 min after contrast administration. LGE was quantified semi-automatically (cvi42, Circle Cardiovascular Imaging, Calgary, Canada) using a threshold of ≥6 standard deviations above that of remote reference myocardium and expressed as a percentage of LV myocardial mass (LGE%).[19] An LV apical aneurysm was defined as an akinetic or dyskinetic thinned segment in the LV apex, confirmed by standard echocardiography, contrast echocardiography, or CMR.

Myocardial strain analysis

The LV global longitudinal strain (LV-GLS) and LARS were analysed using vendor-independent software (Imaging Arena 4.6; TomTec Imaging Systems, Munich, Germany), as previously described.[11–13,16] LARS was obtained by tracing the LA border at end-systole in a non-foreshortened apical four-chamber view and tracking its deformation over the cardiac cycle to construct the strain curve.[16] In patients with atrial fibrillation (AF), strain values were averaged over three consecutive cardiac cycles. The excellent reproducibility of LV-GLS and LARS has been previously reported.[16,20] LV-GLS and LARS data were available in 94.8% and 98.6% of patients, respectively.

Outcome assessment

The primary outcome was progression to end-stage HCM, defined as an LVEF <50% occurring after the baseline echocardiography in the absence of reversible causes (e.g. AF with rapid ventricular response). Follow-up echocardiography was performed at the discretion of HCM-specialized physicians, and all serial studies were comprehensively reviewed. Transient reduction in LVEF that recovered on subsequent echocardiography was not classified as progression to end-stage HCM. Similarly, reductions in LVEF due to myocardial infarction or following surgical myectomy, alcohol septal ablation, or treatment with mavacamten were not considered progression to end-stage HCM. Echocardiographic follow-up duration was defined as the interval from baseline to the last follow-up echocardiography.

To evaluate the prognostic significance of end-stage HCM, the secondary outcome was defined as a composite of cardiovascular (CV) events, including CV death (including SCD), aborted SCD, and appropriate implantable cardioverter–defibrillator (ICD) shock. For non-progressors, follow-up duration was from baseline echocardiography to the last clinical visit or CV event. For progressors, follow-up duration was from the echocardiography that first identified end-stage HCM to a CV event or the last follow-up, reflecting prognosis after transition to end-stage HCM. Outcome events were adjudicated using electronic medical records, national death registry data, and, when available, reports from family members.

Statistical analysis

Continuous variables are summarized as medians with interquartile ranges (IQRs), and categorical variables are presented as counts with percentages. Group differences were assessed using the Mann–Whitney U test or Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables. Associations between the risk factors and outcomes were examined using Cox proportional hazards regression, with results expressed as hazard ratios (HRs)

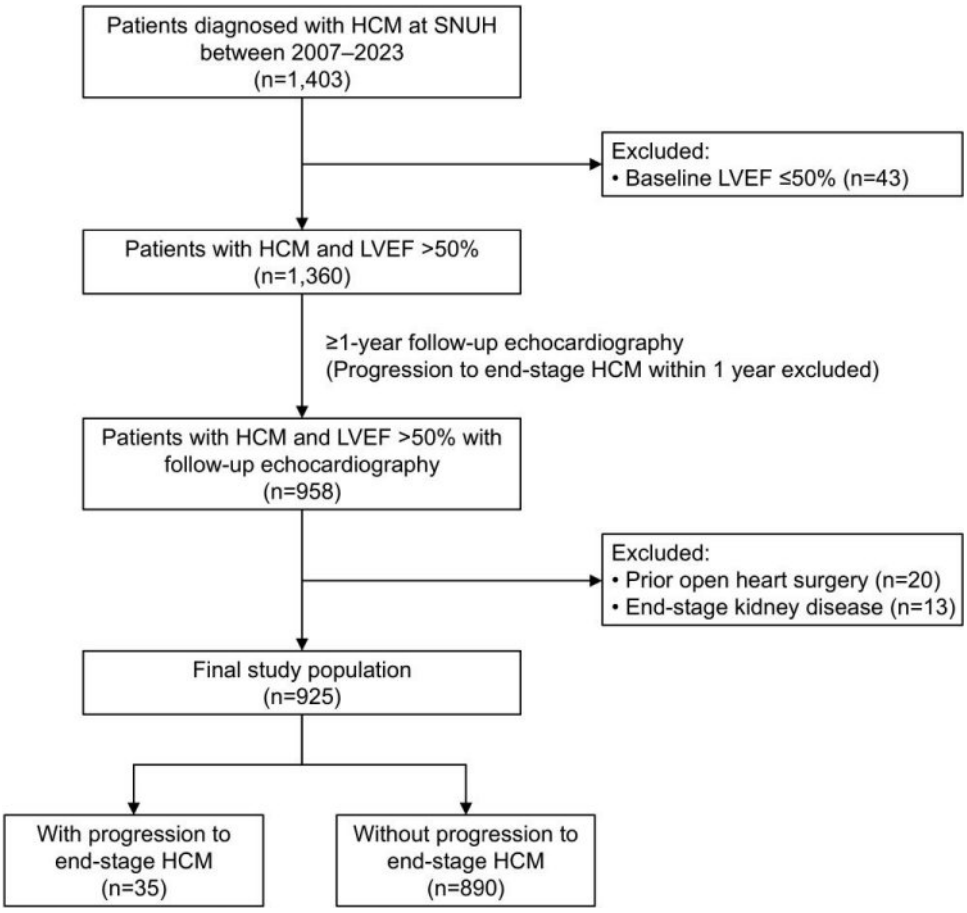


Figure 1 Patient selection flowchart. HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction.

and 95% confidence intervals (CIs). Multivariable models included age and variables with significance in univariable analyses, while also considering clinical relevance to HCM. For the CMR subcohort, multivariable models were constructed to incorporate LGE%. Given the limited number of events in this cohort, more parsimonious models were used, including variables identified as independent predictors in the entire cohort (LVEF, LV apical aneurysm, and LARS), with additional adjustment for LGE%. Proportional hazards assumptions were tested using Schoenfeld residuals. Firth penalized Cox regression analyses were additionally performed. Kaplan–Meier survival curves were generated and compared using log-rank tests. The LARS cutoff value was determined by maximally selected rank statistics. The incremental predictive value of LARS was assessed by comparing nested Cox models with the likelihood ratio χ^2 test. In patients with progression to end-stage HCM, changes in echocardiographic parameters were compared using the paired Wilcoxon signed-rank test. All analyses were performed using R (version 4.5.0). Statistical significance was defined as a two-sided *P*-value of <0.05.

Results

Cohort characteristics

The study cohort comprised 925 patients with HCM. During a median echocardiographic follow-up of 6.5 years (IQR, 3.3–10.7 years), 35 patients (3.8%) progressed to end-stage HCM. The 10-year cumulative incidence was 4.4% (95% CI, 2.5–6.2%), corresponding to 5.2 events per 1000 person-years. Patients with progression to end-stage HCM had higher HCM Risk-SCD scores, lower LVEF, larger LA size, and more prevalent apical aneurysms (*Table 1*). LARS was significantly lower in the progressors than in the non-progressors (16.7% vs. 24.1%, $P < 0.001$).

The CMR subcohort included 491 patients who underwent baseline CMR, among whom 17 (3.5%) progressed to end-stage HCM. Patients in the CMR subcohort were younger and had a higher prevalence of family history of HCM and higher HCM Risk-SCD scores compared with those without baseline CMR (see Supplementary data online, *Table S1*). In this subcohort, LGE% was greater in patients who progressed to end-stage HCM (16.8% vs. 3.1%, $P < 0.001$) (*Table 1*).

Risk factors for progression to end-stage HCM

The univariable Cox analysis for progression to end-stage HCM is shown (see Supplementary data online, *Table S2*). Advanced symptoms, HCM Risk-SCD score, LVEF, LA dimension and volume index, LARS, LGE%, non-apical HCM, and LV apical aneurysm were significantly associated with progression to end-stage HCM.

Table 1 Baseline characteristics of the study population according to progression to end-stage HCM

Variable	Entire cohort (*n* = 925)	With progression to end-stage HCM (*n* = 35)	Without progression to end-stage HCM (*n* = 890)	*P*
Age, years	62 (53–70)	61 (48–71)	62 (53–70)	0.371
Male	614 (66.4)	20 (57.1)	594 (66.7)	0.319
Body mass index, kg/m^2	24.7 (22.9–26.7)	24.2 (23.0–26.5)	24.7 (22.9–26.7)	0.848
SBP, mmHg	127 (117–137)	120 (110–128)	127 (118–137)	0.011
DBP, mmHg	75 (69–81)	71 (67–80)	75 (69–81)	0.308
HR, bpm	66 (59–76)	66 (56–75)	66 (59–76)	0.674
NYHA functional class ≥III	57 (6.2)	4 (11.4)	53 (6.0)	0.344
Family history of HCM	83 (9.0)	6 (17.1)	77 (8.7)	0.116
Family history of SCD	76 (8.2)	7 (20.0)	69 (7.8)	0.023
Non-sustained VT[a]	163 (25.1)	13 (44.8)	150 (24.2)	0.022
Syncope	127 (13.7)	6 (17.1)	121 (13.6)	0.728
HCM Risk-SCD score, %[b]	1.8 (1.3–2.8)	2.6 (1.7–4.8)	1.8 (1.3–2.8)	0.005
HCM Risk-SCD categories[b]				0.005
Low (<4%)	798 (86.6)	24 (68.6)	774 (87.3)	
Intermediate (4–6%)	75 (8.1)	6 (17.1)	69 (7.8)	
High (≥6%)	49 (5.3)	5 (14.3)	44 (5.0)	
ICD at baseline	6 (0.6)	0 (0.0)	6 (0.7)	>0.99
Comorbidities				
Hypertension	460 (49.7)	8 (22.9)	452 (50.8)	0.002
Diabetes mellitus	178 (19.2)	3 (8.6)	175 (19.7)	0.157
Dyslipidaemia	281 (30.4)	7 (20.0)	274 (30.8)	0.241
Atrial fibrillation	165 (17.8)	7 (20.0)	158 (17.8)	0.908
Echocardiography at baseline				
LV end-diastolic diameter, mm	47.0 (43.0–50.0)	48.0 (43.5–50.0)	47.0 (43.0–50.0)	0.676
LV end-systolic diameter, mm	28.0 (25.0–31.0)	29.0 (24.0–32.0)	28.0 (25.0–30.0)	0.279
LVEF, %	64.0 (60.0–68.0)	60.0 (57.0–67.0)	64.0 (60.0–68.0)	0.022
Maximal wall thickness, mm	18.0 (16.0–20.0)	19.0 (16.0–22.1)	18.0 (16.0–20.0)	0.231
LA dimension, mm	44.0 (40.0–49.0)	51.0 (43.0–53.0)	44.0 (40.0–49.0)	<0.001
LA volume index, mL/m^2	42.7 (33.0–54.9)	48.3 (43.4–67.6)	42.2 (32.9–54.5)	0.022
Septal *e′*-wave, cm/s	4.6 (3.7–5.8)	4.2 (3.4–5.3)	4.6 (3.8–5.8)	0.322
E/*e′* ratio	12.5 (10.0–16.7)	13.6 (10.0–17.0)	12.5 (10.0–16.7)	0.451
TR peak velocity, m/s	2.3 (2.2–2.5)	2.3 (2.0–2.5)	2.3 (2.2–2.5)	0.269
Peak LVOT gradient, mmHg	5.8 (4.0–10.5)	4.7 (3.0–7.8)	5.9 (4.0–10.8)	0.015
Obstructive HCM	133 (14.4)	2 (5.7)	131 (14.7)	0.211
LV-GLS, %	−14.3 (−17.4−−11.6)	−13.6 (−17.1−−10.0)	−14.3 (−17.5−−11.7)	0.358
LARS, %	23.9 (17.9–29.4)	16.7 (13.8–22.8)	24.1 (18.2–29.5)	<0.001
Apical HCM	410 (44.3)	5 (14.3)	405 (45.5)	0.001
LV apical aneurysm	78 (8.4)	7 (20.0)	71 (8.0)	0.028
LGE%[c]	3.4 (0.8–8.5)	16.8 (7.0–24.6)	3.1 (0.8–7.9)	<0.001
LGE% ≥ 15%[c]	56 (11.4)	9 (52.9)	47 (9.9)	<0.001
Mavacamten at baseline	1 (0.1)	0 (0.0)	1 (0.1)	>0.99

[a]Available in 70.2% of patients.
[b]HCM Risk-SCD score was unavailable in three patients.
[c]Comparison in the CMR subcohort (*n* = 491).
bpm, beats per minute; HCM, hypertrophic cardiomyopathy; HR, heart rate; ICD, implantable cardioverter-defibrillator; LA, left atrial; LARS, left atrial reservoir strain; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LV-GLS, left ventricular global longitudinal strain; NYHA, New York Heart Association; S(D)BP, systolic (diastolic) blood pressure; SCD, sudden cardiac death; VT, ventricular tachycardia.

Table 2 Risk factors for progression to end-stage HCM

	Univariable analysis		Multivariable model A		Multivariable model B	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, years	1.00 (0.98–1.03)	0.779	0.99 (0.96–1.02)	0.559	–	–
NYHA ≥III	2.99 (1.05–8.54)	0.040	1.43 (0.46–4.41)	0.533	1.86 (0.62–5.60)	0.268
Family history of HCM	2.29 (0.94–5.58)	0.069	–	–	2.06 (0.80–5.27)	0.133
HCM Risk-SCD score, %	1.13 (1.06–1.21)	<0.001	–	–	1.06 (0.99–1.14)	0.109
LVEF, per 1% decrease	1.08 (1.02–1.15)	0.006	1.06 (1.00–1.13)	0.038	1.07 (1.00–1.13)	0.039
LA dimension, mm	1.09 (1.05–1.14)	<0.001	1.04 (0.99–1.09)	0.115	–	–
LV apical aneurysm	4.04 (1.75–9.34)	0.001	3.34 (1.40–7.99)	0.007	3.24 (1.26–8.30)	0.015
LARS, per 1% decrease	1.12 (1.07–1.18)	<0.001	1.10 (1.04–1.17)	<0.001	1.11 (1.05–1.18)	<0.001

Analyses were performed using a complete-case approach; multivariable model A was based on 906 (97.9%) patients (35 events), and model B was based on 846 (91.5%) patients (31 events).
CI, confidence interval; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; LA, left atrial; LARS, left atrial reservoir strain; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SCD, sudden cardiac death; HR, hazard ratio.

Table 3 Risk factors for progression to end-stage HCM in the CMR subcohort (*n* = 491)

	Univariable analysis		Multivariable model A		Multivariable model B	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
LVEF, per 1% decrease	1.06 (0.98–1.14)	0.179	1.05 (0.97–1.13)	0.256	–	–
LV apical aneurysm	4.93 (1.71–14.16)	0.003	–	–	2.71 (0.89–8.21)	0.079
LGE%, per 1% increase	1.07 (1.04–1.11)	<0.001	1.07 (1.03–1.11)	<0.001	1.06 (1.03–1.10)	<0.001
LARS, per 1% decrease	1.11 (1.03–1.20)	0.005	1.11 (1.02–1.20)	0.011	1.10 (1.02–1.19)	0.015

Analyses were performed using a complete-case approach; multivariable model A was based on 487 (99.2%) patients (17 events), and model B was based on 487 (99.2%) patients (17 events).
CI, confidence interval; CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; LARS, left atrial reservoir strain; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; HR, hazard ratio.

Two multivariable Cox models were evaluated (*Table 2*). In multivariable model A, three variables remained as independent predictors of progression to end-stage HCM: LVEF (adjusted HR 1.06 per 1% decrease; 95% CI, 1.00–1.13; $P = 0.038$), LV apical aneurysm (adjusted HR 3.34; 95% CI, 1.40–7.99; $P = 0.007$), and LARS (adjusted HR 1.10 per 1% decrease; 95% CI, 1.04–1.17; $P < 0.001$) (*Table 2*). These three variables remained significant in multivariable model B. Results were also consistent in Firth penalized Cox regression analyses (see Supplementary data online, *Table S3*). LARS also remained significantly associated with progression to end-stage HCM across models including LA volume index, AF, or HCM morphological subtype (see Supplementary data online, *Table S4*).

In the CMR subcohort, LGE% was significantly associated with progression to end-stage HCM in univariable Cox analysis (HR 1.07, 95% CI 1.04–1.11, $P < 0.001$) (*Table 3*). Notably, LARS remained an independent predictor after adjustment for LGE% (Model A: adjusted HR 1.11, 95% CI 1.02–1.20, $P = 0.011$) (*Table 3*), with consistent results in a sensitivity analysis including four variables (see Supplementary data online, *Table S5*).

Risk stratification by LARS

When categorized into tertiles, the incidence of progression to end-stage HCM increased progressively with decreasing LARS (*Figure 2A*). A data-driven cutoff value for LARS derived from maximally selected rank statistics was 16.9% (see Supplementary data online, *Figure S1*). Patients with LARS <16.9% were older and had higher HCM Risk-SCD scores, a higher prevalence of AF, larger LA size, and greater LGE burden than those with LARS ≥16.9% (see Supplementary data online, *Table S6*), as well as a higher incidence of progression to end-stage HCM (*Figure 2B*). When stratified by LVEF, this cutoff again provided significant risk discrimination, with a more pronounced and earlier risk observed in the low-normal LVEF (>50% and <60%) subgroup (*Figure 2C*). LARS <16.9% was also associated with a higher risk of progression to end-stage HCM in the CMR subcohort after adjustment for LGE% (see Supplementary data online, *Table S7*).

The cumulative incidence of progression to end-stage HCM was also significantly higher in patients with lower LVEF (<60%), the presence of LV apical aneurysm, and a greater LGE burden (LGE% ≥ 15%) in the CMR subcohort (see Supplementary data online, *Figure S2*).

Of the 925 patients, 410 had apical HCM and 515 had non-apical HCM. Progression to end-stage HCM occurred predominantly in patients with the non-apical subtype (30 events [5.8%] vs. 5 events [1.2%]; Supplementary data online, *Figure S3*). LARS discriminated the risk of progression in both subtypes (see Supplementary data online, *Figure S3* and Supplementary data online, *Table S8*).

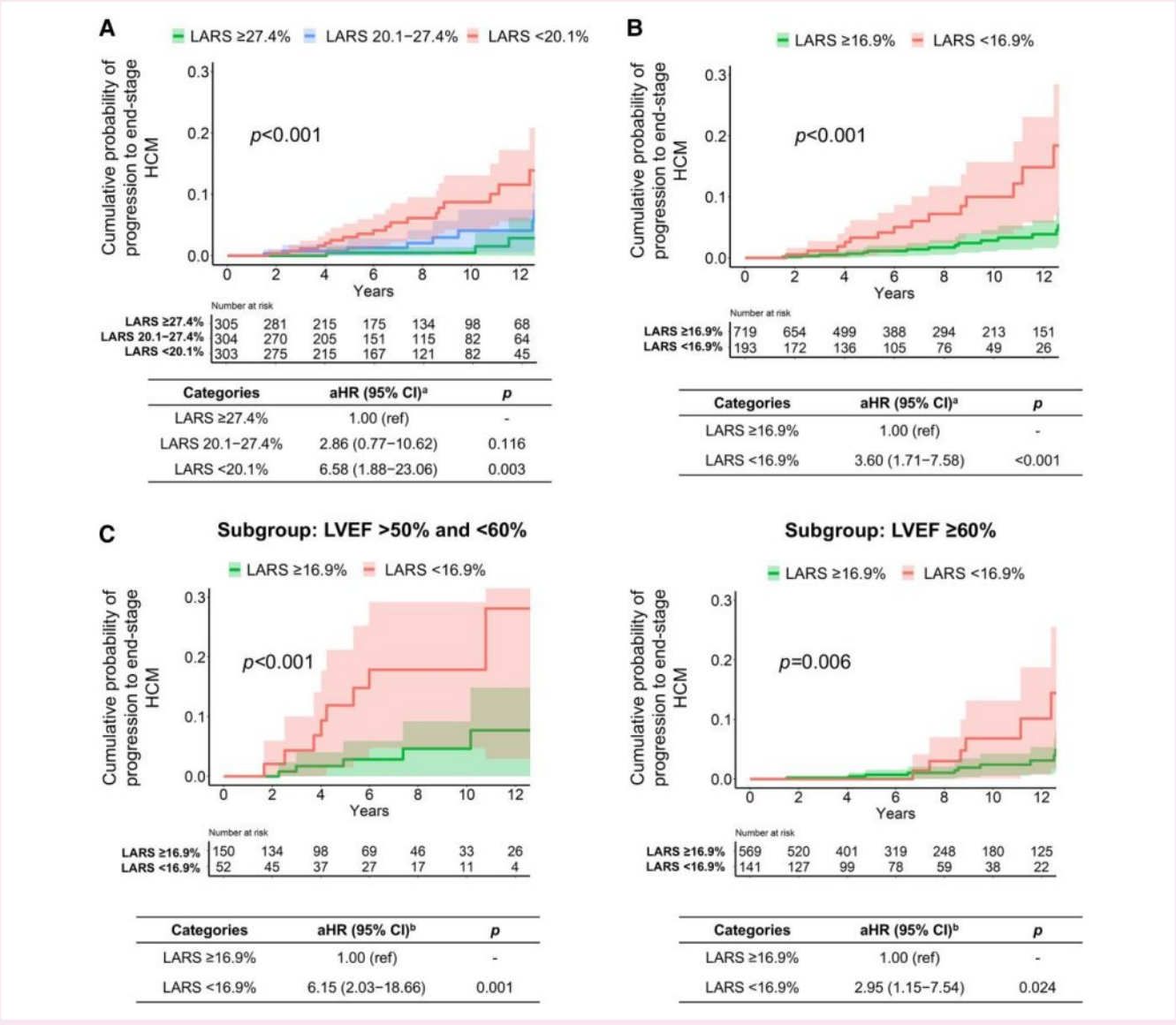


Figure 2 Cumulative incidence of progression to end-stage HCM according to LARS groups. Cumulative incidence stratified by (*A*) LARS tertiles and (*B*) LARS cutoff. Subgroup analyses by LVEF are shown in (*C*). Multivariable Cox results are presented in the lower panel. [a]Adjusted for age, NYHA functional class, LVEF, LA dimension, and LV apical aneurysm [b]Adjusted for HCM Risk-SCD score and LV apical aneurysm. aHR, adjusted hazard ratio; HCM, hypertrophic cardiomyopathy; LA, left atrial; LARS, left atrial reservoir strain; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Incremental prognostic value of LARS

Lower LARS was associated with higher LV maximal wall thickness, higher E/e′ ratio, lower LVEF, and lower absolute LV-GLS (see Supplementary data online, *Figure S4*). In the CMR subcohort, lower LARS was also associated with a higher LV mass index and greater LGE%. LARS was inversely correlated with log-transformed *n*-terminal pro–B-type natriuretic peptide levels (see Supplementary data online, *Figure S5*).

In incremental model comparisons, adding LA dimension to the baseline model with LVEF and LV apical aneurysm significantly improved model fit (χ^2, 15.2 vs. 27.1; $P < 0.001$) (*Figure 3A*). Further addition of LARS provided a substantial incremental improvement ($\chi^2 = 40.1$; $P < 0.001$). In the CMR subcohort, LARS also provided incremental prognostic value to the model including LVEF and LGE% (χ^2, 15.6 vs. 23.3; $P = 0.005$) (*Figure 3B*).

Change in LV and LA remodelling in patients with progression to end-stage HCM

In patients with progression to end-stage HCM ($n = 35$), the median echocardiographic follow-up duration was 8.4 years (IQR, 4.5–12.0 years). From baseline to the last follow-up echocardiography, maximal wall thickness and LVEF significantly decreased, with LVEF declining from 60% to 43% ($P < 0.001$) (*Table 4*). This deterioration was accompanied by impaired LV-GLS, enlargement of the LA, and reduction in LARS (all $P < 0.001$).

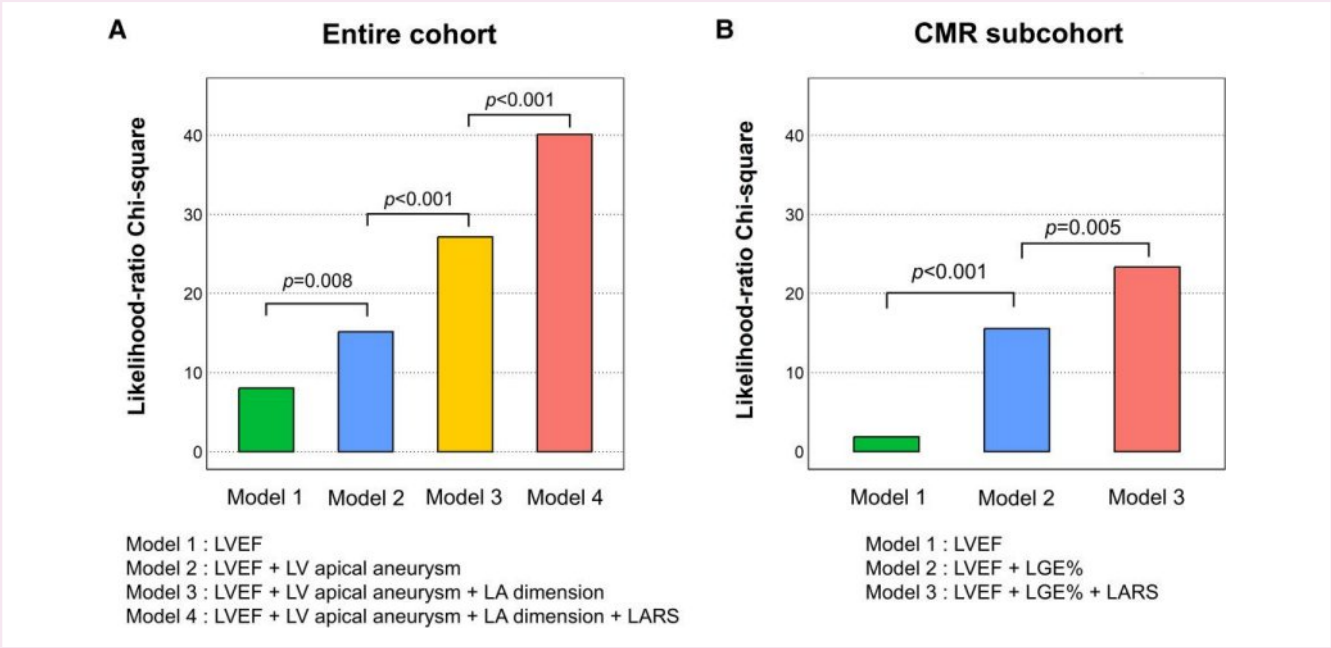


Figure 3 Incremental prognostic value of LARS for progression to end-stage HCM. Bar plots display global likelihood ratio χ^2 values from nested Cox models in (*A*) the entire cohort and (*B*) the CMR subcohort. CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; LARS, left atrial reservoir strain; LGE, late gadolinium enhancement.

Table 4 Changes in LV and LA structure and function between baseline and last follow-up in patients with progression to end-stage HCM (*n* = 35)

Variable	Baseline echocardiography	Last follow-up echocardiography	*P*[a]
Maximal wall thickness, mm	19.0 (16.0–22.1)	15.0 (13.0–18.5)	0.001
LVEF, %	60 (57–67)	43 (40–48)	<0.001
LV-GLS, %	−13.6 (−17.1−−10.0)	−9.4 (−12.6−−7.0)	<0.001
LA volume index, mL/m^2	48.3 (43.4–67.6)	68.0 (53.1–98.0)	<0.001
LARS, %	16.7 (13.8–22.8)	13.4 (11.0–15.9)	<0.001

[a]Compared using the paired Wilcoxon signed-rank test.
HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain; LA, left atrial; LARS, left atrial reservoir strain.

CV outcomes with and without progression to end-stage HCM

Among patients without progression to end-stage HCM (*n* = 890), the median clinical follow-up duration was 7.8 years (IQR, 4.3–11.8 years), during which 57 CV events (6.4%) occurred. These included CV death in 48 patients (including 17 with SCD), aborted SCD in 7 patients, and appropriate ICD shocks in 2 patients. The event-free survival rates were 99.4%, 97.7%, and 91.3% at 2, 5, and 10 years, respectively (*Figure 4A*).

In patients who developed end-stage HCM (*n* = 35), clinical follow-up began at the echocardiography that first identified disease progression, reflecting prognosis after transition to end-stage HCM. During a median follow-up of 2.1 years (IQR, 0.6–3.6 years), 10 patients (28.6%) experienced CV events, including CV death in 6 patients (SCD in 1) and appropriate ICD shocks in 4 patients, with no cases of aborted SCD. The cumulative 2-year event-free survival rate was 71.0% (*Figure 4B*).

Discussion

Our longitudinal echocardiography database of over 900 patients with HCM provides important insights into progression to end-stage HCM. Over a median follow-up of 6.5 years, 35 patients developed end-stage HCM (5.2 events per 1000 person-years). The independent risk factors for progression to end-stage HCM included lower LVEF, LV apical aneurysm, and impaired LARS. LARS was strongly associated with adverse LV remodelling and provided incremental prognostic value in models including LVEF and apical aneurysm, with

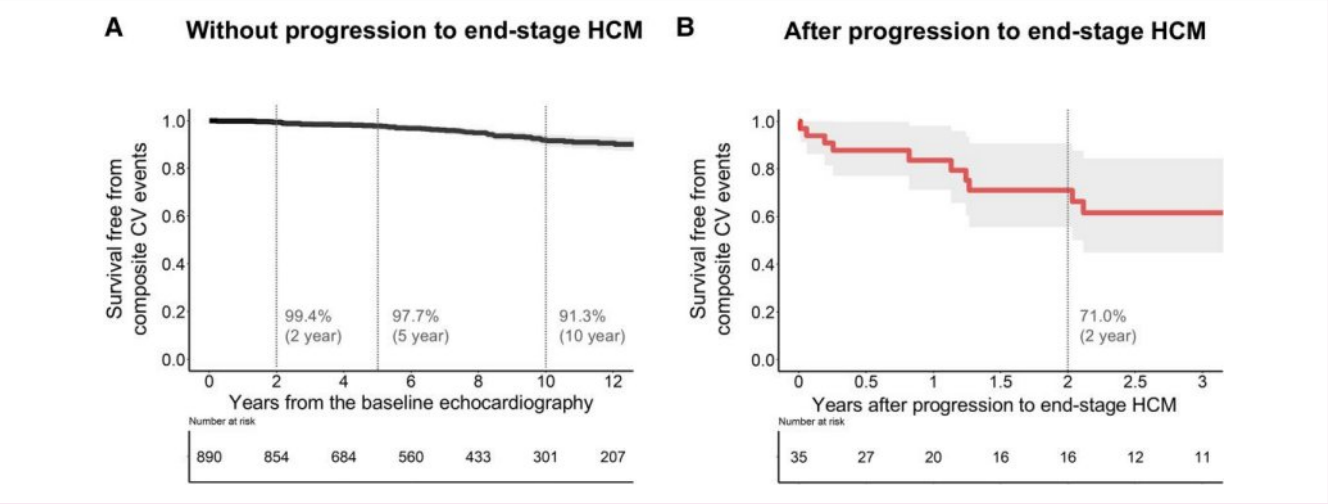


Figure 4 Clinical outcomes in patients with and without progression to end-stage HCM. (*A*) In patients without progression to end-stage HCM, follow-up began at baseline echocardiography. (*B*) In patients with progression to end-stage HCM, follow-up began at the last follow-up echocardiography, which was defined as the first study that identified progression. This demonstrated prognosis after transition to end-stage HCM. CV, cardiovascular; HCM, hypertrophic cardiomyopathy.

similar findings in the CMR subcohort including LGE%. Importantly, outcomes following progression to end-stage HCM were poor. These findings suggest that LARS may serve as a marker of disease progression and help identify patients at high risk of adverse events (**Structured Graphical Abstract**).

LV systolic function is a key determinant of risk stratification in HCM.[21] While many patients maintain preserved systolic function for a substantial period, a subset gradually develops LV systolic dysfunction. Only a small proportion ultimately progresses to end-stage HCM, a process that typically develops over a decade or longer. A previous study reported an average 14-year interval to progression to end-stage HCM,[10] consistent with findings in a Japanese cohort.[8] More recently, data from the SHaRe registry reported a 10-year cumulative incidence of 4.5%,[9] which is similar to our observation (10-year cumulative incidence, 4.4%). Larger LV cavity size and reduced LVEF have been associated with progression to end-stage HCM.[9,10] LV apical aneurysm, particularly larger aneurysm size, may be associated with a higher risk of progression to end-stage HCM.[22]

We found that lower LARS was significantly associated with progression to end-stage HCM. Previous studies have demonstrated the prognostic value of LA strain assessment for predicting adverse CV events in HCM,[16,23,24] including CMR-based assessment.[25] Our findings extend this prognostic role to progression to end-stage HCM. Notably, in the tertile analysis of LARS, patients with preserved LARS (≥27.4%) showed very low event rates, supporting the role of LARS as a sensitive marker. The association between LARS and progression remained robust after adjustment for established risk factors, including LGE% in the CMR subcohort. Reduced LARS was closely associated with greater myocardial thickness, lower systolic function, and higher myocardial fibrosis, further supporting its role as a surrogate for adverse LV remodelling in HCM. Moreover, LARS showed a further decline in patients who progressed to end-stage HCM. These findings are in line with recent serial CMR studies showing worsening myocardial strain and fibrosis over the disease course of HCM.[26] Importantly, LARS can be measured using routine transthoracic echocardiography, and its reproducibility has been well documented.[16] Therefore, close monitoring of LARS may help guide follow-up strategies in HCM.

Although progression to end-stage HCM usually takes many years, once this stage is reached, adverse outcomes occur rapidly.[8,10] In our cohort, patients with progression to end-stage HCM showed a markedly poor short-term prognosis after transition to end-stage HCM. Although these outcomes could not be directly compared, this contrasted with the favourable long-term outcome of those without progression. The grave prognosis of end-stage HCM may be further explained by structural abnormalities frequently observed in this stage, such as LV apical aneurysm.[22] The poor prognosis of end-stage HCM supports prophylactic ICD implantation.

HCM is a heterogeneous disease with diverse clinical outcomes.[27] Our study demonstrated that impaired LARS is an independent predictor of progression to end-stage HCM, incremental to established risk factors including LVEF, LV apical aneurysm, and LGE%. Therefore, incorporating LARS into routine evaluation may help identify patients at high risk before overt systolic dysfunction and facilitate closer surveillance and timely therapeutic decision-making.

Limitations

First, the retrospective design may have introduced selection bias. In addition, follow-up echocardiography was performed according to clinical practice rather than a fixed protocol, which may have influenced the timing of LV systolic dysfunction detection. Second, the number of events was modest, which limited more detailed evaluation of incremental prognostic value. Therefore, parsimonious models and additional Firth penalized Cox analyses were used. Third, the findings would be further strengthened by external validation. Our cohort included a relatively high proportion of apical HCM, consistent with previous

reports from East Asian populations. However, stratified analyses demonstrated that LARS retained prognostic value in both apical and non-apical HCM. Fourth, baseline CMR was not available in all patients. However, the association between LARS and progression to end-stage HCM remained significant after adjustment for LGE% in the CMR subcohort. Fifth, incident AF during follow-up was not considered in the models because of the heterogeneous timing of AF onset. However, the prognostic value of LARS remained significant after adjustment for baseline AF. Future studies are needed to better clarify the potential influence of incident AF on the relationship between LARS and disease progression. Finally, genetic data were not available for all patients, which limited the assessment of genotype–phenotype correlations.

Conclusion

Progression to end-stage HCM occurs in a small proportion of patients but is associated with poor prognosis. Impaired baseline LARS was independently associated with progression to end-stage HCM. Incorporating LARS into routine echocardiographic assessments may enhance risk stratification and guide personalized management in patients with HCM.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Acknowledgements

None.

Author contributions

Soongu Kwak (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing—original draft, Writing—review & editing [lead]), Min-Ha Jeong (Data curation, Investigation [supporting]), Chan Soon Park (Investigation [supporting]), Hyun-Jung Lee (Investigation [supporting]), Jun-Bean Park (Formal analysis, Methodology [supporting]), Seung-Pyo Lee (Investigation, Methodology [supporting]), Yong-Jin Kim (Supervision [lead]), Andrew Wang (Supervision [lead], Writing—original draft [supporting]), and Hyung-Kwan Kim (Supervision, Writing—original draft, Writing—review & editing [lead])

Declaration of generative AI

Artificial intelligence was not used for content generation, data analysis, or any part of this study.

Funding

This study was supported by a research grant from Chong Kun Dang Pharmaceutical Corp. (No. 0620243730).

Conflict of interest: H.-K. K. is a consultant for Bristol Myers Squibb and has received a research grant from Bristol Myers Squibb. The other authors declare no conflicts of interest.

Data availability

The data supporting the findings of this study will be available from the corresponding author upon reasonable request.

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