

Left Atrial Reservoir Strain Improves Sudden Cardiac Death Risk Stratification in Hypertrophic Cardiomyopathy

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Background: Current risk scores for sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM) have limited ability to identify high-risk subgroups. We aimed to investigate the prognostic value of left atrial reservoir strain (LARS) for SCD-related events and its utility for risk stratification.

Methods: This retrospective cohort study included 1,761 patients with HCM from 2 referral centers. The primary outcome was SCD-related events, including SCD, aborted SCD, and appropriate implantable cardioverter-defibrillator shocks. Explainable machine learning approaches were used to explore the importance of LARS and identify a clinically relevant threshold. The prognostic value of LARS was evaluated using Cox regression analyses, particularly among patients classified as low-to-intermediate risk (HCM Risk-SCD score <6%).

Results: During a median follow-up of 6.8 years (interquartile range, 3.0-10.7 years), 69 (3.9%) SCD-related events occurred. Decreased LARS was independently associated with a higher risk of SCD-related events (per 1% decrease; adjusted HR, 1.11; 95% CI, 1.07-1.15; $P < .001$). SHapley Additive exPlanation analysis identified LARS as the top-ranked predictor and a clinically relevant threshold of <21%. LARS <21% was significantly associated with a higher risk of SCD-related events (adjusted HR, 5.01; 95% CI, 2.77-9.03; $P < .001$), even among patients without atrial fibrillation. Adding LARS to the HCM Risk-SCD score significantly improved risk discrimination in the low-to-intermediate risk population (5-year time-dependent area under the receiver operating characteristic curve [AUC], 0.73 vs 0.63; $P = .005$). Among low-to-intermediate risk patients, LARS <21% was associated with a significantly higher risk of SCD-related events (adjusted HR, 6.13; 95% CI, 3.13-12.03; $P < .001$), whereas the original low- and intermediate-risk categories showed limited risk discrimination.

Conclusions: LARS was an independent predictor of SCD-related events and effectively stratified risk among patients classified as low-to-intermediate risk by the HCM Risk-SCD score. Integrating LARS into the HCM Risk-SCD score may enhance risk stratification and guide preventive strategies. (J Am Soc Echocardiogr 2026; ■: ■-■.)

Keywords: Cardiomyopathy, Hypertrophic, Death, Sudden, Cardiac, Machine learning

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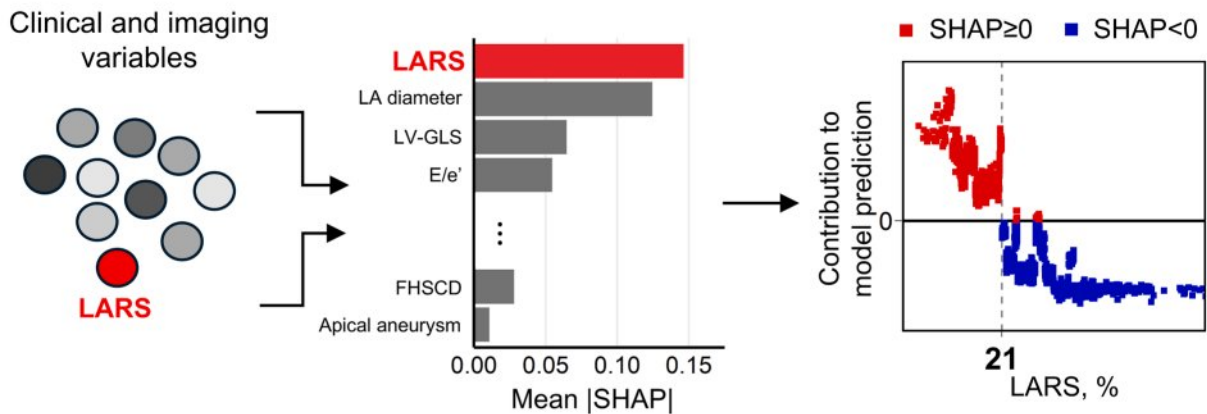
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Sudden cardiac death (SCD) is the most devastating complication in patients with hypertrophic cardiomyopathy (HCM).¹ The European Society of Cardiology guidelines recommend calculating the HCM Risk-SCD score to stratify risk and guide decisions on implantable cardioverter-defibrillator (ICD) implantation as a primary prevention strategy.^{2,3} However, this model has limited sensitivity, potentially failing to identify high-risk patients.^{4,6} Therefore, identifying novel predictors to enhance risk stratification beyond this scoring system is of significant clinical importance.⁷

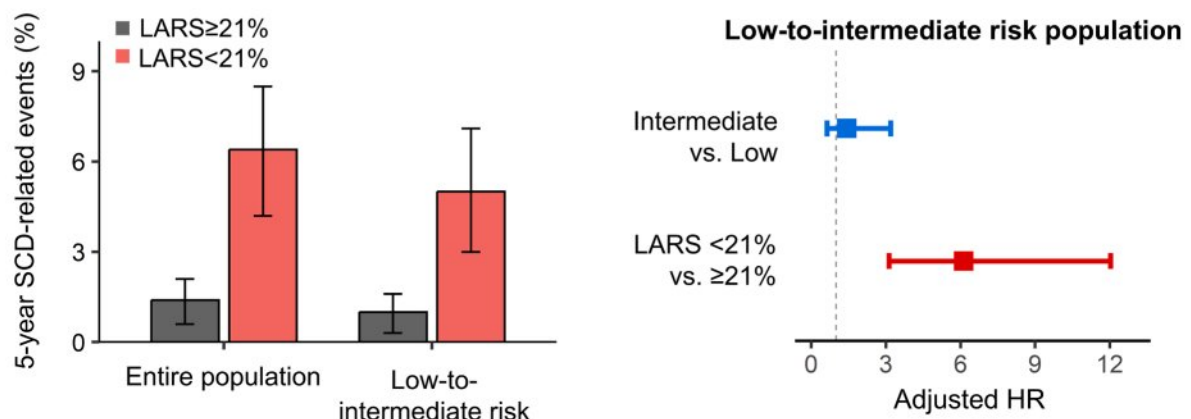
Advances in imaging techniques have provided opportunities to enhance SCD risk prediction. Among these techniques, echocardiographic measures of myocardial strain are closely associated with adverse events in HCM.^{8,9} In particular, left atrial (LA) reservoir strain (LARS) has emerged as a novel marker of left ventricular (LV) diastolic dysfunction and is associated with heart failure and SCD,^{5,10} highlighting its potential for improving SCD risk prediction. However, it remains unclear whether LARS offers significant predictive benefits

Central Illustration

Identification of LARS as a key marker for SCD risk stratification



Enhanced risk stratification in low-to-intermediate risk patients



Kwak: J Am Soc Echocardiogr 2026

Central Illustration Summary of the main study findings. LARS was identified as the most important predictor of SCD-related events using an explainable machine learning framework. The SHAP dependence plot demonstrated a marked nonlinear increase in SHAP values at an LARS threshold of 21%. Patients with LARS $< 21\%$ had a higher incidence of SCD-related events in the entire population. Importantly, among patients classified as low-to-intermediate risk according to the HCM Risk-SCD score ($< 6\%$), LARS $< 21\%$ identified a subgroup at markedly increased risk, whereas the original low- and intermediate-risk categories showed limited risk discrimination. These findings suggest that incorporation of LARS may improve risk stratification beyond the HCM Risk-SCD score alone. FHSCD, family history of sudden cardiac death; NSVT, nonsustained ventricular tachycardia.

beyond the current HCM Risk-SCD scoring system, especially for individuals categorized as low-to-intermediate risk. In addition, machine learning feature-extraction techniques can elucidate the relationship between a variable of interest and outcome, potentially identifying clinically relevant thresholds.¹¹⁻¹³ Incorporating imaging markers into such analytical frameworks may provide valuable insights for SCD risk prediction in HCM.

This study aimed to investigate the prognostic association of LARS with SCD-related events in patients with HCM and to evaluate its utility for risk stratification beyond the HCM Risk-SCD score. We used explainable machine learning approaches to explore

the relative importance of LARS and identify a clinically relevant threshold.

METHODS

Cohort Characteristics

Our retrospective cohort comprised consecutive adult patients diagnosed with HCM at 2 tertiary referral centers (Seoul National University Hospital and Samsung Medical Center, Seoul, Republic

Abbreviations

AF = Atrial fibrillation
AUC = Area under the receiver operating characteristic curve
CMR = Cardiovascular magnetic resonance
HCM = Hypertrophic cardiomyopathy
HR = Hazard ratio
ICD = Implantable cardioverter-defibrillator
IDI = Integrated discrimination index
LA = Left atrial
LARS = Left atrial reservoir strain
LGE = Late gadolinium enhancement
LV-GLS = LV global longitudinal strain
LV = Left ventricular
NRI = Net reclassification index
SCD = Sudden cardiac death
SHAP = SHapley Additive exPlanation
VT = Ventricular tachycardia

of Korea), with enrollment periods of 2007 to 2023 and 2007 to 2017, respectively. The diagnosis of HCM was established at dedicated HCM clinics at each center using an integrated assessment of clinical, genetic, and multimodality imaging findings, including echocardiography and cardiovascular magnetic resonance (CMR). HCM was defined as an abnormally increased LV end-diastolic wall thickness of ≥ 15 mm in the absence of other causes of hypertrophy. A lower threshold of hypertrophy (≥ 13 mm) was applied in patients with a family history of HCM or a positive genetic test.¹⁴ Patients with infiltrative cardiomyopathy, such as cardiac amyloidosis, mitochondrial disease, or Fabry disease, were excluded. In patients with long-standing hypertension, the diagnosis of HCM was further supported by clinical information and imaging findings, including information on blood pressure control, family history, genetic evidence, characteristic patterns of LV hypertrophy, and systolic anterior motion of the mitral valve.¹⁵ In addition, patients without available LARS measurements were excluded.

This study conformed to the

Declaration of Helsinki and was approved by the ethics committees of both participating study centers. The committee waived the requirement for written informed consent due to the retrospective nature of the data.

Variable Definitions

Clinical information at the time of the echocardiographic diagnosis of HCM was collected. Nonsustained ventricular tachycardia (VT) was defined as 3 or more consecutive ventricular beats at a rate of ≥ 120 beats per minute, lasting less than 30 seconds. Data on the history of unexplained syncope were also collected. The HCM Risk-SCD Score, which estimates the 5-year risk of SCD, was calculated based on the recommendations outlined in the guidelines.^{2,3}

Standard transthoracic echocardiography was performed in all patients. Maximal LV wall thickness was measured at end-diastole, and LA diameters were obtained from the standard parasternal view at end-systole. The LA volume index was calculated using the area-length method and indexed to body surface area. Mitral inflow velocities were recorded at the tip of the mitral valve, and tissue Doppler velocities were recorded at the medial portion of the mitral annulus. The maximal LV outflow tract gradient was measured at rest or during the Valsalva maneuver. Both LV and LA strain measurements were performed using vendor-independent postprocessing software

(Imaging Arena 4.6; TomTec Imaging Systems).^{5,8-10} For LV global longitudinal strain (LV-GLS), the endocardial borders of the LV were manually traced in 2-, 3-, and 4-chamber views at end-systole, with tracking throughout the cardiac cycle to calculate the average value. For LARS, the endocardial borders of the LA were manually traced on the end-systolic frame of a nonforeshortened apical 4-chamber view, with tracking across the cardiac cycle to generate an LA longitudinal strain curve. Both LV-GLS and LARS measurements were averaged over 3 cardiac cycles in patients with atrial fibrillation (AF). The reproducibility of LARS measurements has been reported previously, with excellent intraobserver and interobserver agreement.¹⁰

A total of 933 patients (53.0%) underwent baseline CMR and comprised the CMR subcohort, including 527 (39.4%) from Seoul National University Hospital and 406 (96.2%) from Samsung Medical Center. Among them, late gadolinium enhancement (LGE) data were available in 887 (95.1%) patients, who were included in analyses incorporating LGE. LGE imaging was performed 10 to 15 minutes after contrast administration. LGE was defined as areas with a signal intensity ≥ 6 SDs above that of the remote normal myocardium and was expressed as a percentage of total myocardial mass (LGE%).¹⁶

Outcome Assessment

The primary outcome was SCD-related events, including SCD, aborted SCD, and appropriate ICD shocks to terminate life-threatening ventricular arrhythmias. Event adjudication was based on official national death records, electronic medical records from each study center, records from outside institutions, emergency department documentation, and emergency medical service reports when available. Information obtained from family members was also used as supplementary data. Appropriate ICD shocks were adjudicated based on device interrogation records from each center.

Machine Learning Analyses

To explore the relative variable importance for predicting SCD-related events, machine learning analyses were performed in the combined cohort from both participating centers. Candidate variables for model development were selected from baseline characteristics, clinical SCD risk factors, comorbidities, echocardiographic parameters, myocardial strain markers, and CMR findings (Supplemental Table 1). The calculated HCM Risk-SCD score was excluded from model development; however, its individual components were included. Variables exhibiting substantial collinearity (pairwise Pearson correlation coefficient >0.6) or missingness $>10\%$ were excluded. For variables with $<10\%$ missingness, missing values were imputed using the MissForest algorithm.¹⁷

Feature selection was performed using a multimethod approach, including univariable association-based ranking methods, recursive feature elimination with random forest, and least absolute shrinkage and selection operator regression. Variables ranked in the upper half of the aggregated importance ranking were selected for machine learning analyses. The final 10 variables included LARS, LA diameter, LV-GLS, E/e' ratio, syncope, LV ejection fraction, dyslipidemia, AF, family history of SCD, and LV apical aneurysm.

Four machine learning algorithms (LightGBM, XGBoost, Random Forest, and Generalized Linear Model) were evaluated using 5-fold cross-validation, with hyperparameters optimized using a Bayesian optimization algorithm.¹⁸ To address class imbalance, class weighting was applied to the minority class during model training. The best

HIGHLIGHTS

- LARS is an independent predictor of SCD-related events in HCM.
- An LARS threshold of <21% identifies patients at increased risk of SCD-related events.
- LARS improves risk stratification in low-to-intermediate-risk patients with HCM.

performing model was subsequently used for feature importance analysis. As a sensitivity analysis, machine learning analyses were repeated after including nonsustained VT and LGE%, with missing values imputed using the MissForest algorithm.

Feature Importance and Dependence Plot

Feature importance was assessed from the best performing model based on SHapley Additive exPlanation (SHAP) values.^{11,12} The SHAP summary plot illustrates the importance of each variable and the distribution of its effects across the data set. An SHAP dependence plot was generated to visualize the relationship between LARS and model prediction.¹⁹ Positive SHAP values indicate that a feature contributes to a higher model prediction, whereas negative SHAP values indicate a lower prediction. A clinically relevant LARS threshold was identified based on the SHAP dependence plot, focusing on the point of marked nonlinear increase in SHAP values.¹²

Statistical Analysis

Continuous variables were presented as medians with interquartile ranges and categorical variables as frequencies with percentages. Group comparisons were performed using the Mann-Whitney *U* test for continuous variables and the χ^2 test for categorical variables.

After identifying an LARS threshold using SHAP analysis, its clinical relevance was evaluated using Cox regression and survival analyses. Maximally selected rank statistics were also used to assess whether a similar threshold could be identified. Kaplan-Meier analyses were performed according to LARS categories and compared using the log-rank test. Cox regression analyses were conducted to evaluate the association between LARS and SCD-related events, with results reported as hazard ratios (HRs) and 95% CIs. Considering the modest number of SCD-related events, multivariable Cox models were adjusted for established SCD risk factors, including the HCM Risk-SCD score, LV ejection fraction, and LV apical aneurysm. Sensitivity analyses were performed in patients without AF. In the LGE-available CMR subcohort, models were adjusted for the HCM Risk-SCD score and LGE%.

Among patients with low-to-intermediate HCM Risk-SCD scores (<6%), the incremental prognostic value of LARS beyond the HCM Risk-SCD score was assessed using 5-year time-dependent area under the receiver operating characteristic curve (AUC) analysis with bootstrap-based comparisons, as well as the net reclassification index (NRI) and integrated discrimination index (IDI). We additionally evaluated the prognostic value of LARS-integrated risk categories based on the identified LARS threshold in this population. All analyses were performed using Python (version 3.10.12) and R (version 4.3.0). Statistical significance was set at a 2-tailed *P* value <0.05.

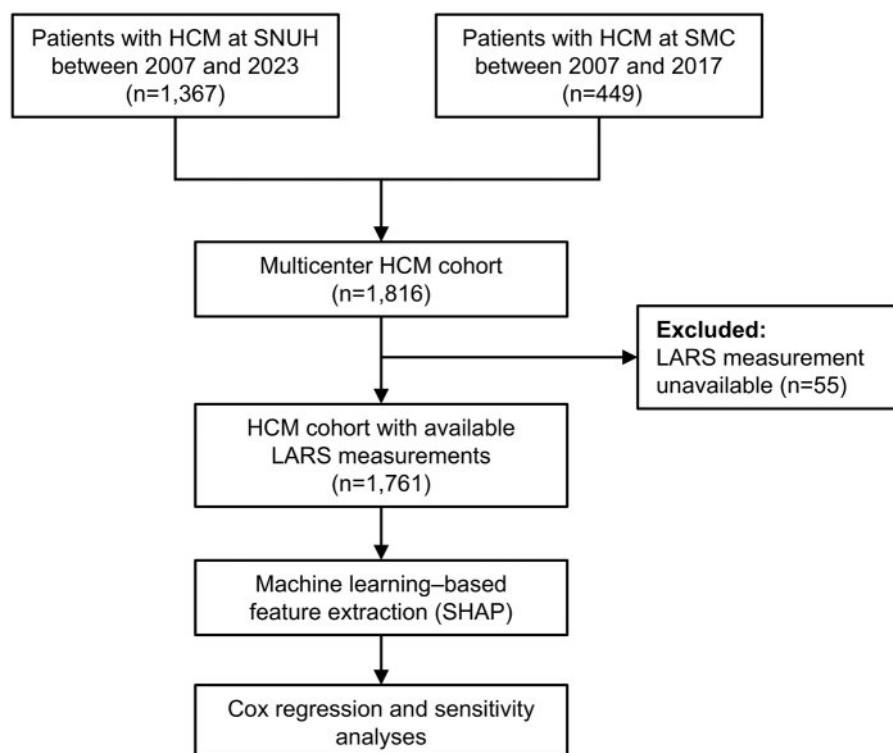


Figure 1 Overall study flowchart. A multicenter HCM cohort with available LARS measurements was analyzed. The SHAP analysis was used for feature extraction and threshold identification, and Cox regression was used to evaluate the association between LARS and SCD-related events. SMC, Samsung Medical Center; SNUH, Seoul National University Hospital.

Table 1 Baseline characteristics of patients with and without SCD-related events

Characteristics	Entire cohort (N = 1,761)	With SCD-related events (n = 69)	Without SCD-related events (n = 1,692)	P value
Age, years	61 (52-69)	63 (52-71)	61 (52-69)	.176
Male	1,229 (69.8)	42 (60.9)	1,187 (70.2)	.130
Body mass index, kg/m ²	24.8 (22.9-26.8)	25.2 (22.4-27.8)	24.8 (22.9-26.8)	.539
Body surface area	1.8 (1.6-1.9)	1.7 (1.6-1.9)	1.8 (1.6-1.9)	.265
SBP, mm Hg	127 (116-138)	122 (111-140)	127 (116-138)	.171
DBP, mm Hg	75 (69-82)	74 (66-80)	75 (69-82)	.357
NYHA ≥III	95 (5.4)	5 (7.2)	90 (5.3)	.666
Family history of HCM	132 (7.5)	9 (13.0)	123 (7.3)	.111
Family history of SCD	153 (8.7)	15 (21.7)	138 (8.2)	<.001
Nonsustained VT*	267 (21.1)	23 (47.9)	244 (20.0)	<.001
Syncope	215 (12.2)	18 (26.1)	197 (11.6)	.001
HCM Risk-SCD score, % [†]	1.7 (1.3-2.7)	2.6 (1.7-6.6)	1.7 (1.3-2.6)	<.001
HCM Risk-SCD categories [‡]				<.001
Low (<4%)	1,534 (87.4)	44 (63.8)	1,490 (88.3)	
Intermediate (4-6%)	128 (7.3)	7 (10.1)	121 (7.2)	
High (≥6%)	94 (5.4)	18 (26.1)	76 (4.5)	
Comorbidities				
Hypertension	818 (46.5)	30 (43.5)	788 (46.6)	.702
Diabetes mellitus	320 (18.2)	14 (20.3)	306 (18.1)	.759
Dyslipidemia	475 (27.0)	11 (15.9)	464 (27.4)	.049
Atrial fibrillation	316 (17.9)	28 (40.6)	288 (17.0)	<.001
Echocardiography				
LV end-diastolic diameter, mm	47 (43-51)	48 (45-52)	47 (43-51)	.113
LV end-systolic diameter, mm	28 (25-31)	30 (26-33)	28 (25-31)	.036
LV ejection fraction, %	64 (60-68)	61 (57-68)	64 (60-68)	.004
LV ejection fraction <50%	40 (2.3)	9 (13.0)	31 (1.8)	<.001
Maximal wall thickness, mm	17.0 (15.3-20.0)	18.1 (16.3-20.0)	17.0 (15.2-20.0)	.058
Maximal wall thickness ≥30 mm	26 (1.5)	1 (1.4)	25 (1.5)	>.99
LA diameter, mm	44.0 (40.0-49.0)	50.0 (46.0-55.0)	44.0 (40.0-49.0)	<.001
LA volume index, mL/m ²	42.6 (33.3-55.3)	56.4 (44.8-75.3)	42.1 (33.0-54.5)	<.001
E/e' ratio	12.3 (9.8-16.6)	13.8 (10.0-21.0)	12.2 (9.8-16.2)	.008
Maximal LVOT gradient, mm Hg	5.8 (4.0-11.4)	6.9 (3.8-23.8)	5.8 (4.0-11.0)	.210
Maximal LVOT gradient ≥30 mm Hg	286 (16.2)	14 (20.3)	272 (16.1)	.452
Peak TR velocity, m/s	2.3 (2.2-2.6)	2.5 (2.3-2.8)	2.3 (2.2-2.6)	<.001
LV-GLS, %	-14.1 (-17.2 to -11.4)	-11.9 (-14.0 to -9.1)	-14.2 (-17.3 to -11.5)	<.001
LARS, %	24.1 (17.9-30.3)	16.5 (12.0-20.7)	24.3 (18.4-30.5)	<.001
LV apical aneurysm	153 (8.7)	13 (18.8)	140 (8.3)	.005
Apical HCM	728 (41.3)	21 (30.4)	707 (41.8)	.080
LGE% [‡]	3.1 (0.5-8.7)	10.0 (2.9-20.5)	2.9 (0.5-8.3)	.001
LGE% >15% [‡]	121 (13.6)	11 (42.3)	110 (12.8)	<.001

DBP, diastolic blood pressure; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; SBP, systolic blood pressure.

Continuous variables are expressed as the median (interquartile range), and categorical variables are expressed as frequency (percentage).

*Available in 71.9% of patients.

[†]HCM Risk-SCD score was unavailable in 5 patients.[‡]Data available in the LGE-available CMR subcohort (n = 887, 50.4%).

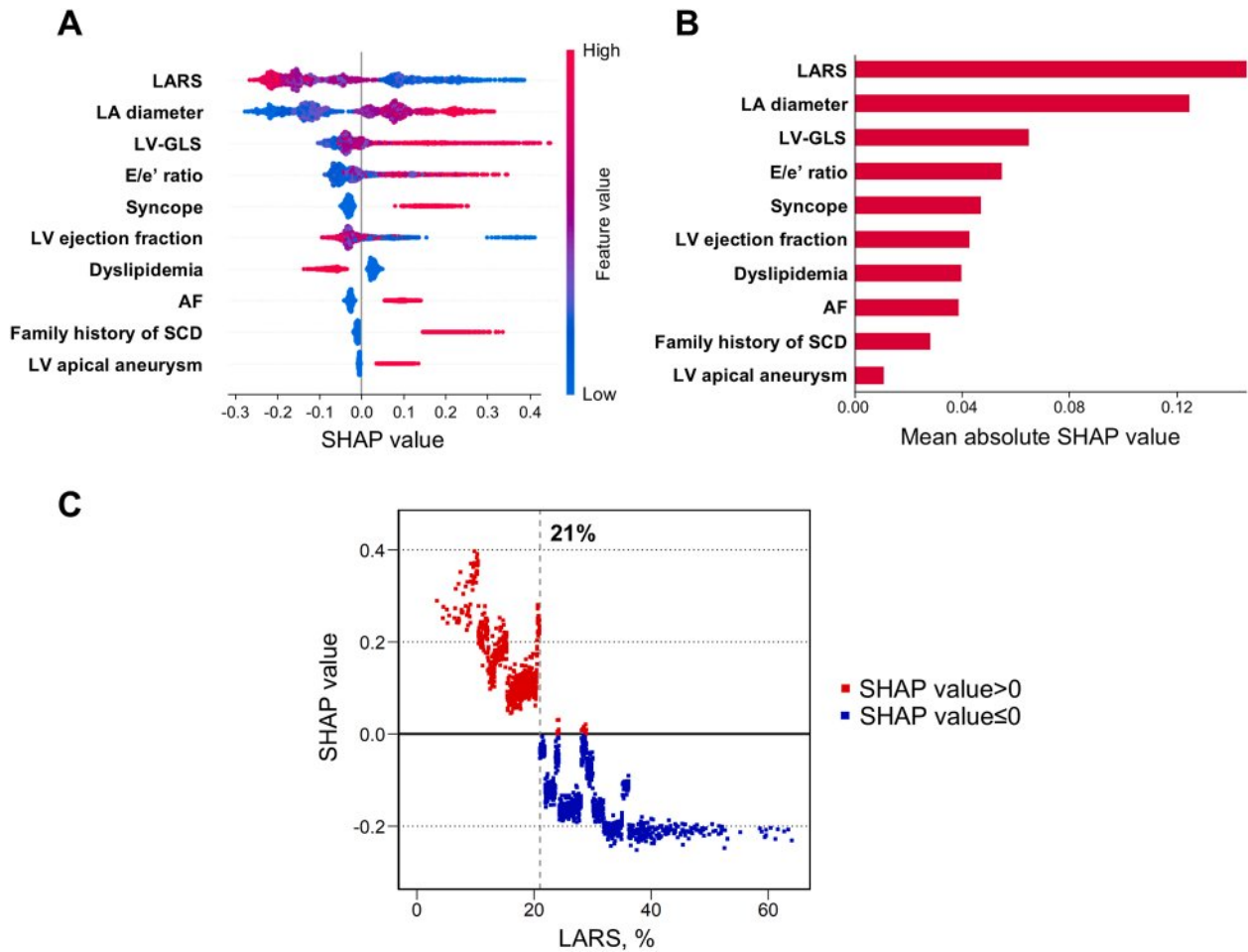


Figure 2 Identification of LARS as a key predictor and clinically relevant threshold using explainable machine learning. **(A)** SHAP summary plot from the best performing LightGBM model showing relative variable importance. **(B)** Mean absolute SHAP values summarizing the overall variable importance. **(C)** SHAP dependence plot illustrating the relationship between LARS and model prediction. Positive SHAP values indicate that a feature contributes to a higher model prediction, whereas negative SHAP values indicate a lower prediction. A sharp increase in SHAP values was observed when LARS fell below 21%, suggesting this value as a prognostic cutoff.

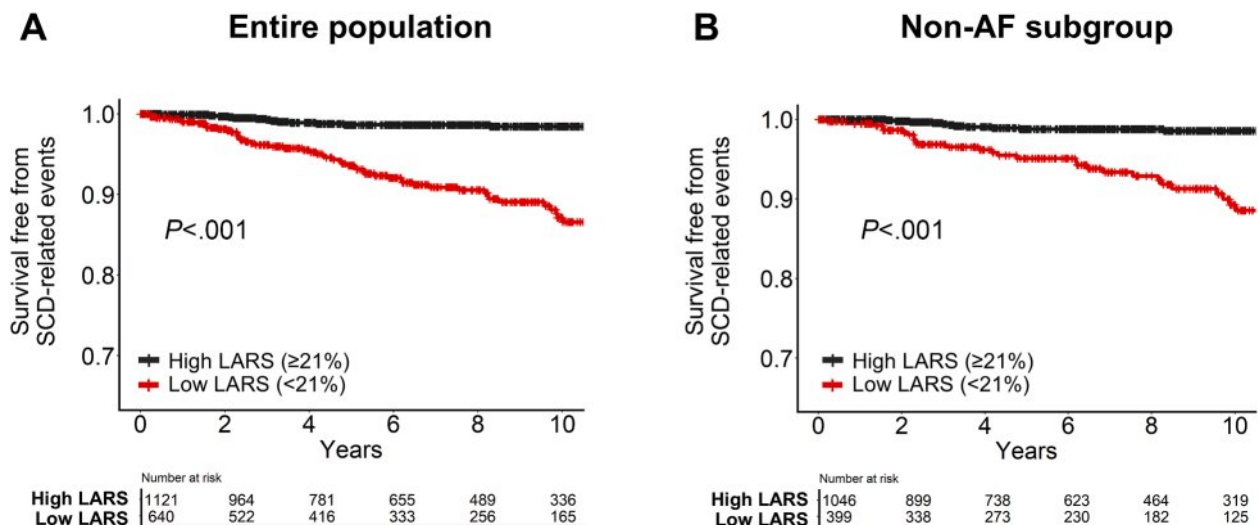


Figure 3 Cumulative survival free from SCD-related events according to LARS. Kaplan-Meier curves for cumulative survival free from SCD-related events according to LARS (<21% vs ≥21%) in **(A)** the entire population and **(B)** non-AF subgroup.

Table 2 Association between LARS with the risk of SCD-related events

	Univariable analysis		Adjusted analysis*	
	HR (95% CI)	P value	HR (95% CI)	P value
Entire population (N = 1,761)				
LARS, per 1% decrease	1.13 (1.09-1.17)	<.001	1.11 (1.07-1.15)	<.001
LARS <21% vs ≥21%	6.78 (3.83-12.01)	<.001	5.01 (2.77-9.03)	<.001
Non-AF subgroup (n = 1,445)				
LARS, per 1% decrease	1.13 (1.08-1.19)	<.001	1.12 (1.07-1.17)	<.001
LARS <21% vs ≥21%	6.38 (3.25-12.50)	<.001	5.10 (2.55-10.19)	<.001
LGE-available CMR subcohort (n = 887)				
LARS, per 1% decrease	1.12 (1.06-1.18)	<.001	1.09 (1.04-1.15)	<.001
LARS <21% vs ≥21%	5.40 (2.27-12.86)	<.001	3.83 (1.57-9.33)	.003

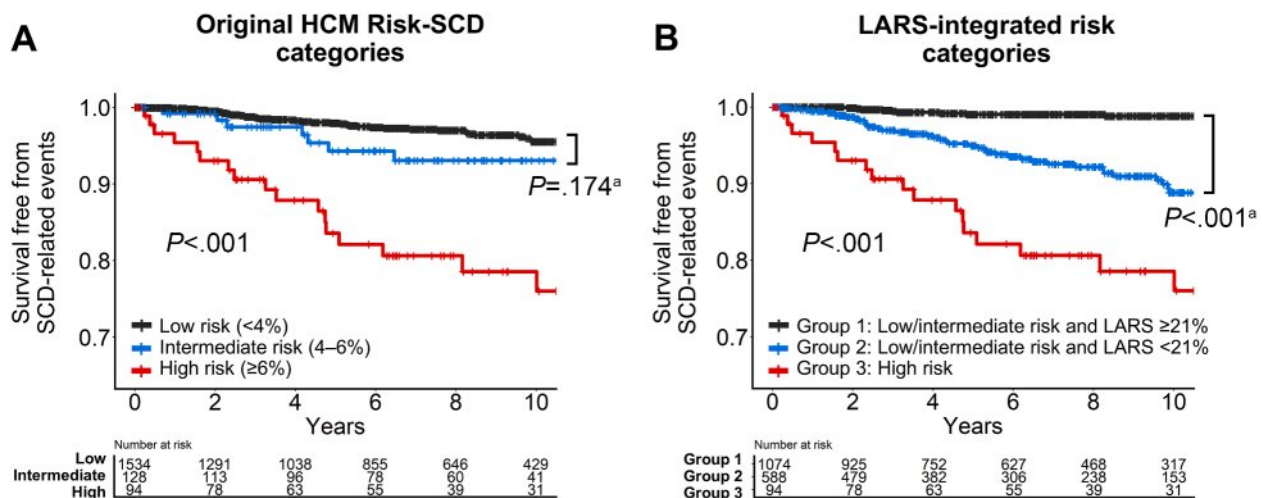
HR, hazard ratio.

*Adjusted analyses in the entire population and non-AF subgroup included HCM Risk-SCD score, LV ejection fraction, and LV apical aneurysm as covariates. In the LGE-available CMR subcohort, analyses were adjusted for HCM Risk-SCD score and LGE%.

Table 3 Incremental value of LARS for prediction of SCD-related events in patients with low-to-intermediate HCM Risk-SCD score

Prediction models	5-year time-dependent AUC (95% CI)	P value	NRI (95% CI)	P value	IDI (95% CI)	P value
Low-to-intermediate risk population*						
HCM Risk-SCD score	0.63 (0.53-0.72)	Ref	Ref	Ref	Ref	Ref
HCM Risk-SCD score + LARS <21%	0.73 (0.64-0.82)	.005	0.396 (0.194-0.536)	<.001	0.019 (0.007-0.036)	<.001

*Low-to-intermediate risk was defined as an HCM Risk-SCD score of <6%.

**Figure 4** Cumulative survival free from SCD-related events according to original HCM Risk-SCD categories and LARS-integrated risk categories. Kaplan-Meier curves for cumulative survival free from SCD-related events according to (A) the original HCM Risk-SCD categories and (B) the LARS-integrated risk categories, in which patients with low-to-intermediate HCM Risk-SCD scores were further stratified according to an LARS threshold of 21%.

RESULTS

Baseline Characteristics

The study cohort included 1,761 patients with HCM from both study centers (Figure 1). During a median follow-up of 6.8 years (interquar-

tile range, 3.0-10.7 years), 69 (3.9%) SCD-related events occurred, corresponding to an incidence rate of 5.5 events per 1,000 person-years. Patients who experienced SCD-related events during follow-up had a higher prevalence of family history of SCD, nonsustained VT, syncope, AF, lower LV ejection fraction, greater maximal wall

Table 4 Association of original and LARS-integrated HCM Risk-SCD categories with SCD-related events

	Univariable analysis		Adjusted analysis*	
	HR (95% CI)	P value	HR (95% CI)	P value
Original HCM Risk-SCD categories				
Low risk	1.00 (Ref.)	-	1.00 (Ref.)	-
Intermediate risk	1.74 (0.78-3.87)	.173	1.43 (0.64-3.19)	.385
High risk	6.55 (3.78-11.34)	<.001	5.42 (3.05-9.61)	<.001
LARS-integrated risk categories				
Group 1: Low/intermediate risk and LARS $\geq$ 21%	1.00 (Ref.)	-	1.00 (Ref.)	-
Group 2: Low/intermediate risk and LARS <21%	7.10 (3.64-13.84)	<.001	6.13 (3.13-12.03)	<.001
Group 3: High risk	18.90 (8.92-40.04)	<.001	15.79 (7.33-34.04)	<.001

*Adjusted analyses included LV ejection fraction and LV apical aneurysm as covariates.

thickness, larger LA diameter and volume index, higher E/e' ratio, lower absolute LV-GLS, LV apical aneurysm, and a higher HCM Risk-SCD score (median, 2.6% vs 1.7%; $P < .001$; [Table 1](#)). Notably, LARS was significantly lower among those with SCD-related events compared with those without events (median, 16.5% vs 24.3%; $P < .001$). In the CMR subcohort, patients with SCD-related events had a higher LGE% than those without events.

When compared between study centers, patients from Seoul National University Hospital were older, more likely to be female, had a higher prevalence of AF, and more frequently exhibited apical HCM ([Supplemental Table 2](#)). The incidence rates of SCD-related events were similar between the 2 centers ([Supplemental Figure 1](#)). Patients in the CMR subcohort were younger, had a higher HCM Risk-SCD score, and less frequently exhibited apical HCM than those in the non-CMR cohort ([Supplemental Table 3](#)).

Feature Importance Analysis Using Explainable Machine Learning

The performance of the machine learning models is summarized in [Supplemental Table 4](#). Among them, LightGBM demonstrated the best performance, achieving an AUC of 0.783. Calibration of the LightGBM model is presented in [Supplemental Figure 2](#), demonstrating overall agreement between predicted and observed event rates.

In the LightGBM model, SHAP summary analysis identified LARS as the most important predictor, followed by LA diameter and LV-GLS ([Figure 2A](#)). Consistently, LARS showed the highest mean absolute SHAP value (0.146), indicating the greatest contribution to model prediction ([Figure 2B](#)). The SHAP dependence plot for LARS is shown in [Figure 2C](#). A marked nonlinear increase in SHAP values was observed below an LARS value of approximately 21%, identifying this point as a potential threshold.

In a sensitivity machine learning analysis that additionally included nonsustained VT and LGE%, LARS remained the highest ranked predictor, and a similar threshold of approximately 21% was identified on the SHAP dependence plot ([Supplemental Figure 3](#)).

LARS for SCD Risk Stratification

Maximally selected rank statistics identified a similar cutoff (20.9%), supporting the 21% threshold identified from the SHAP dependence plot ([Supplemental Figure 4](#)). When stratified by the LARS 21% threshold, patients with LARS <21% exhibited a higher risk profile,

including a higher HCM Risk-SCD score and more adverse structural remodeling and functional impairment ([Supplemental Table 5](#)).

Kaplan-Meier curve analyses demonstrated that patients with LARS <21% had significantly higher rates of SCD-related events compared with those with $\geq$ 21% ($P < .001$) ([Figure 3A](#)). Similar findings were observed in patients without AF ($P < .001$; [Figure 3B](#)). In Cox analyses, decreased LARS was associated with a significantly higher risk of SCD-related events, even after adjusting for the HCM Risk-SCD score, LV ejection fraction, and LV apical aneurysm (per 1% decrease in LARS; adjusted HR, 1.11; 95% CI, 1.07-1.15; $P < .001$; [Table 2](#)). The adjusted HR for LARS <21% was 5.01 (95% CI, 2.77-9.03; $P < .001$). These associations remained significant in patients without AF and in the CMR subcohort after adjustment for LGE% ([Table 2](#)). Similar findings were observed in sensitivity analyses that additionally incorporated LV-GLS in the CMR subcohort ([Supplemental Table 6](#)). These associations remained consistent across apical and nonapical HCM subgroups ([Supplemental Table 7](#)).

Risk Reclassification of Low-to-Intermediate Risk Patients Using LARS

In patients with low-to-intermediate risk, the 5-year time-dependent AUC of the HCM Risk-SCD score was 0.63 (95% CI, 0.53-0.72; [Table 3](#)). The addition of LARS <21% significantly improved discrimination for SCD-related events (AUC, 0.73; 95% CI, 0.64-0.82; $P = .005$). Both the NRI and IDI also showed significant improvement with the addition of LARS (NRI, 0.396; 95% CI, 0.194-0.536; $P < .001$; IDI, 0.019; 95% CI, 0.007-0.036; $P < .001$).

In the original HCM Risk-SCD categories, patients with high risk ($\geq$ 6%) showed the worst survival free from SCD-related events, whereas no significant difference was observed between the low- and intermediate-risk groups ($P = .174$; [Figure 4A](#)). Consistently, the intermediate-risk group was not associated with a significantly higher risk than the low-risk group in Cox analyses ([Table 4](#)).

We reclassified patients according to the HCM Risk-SCD score and LARS threshold into 3 groups: group 1, low-to-intermediate risk with LARS $\geq$ 21%; group 2, low-to-intermediate risk with LARS <21%; and group 3, high risk (HCM Risk-SCD score $\geq$ 6%). In this LARS-integrated categorization, group 2 showed a significantly higher incidence of SCD-related events than group 1 ($P < .001$; [Figure 4B](#)). In Cox analyses, group 2 was independently associated with a higher

risk of SCD-related events compared with group 1 (adjusted HR, 6.13; 95% CI, 3.13–12.03; $P < .001$; Table 4).

DISCUSSION

This multicenter study demonstrates the prognostic significance of LARS for SCD-related events in patients with HCM. Decreased LARS was independently associated with a higher risk of SCD-related events. Using an explainable machine learning framework, we identified a clinically relevant threshold of LARS $<21\%$, which was associated with a markedly increased risk of SCD-related events. Importantly, these associations remained robust in patients without AF and in the CMR subcohort after adjustment for LGE. Among patients classified as low-to-intermediate risk according to the HCM Risk-SCD score, impaired LARS identified a subgroup with substantially higher risk of SCD-related events. These findings suggest that incorporating LARS into risk assessment may improve SCD risk stratification beyond the current guideline-based approach (Central Illustration).

Although advancements in contemporary management strategies for HCM have significantly reduced the burden of SCD,²⁰ it remains the most lethal complication.²¹ Identifying high-risk populations is clinically important because ICD implantation has been established as an effective primary prevention strategy for patients at high risk of SCD.²² At the same time, avoiding unnecessary ICD implantation in low-risk patients is equally important to reduce complications, such as infection, lead failure, and inappropriate shocks,²³ as well as device-related burden. However, the risk factors for SCD in HCM have not been fully elucidated, and American and European guidelines propose different sets of risk factors.^{2,3,14} This discrepancy may reflect heterogeneity in clinical characteristics, comorbidities, and cardiac remodeling among patients.²⁴ Therefore, establishing novel markers for SCD and integrating them into risk models is essential for enhancing the stratification of high-risk populations.

The European guideline currently uses the HCM Risk-SCD score to guide decisions on primary prevention.^{2,3} However, its low sensitivity leaves some high-risk individuals undetected.^{4,25,26} The recent European guideline suggests ICD implantation for patients in the low-risk category ($<4\%$) with either extensive myocardial scarring on CMR (LGE% $\geq 15\%$) or reduced LV ejection fraction ($<50\%$), while acknowledging the limited robust data supporting this recommendation.³ In our study, LARS was identified as a strong risk factor for SCD-related events, independent of the HCM Risk-SCD score. Importantly, this marker further stratified the risk among patients classified as low-to-intermediate risk according to the HCM Risk-SCD score. Therefore, incorporating LARS into risk assessments may help identify high-risk individuals and support more effective preventive strategies.

Diastolic dysfunction is the main pathophysiological feature of HCM; however, accurately determining diastolic function in this condition remains challenging. Traditional Doppler echocardiographic diastolic parameters, including the E/e' ratio, provide limited information for assessing LV filling pressure in HCM.²⁷ LARS, which measures the deformation of the LA myocardium,²⁸ has emerged as a novel marker of LV diastolic function across various cardiovascular conditions and is closely associated with invasively measured LV filling pressure.²⁹ Previous studies have reported that LARS is a strong predictor of incident heart failure in patients with HCM and has the potential to predict SCD-related events.^{5,10} During the course of

HCM, worsening diastolic dysfunction is accompanied by the development of AF, increased myocardial fibrosis, impaired systolic function, and LV apical aneurysm formation. We speculate that impaired LARS serves as a sensitive marker of more advanced cardiac remodeling in HCM and may therefore identify patients at increased risk of SCD-related events. Using an explainable machine learning framework, we identified that an LARS threshold of $<21\%$ was strongly associated with SCD risk, even among patients classified as low-to-intermediate risk by the HCM Risk-SCD score. Therefore, LARS has the potential to improve the sensitivity of the HCM Risk-SCD score. Because cardiac remodeling in HCM evolves over time and LARS may be influenced by loading conditions, serial assessment of LARS may provide additional information beyond a single baseline measurement.

A detailed assessment of cardiac remodeling, including systolic function, myocardial thickness, and fibrosis, is essential for predicting SCD in HCM.^{30–32} Moreover, myocardial strain parameters such as LV-GLS and LARS may address existing gaps in risk stratification, as demonstrated in our study. In addition, the direct incorporation of raw imaging data, such as pixel-level analysis of CMR, echocardiography videos, and electrocardiography, has the potential to uncover subtle features that traditional data formats might miss. Leveraging multimodality imaging with data-driven approaches may further enhance the accuracy of SCD prediction. These advancements may hold promise for improving outcomes and quality of life in the HCM population.

Our study has several limitations. First, although we used a large multicenter HCM cohort, the number of SCD-related events was modest, consistent with contemporary HCM cohort studies.²⁰ Nevertheless, the association between LARS and SCD-related events remained consistent across the overall cohort and key sensitivity analyses. Second, LGE% was not available in all patients because baseline CMR was not routinely performed in this observational cohort. In addition, CMR availability differed between study centers, and baseline characteristics differed between patients with and without CMR. Analyses incorporating LGE% were therefore restricted to the CMR subcohort with available LGE data. In this subcohort, LARS remained independently associated with SCD-related events after adjustment for LGE%, supporting its prognostic value beyond myocardial fibrosis. Third, although studies with substantial LA foreshortening were excluded, dedicated nonforeshortened LA views were not routinely acquired during the earlier study period. Therefore, variability in image acquisition may have affected LARS measurements, particularly in earlier studies. Finally, more detailed phenotypic information, including genetic testing, could provide further insights into SCD risk factors in patients with HCM.

CONCLUSION

LARS was an independent predictor of SCD-related events in patients with HCM. It further stratifies risk among patients classified as low-to-intermediate risk according to the HCM Risk-SCD score. Incorporation of LARS may improve risk stratification and support clinical decision-making regarding primary SCD prevention.

DATA AVAILABILITY

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

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

Generative artificial intelligence was not used for content generation or any part of this study.

DISCLOSURES STATEMENT

H. K. Kim is a consultant for BMS Korea and receives research grants from BMS and Chong Kun Dang Pharmaceutical Corp. The other authors had no conflicts to declare.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.echo.2026.08.007>.

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