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ORIGINAL PAPER

Left ventricular global longitudinal strain as a prognosticator in hypertrophic cardiomyopathy with a low-normal left ventricular ejection fraction

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Aims The aim of this study was to investigate the prognostic utility of left ventricular (LV) global longitudinal strain (LV-GLS) in patients with hypertrophic cardiomyopathy (HCM) and an LV ejection fraction (LVEF) of 50–60%.

Methods and results This retrospective cohort study included 349 patients with HCM and an LVEF of 50–60%. The primary outcome was a composite of cardiovascular death, including sudden cardiac death (SCD) and SCD-equivalent events. The secondary outcomes were SCD/SCD-equivalent events, cardiovascular death (including SCD), and all-cause death. The final analysis included 349 patients (mean age 59.2 ± 14.2 years, men 75.6%). During a median follow-up of 4.1 years, the primary outcome occurred in 26 (7.4%), while the secondary outcomes of SCD/SCD-equivalent events, cardiovascular death, and all-cause death occurred in 15 (4.2%), 20 (5.7%), and 34 (9.7%), respectively. After adjusting for age, atrial fibrillation, ischaemic stroke, LVEF, and left atrial volume index, absolute LV-GLS (%) was independently associated with the primary outcome [adjusted hazard ratio (HR) 0.88, 95% confidence interval (CI) 0.788–0.988, $P = 0.029$]. According to receiver operating characteristic analysis, 10.5% is an optimal cut-off value for absolute LV-GLS in predicting the primary outcome. Patients with an absolute LV-GLS ≤ 10.5% had a higher risk of the primary outcome than those with an absolute LV-GLS > 10.5% (adjusted HR 2.54, 95% CI 1.117–5.787, $P = 0.026$). Absolute LV-GLS ≤ 10.5% was an independent predictor for each secondary outcome ($P < 0.05$).

Conclusions LV-GLS was an independent predictor of a composite of cardiovascular death, including SCD/SCD-equivalent events, in patients with HCM and an LVEF of 50–60%. Therefore, LV-GLS can help in risk stratification in these patients.

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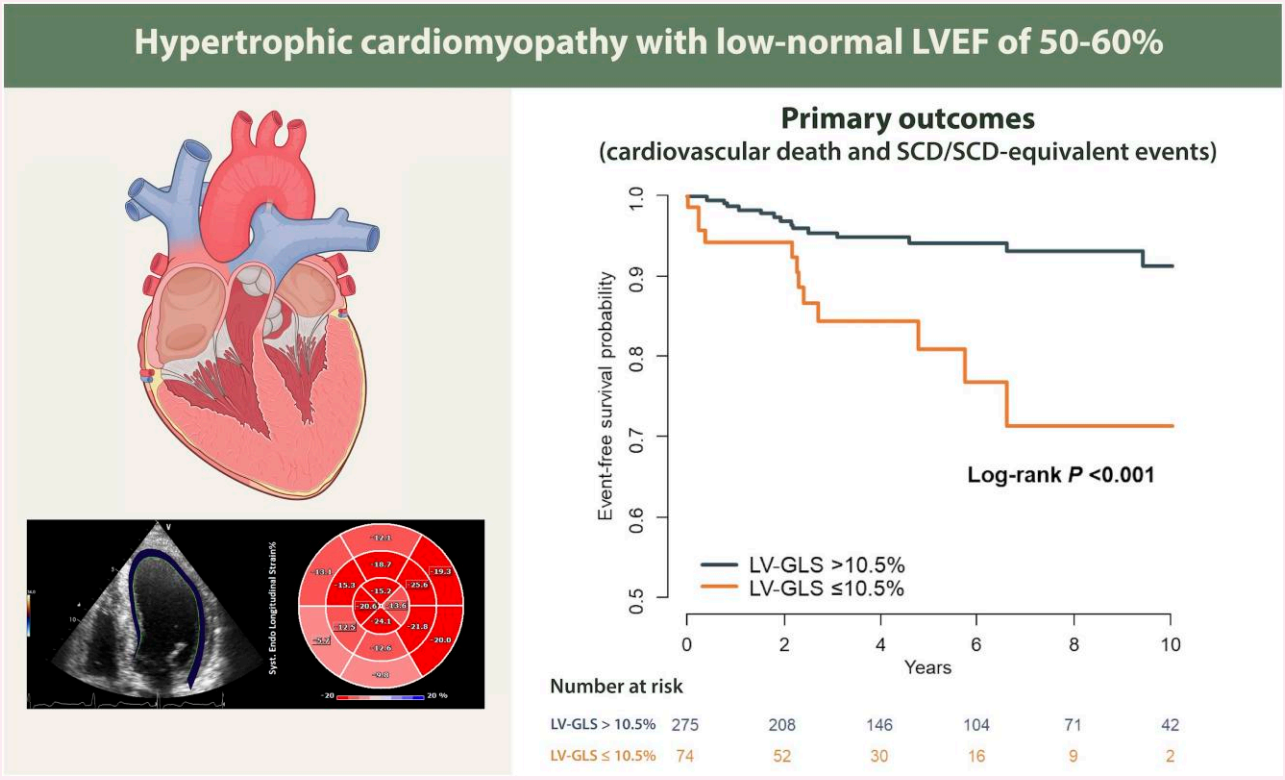
Graphic Abstract



Left ventricular global longitudinal strain (LV-GLS) predicts cardiovascular outcomes, encompassing cardiovascular death including sudden cardiac death (SCD) and SCD-equivalent events over 10 years of follow-up, with a median follow-up of 4.1 years in patients with hypertrophic cardiomyopathy and low-normal left ventricular ejection fraction of 50–60%. According to the receiver operating characteristic analysis, the best cut-off value of the absolute LV-GLS was ≤10.5% for predicting cardiovascular outcomes in this population.

Keywords left ventricular systolic dysfunction • sudden cardiac death • mortality • risk stratification

Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common inherited cardiomyopathy, with an estimated prevalence of approximately 1 in 500 of the general population.[1] Over the last decades, advances in diagnostic and therapeutic strategies for HCM have improved risk stratification for sudden cardiac death (SCD) and allowed patients with HCM to expect a normal lifespan.[2–4] However, cardiovascular complications, emerging as the leading causes of morbidity and mortality in these patients, are yet to be resolved.[5–8]

Left ventricular (LV) systolic dysfunction, defined as an LV ejection fraction (LVEF) of less than 50%, is an uncommon but serious condition that can lead to life-threatening events in patients with HCM.[9,10] The 2020 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for HCM endorse LVEF < 50% as a Class IIa indication for implantable cardioverter-defibrillator (ICD) therapy for primary prevention.[11] We recently reported that patients with HCM and low-normal LVEF of 50–60% had a poorer long-term prognosis than those with LVEF > 60%, owing to increased hospitalizations for heart failure and cardiovascular death.[12] However, some patients with HCM with a low-normal LVEF may transition from a normal LVEF of >60% to a reduced LVEF of <50%, while others may not.[13] As a result, a strategy for more detailed risk stratification in patients with HCM and low-normal LVEF is necessary.

Assessing of LV global longitudinal strain (LV-GLS) by speckle-tracking echocardiography is a reliable and reproducible technique for measuring myocardial function.[14] Furthermore, over the last few decades, evidence has consistently shown that LV-GLS is more sensitive and superior to LVEF in detecting early or subclinical LV systolic dysfunction.[15,16] Therefore, this study aimed to determine the predictive usefulness of LV-GLS for risk stratification in patients with HCM and an LVEF of 50–60%.

Methods

Study population

This cohort study enrolled adult patients with HCM diagnosed between 2008 and 2019 at two tertiary university hospitals (Seoul National University Hospital and Seoul National University Bundang Hospital). The standard diagnostic criteria for HCM were met by all patients, which included a hypertrophied, non-dilated LV with a maximal wall thickness of ≥15 mm without abnormal loading conditions sufficient to explain LV hypertrophy; a more limited wall thickness of ≥13 mm was used as a cut-off when a family history of HCM was present (see Supplementary data online, *Methods*).[17,18] The study's flowchart is depicted in *Figure 1*. Following the exclusion of patients with reduced or preserved LVEF (i.e. LVEF of ≤50% or ≥60%), those with LVEF of 50–60% were ultimately included.

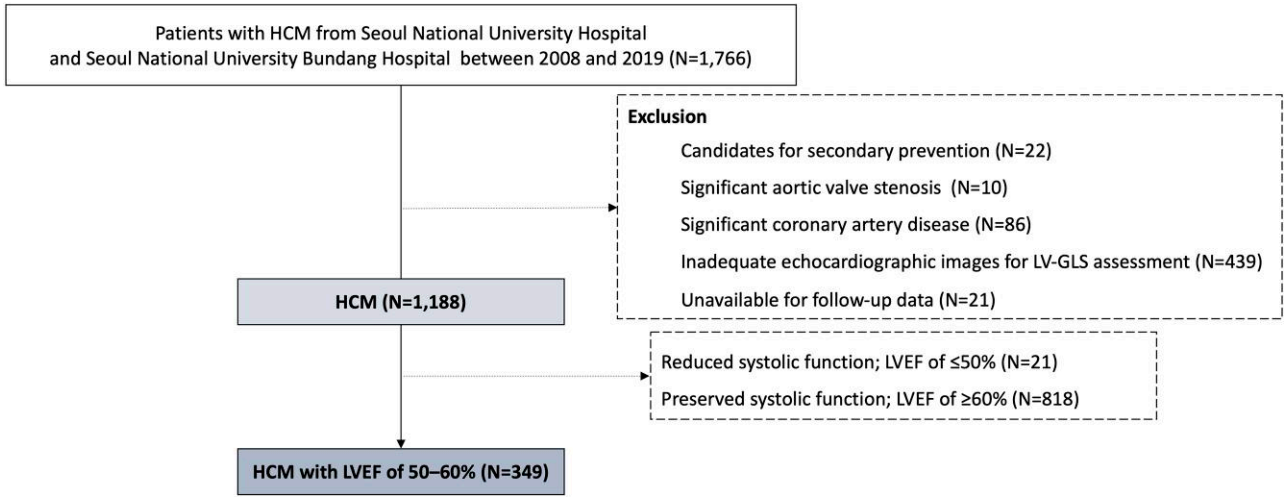


Figure 1 Flow chart of the study design. HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain.

The institutional review boards of Seoul National University Hospital (No. H-2003-502-1107) and Seoul National University Bundang Hospital (No. B-2004/604-40) approved this study as adhering to the Declaration of Helsinki. The requirement to obtain informed patient consent was waived due to the study's retrospective nature and analysis.

Measurement of LV-GLS

A comprehensive transthoracic 2D Doppler echocardiography was performed according to the current guidelines using commercial ultrasound machines (see Supplementary data online, *Methods*).[19–22] The retrospective measurement of LV-GLS was performed by an experienced, blinded echocardiographer using the initial echocardiographic images used for measuring LVEF. The LV-GLS analysis was conducted offline using Imaging Arena Cardiac Performance Analysis software (Version 4.6, Tomtec Imaging System, Munich, Germany), allowing reproducible and reliable offline strain analysis at the core laboratory.[23] The endocardial border was manually traced at end-systole after carefully obtaining apical two-, three-, and four-chamber images at a 40–90 Hz frame rate. The LV-GLS was calculated automatically from all segmental longitudinal strain values (*Figure 2*). The inter-class correlation coefficients for inter- and intra-observer variability for LV-GLS were 0.96 and 0.94, respectively.[24,25] LV-GLS was calculated as the average of three cardiac cycles in patients with atrial fibrillation. LV-GLS values are negative; however, this study used absolute LV-GLS for intuitive interpretation, with higher absolute values (more negative) indicating better function.

Primary and secondary outcomes

The primary outcome was a composite of cardiovascular death, including SCD and SCD-equivalent events, such as documented ventricular tachycardia/fibrillation, appropriate ICD shocks, and aborted SCD. The secondary outcomes were SCD/SCD-equivalent events, cardiovascular death (including SCD), and all-cause death. Detailed definitions of the outcomes were explained in Supplementary data online, *Methods*.

Each patient was followed from the date of the initial echocardiography until the occurrence of the study endpoints, death from any cause, or the end of the study follow-up (31 December 2020), whichever came first, or for up to 10 years.

Statistical analysis

The baseline characteristics of the study population were expressed as mean ± standard deviation or median (interquartile range) for continuous variables and as numbers (percentages) for categorical variables. Continuous variables were compared using Student's *t*-test and Wilcoxon-signed rank sum test, and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Event rates were expressed as a percentage of 100 person-years. Kaplan–Meier methods with the log-rank test and the Cox proportional hazards model were used for survival analysis. The initial echocardiographic evaluation for HCM was used as the index date. After verifying the proportional hazards assumption based on the Schoenfeld residuals, Cox proportional hazard regression analysis was performed to calculate hazard ratios (HRs) with a 95% confidence interval (CI) and a *P*-value. Variables achieving a *P*-value of <0.1 in the univariate Cox regression model were included in a multivariate model. The optimal cut-off value of LV-GLS (%) was calculated by receiver operating characteristic (ROC) analysis and the likelihood ratio test statistic.

A two-tailed *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed with the R programming version 4.2.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline clinical profile and echocardiographic data

The final analysis included 349 patients with HCM. The mean age of the study population was 59.2 ± 14.2 years, with 264 (75.6%) men. In the entire study population, the mean value of LV-GLS was 13.9 ± 4.0%, which was normally distributed in patients with a low-normal LVEF of 50–60% (see Supplementary data online, *Figure S1*).

When the study population was divided into two groups based on the mean value of 13.9%, the mean values of LV-GLS in the high (more negative) and low (less negative) absolute LV-GLS groups were 17.1 ± 2.5% and 10.7 ± 2.3%, respectively. The low LV-GLS group was older than the high LV-GLS group (mean age, 60.9 ± 13.9

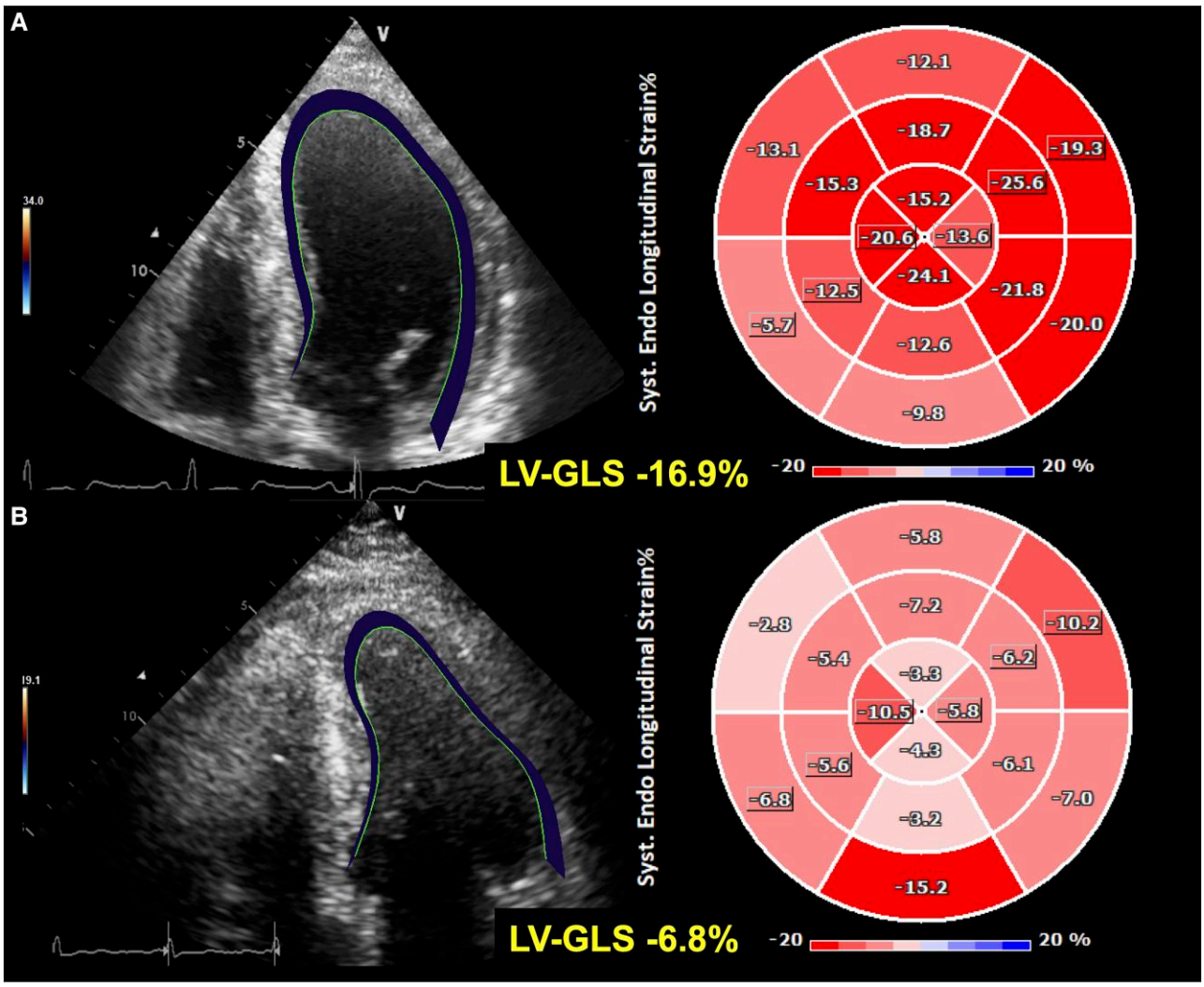


Figure 2 Two representative cases of LV-GLS measurement. (*A*) A 49-year-old male with LVEF of 57% and LV-GLS of 16.9% showing no primary outcomes during the follow-up. (*B*) A 48-year-old male with LVEF of 57% and LV-GLS of 10.4% who experienced sudden cardiac death during the follow-up. For abbreviations, see *Figure 1*.

years vs. 57.5 ± 14.4 years, $P = 0.028$). The prevalence of baseline comorbidities did not differ significantly between the two groups, except for atrial fibrillation (13.7% in the high LV-GLS group vs. 27.6% in the low LV-GLS group, $P = 0.002$). Regarding the echocardiographic parameters, the high LV-GLS group had lower maximal LV wall thickness (18.2 ± 3.0 mm vs. 20.0 ± 3.9 mm, $P < 0.001$) and left atrial (LA) volume index (46.6 ± 20.7 vs. 56.2 ± 25.1, $P < 0.001$) than the low LV-GLS group. *Table 1* shows the baseline demographic and echocardiographic data for the low and high LV-GLS groups.

Primary outcome

During a median follow-up of 4.1 years (1.9–7.6 years), the primary outcome occurred in 26 (7.5%) patients with an incidence rate of 1.58/100 person-years. According to the ROC analysis, the optimal cut-off point of LV-GLS for the primary outcome was 10.5% (area under the curve = 0.674, 95% CI 0.578–0.770) (see Supplementary data online, *Figure S2*), which was verified by the likelihood ratio test statistic (see Supplementary data online, *Figure S3*). Patients with LV-GLS ≤ 10.5% (less negative) had higher incidence rates of primary outcomes than those with LV-GLS > 10.5% (more negative) (4.26/100 person-years vs. 1.03/100 person-years, $P = 0.003$; *Figure 3*).

In the survival analysis, Kaplan–Meier curves for the primary outcomes showed that patients with LV-GLS ≤ 10.5% had a worse prognosis than those with LV-GLS > 10.5% (*Figure 4A*). In the univariate analysis, LV-GLS (%) as a continuous variable was associated with the primary outcome (HR 0.85, 95% CI 0.769–0.940, $P = 0.002$). After adjusting for variables with $P < 0.1$ in the univariate analysis, such as age, atrial fibrillation, ischaemic stroke, LVEF (%), and LA volume index (mL/m^2) (see Supplementary data online, *Table S1*), higher absolute (more negative) LV-GLS (%), as a continuous variable, was independently associated with a lower risk of the primary outcome (adjusted HR 0.88, 95% CI 0.789–0.991, $P = 0.035$). In addition, LV-GLS ≤ 10.5%, as a categorical variable, was an independent predictor of the primary outcome in patients with HCM and LVEF of 50–60% (adjusted HR 2.52, 95% CI 1.103–5.743, $P = 0.028$, *Table 2*).

A spline-based HR curve to explore the impact of LV-GLS on primary outcomes in patients with HCM indicates an increased risk

Table 1 Baseline characteristics of the study population

Variable	Total $N = 349$	LVEF 50–60%		P
		High |LV-GLS| $n = 175$	Low |LV-GLS| $n = 174$	
Demographic data				
Age, years	59.2 ± 14.2	57.5 ± 14.4	60.9 ± 13.9	0.028
Male, *n* (%)	264 (75.6)	128 (73.1)	136 (78.2)	0.333
Systolic BP, mmHg	128.9 ± 17.2	127.9 ± 17.6	129.8 ± 16.8	0.365
Diastolic BP, mmHg	77.7 ± 11.3	77.6 ± 12.0	77.8 ± 0.7	0.896
Body mass index, kg/m^2	25.1 ± 3.6	24.6 ± 3.2	25.6 ± 3.9	0.007
Comorbidities, *n* (%)				
Hypertension	168 (48.1)	75 (42.9)	93 (53.4)	0.061
Diabetes mellitus	63 (18.1)	27 (15.4)	36 (20.7)	0.255
Dyslipidaemia	90 (25.8)	40 (22.9)	50 (28.7)	0.257
Atrial fibrillation	72 (20.6)	24 (13.7)	48 (27.6)	0.002
Ischaemic stroke	21 (6.0)	6 (3.4)	15 (8.6)	0.070
Risk factors for SCD, *n* (%)				
Family history of SCD	27 (7.7)	16 (9.1)	11 (6.3)	0.432
Unexplained syncope	42 (12.0)	22 (12.6)	20 (11.5)	0.885
NSVT	57 (30.3)	27 (28.7)	30 (31.2)	0.825
Maximal LV wall thickness	19.1 ± 3.6	18.2 ± 3.0	20.0 ± 3.9	<0.001
LVOTmaxPG, mmHg	13.8 ± 29.8	14.7 ± 37.3	12.8 ± 19.8	0.589
Echocardiographic data				
LV end-diastolic volume, mL	69.2 ± 20.9	70.9 ± 1.1	67.7 ± 20.7	0.176
LV end-systolic volume, mL	29.8 ± 9.2	30.2 ± 9.2	29.3 ± 9.1	0.407
LVEF, %	57.0 ± 2.3	57.3 ± 1.9	56.6 ± 2.5	0.002
|LV-GLS|, %	13.9 ± 4.0	17.1 ± 2.5	10.7 ± 2.3	<0.001
E velocity, m/s	0.63 ± 0.23	0.61 ± 0.22	0.64 ± 0.23	0.302
e′ velocity, cm/s	5.0 ± 2.2	5.1 ± 2.0	4.9 ± 2.4	0.352
E/e′ ratio	13.2 ± 7.1	12.9 ± 0.6	13.6 ± 7.6	0.402
LA volume index, mL/m^2	51.5 ± 23.5	46.6 ± 20.7	56.2 ± 25.1	<0.001

Continuous variables were presented as mean ± SD; categorical variables were presented as frequencies (percentages).
BP, blood pressure; *E* velocity, early diastolic transmitral inflow velocity; e′ velocity, early diastolic mitral annular velocity; LA, left atrial; LV, left ventricular; LVEF, LV ejection fraction; LV-GLS, LV global longitudinal strain; LVOTmaxPG, maximal LV outflow tract pressure gradient; NSVT, non-sustained ventricular tachycardia; SCD, sudden cardiac death.

when LV-GLS was >10.5% (*Figure 5*). Subgroup analyses were performed based on sex (men and women), maximal wall thickness (median value of maximal wall thickness; >18 and ≤18 mm), and LA volume index (median value of LA volume index; >50 and ≤50 mL/m^2). All analyses revealed a similar trend in the association between LV-GLS ≤ 10.5% and the risk of the primary outcome as in the original main analysis, with no heterogeneity observed (*P* for interaction >0.05 in all; Supplementary data online, *Table S2*).

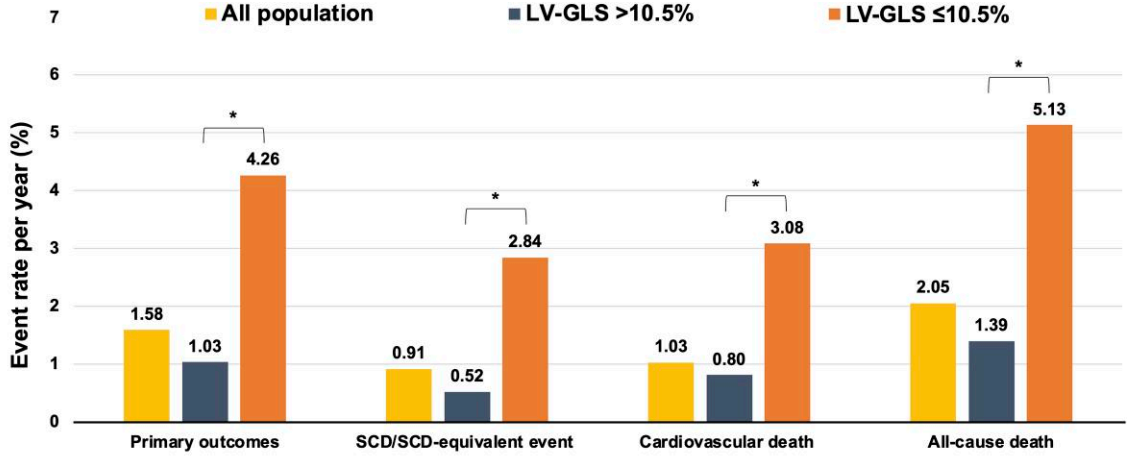
Secondary outcomes

Regarding secondary outcomes, 15 (4.3%), 20 (5.7%), and 34 (9.7%) patients experienced SCD/SCD-equivalent events, cardiovascular death, and all-cause death, respectively. The incidence rates of SCD/SCD-equivalent events, cardiovascular death, and all-cause death were 0.91, 1.03, and 2.05/100 person-years, respectively. Patients with LV-GLS ≤ 10.5% had higher incidence rates of individual secondary outcomes than those with LV-GLS > 10.5% (*Figure 3*).

Kaplan–Meier curves for SCD/SCD-equivalent events, cardiovascular death, and all-cause death demonstrated that event-free survival probability was significantly lower in patients with LV-GLS ≤ 10.5% than in those with LV-GLS > 10.5% (all $P < 0.05$ by log-rank test; *Figure 4B–D*). In univariate analysis, LV-GLS (%), as a continuous variable, was associated with the secondary outcomes (see Supplementary data online, *Table S3*). After adjusting for variables with $P < 0.1$ on the univariate analysis for each secondary outcome, a higher absolute LV-GLS% showed a significantly lower risk for cardiovascular death and all-cause death; LV-GLS ≤ 10.5% was an independent predictor for each secondary outcome, including SCD/SCD-equivalent events, cardiovascular death, and all-cause death (*Table 2*).

Discussion

This study demonstrated that an impaired LV-GLS was independently associated with a composite of cardiovascular death, including SCD and SCD-equivalent events in patients with HCM and an LVEF of 50–60%. Our findings contribute to sophisticated risk stratification of patients with HCM and a low-normal LVEF who are at risk of



Outcomes	Primary outcomes	SCD/SCD-equivalent events	Cardiovascular death	All-cause death
All population (N=349)	26 (7.5%)	15 (4.3%)	20 (5.7%)	34 (9.7%)
LV-GLS >10.5% (N=275)	14 (5.1%)	7 (2.5%)	11 (4.0%)	19 (6.9%)
LV-GLS ≤10.5% (N=74)	12 (16.2%)	8 (10.8%)	9 (12.2%)	15(20.3%)

Figure 3 The incidence rate of primary and secondary outcomes. Bar graphs illustrate the incidence rates of primary and secondary outcomes in patients with HCM and LVEF of 50–60% and two groups stratified by the optimal cut-off value of absolute LV-GLS (i.e. >10.5% and ≤10.5%). Compared with the high absolute LV-GLS group, the incidence rates were significantly higher in the low absolute LV-GLS group for the primary outcome ($P = 0.003$) and secondary outcomes, including sudden cardiac death (SCD)/SCD-equivalent events ($P = 0.005$), cardiovascular death ($P = 0.016$), and all-cause death ($P = 0.001$). An asterisk (*) indicates a significant difference between LV-GLS > 10.5% and ≤10.5% at $P < 0.05$. For abbreviations, see *Figure 1*.

cardiovascular complications. This study highlights the potential clinical value of impaired LV-GLS in patients with HCM and an LVEF of 50–60% as an additional independent predictor of long-term prognosis, particularly cardiovascular deaths, including SCD and SCD-equivalents events.

LV systolic function assessed by LVEF or LV-GLS in HCM

LV systolic dysfunction with progressive ventricular remodelling can occur over extended periods in patients with HCM.[9,26] Differentiating high-risk patients in this overlooked HCM population with a low-normal LVEF is clinically relevant because some patients with HCM and a low-normal LVEF can be in a transition phase to overt LV systolic dysfunction and end-stage HCM, necessitating early detection, management with heart failure medications, and close follow-up.[13] The potential mechanism underlying LV systolic dysfunction in HCM is partly associated with significant myocardial fibrosis and adverse remodelling,[27,28] which are explained by the interaction of micro-vascular ischaemia in the hypertrophied myocardium and apoptotic changes in cardiomyocytes, leading to progressive cardiomyocyte loss and fibrous replacement of the myocardium.[13]

Olivotto *et al.*[13] proposed four clinical stages of HCM: non-hypertrophic HCM, classic HCM phenotype, adverse remodelling, and overt dysfunction. Among these, the *adverse remodelling stage*, LVEF of 50–60%, represents worsening LV systolic function with relatively preserved clinical and haemodynamic balance. Notably, several structural and functional features may coexist during this stage, including a low-normal LVEF.[29] However, these phenomena are unlikely to be present in a single patient at the same time, given that HCM is a heterogeneous disease and that all clinical and pathological manifestations are not always present simultaneously.[13] Accordingly, a subset of HCM patients with an LVEF in the low-normal range may be at high risk and require more clinical attention. As a result, a more sensitive imaging marker other than LVEF can be helpful for this purpose, and LV-GLS is the best option due to its high sensitivity, reliability, and reproducibilitym.[15,16]

Previous studies have been conducted on the clinical implications of LV-GLS in assessing LV systolic function and clinical outcomes in patients with HCM.[30–33] Due in part to LVEF's limited usefulness in hypertrophic ventricles, LV-GLS appears to be more reliable and sensitive than LVEF at systolic dysfunction detection in HCM. LVEF is calculated by the changes in LV cavity volumes; therefore, hypertrophic ventricles result in preserved or even supernormal values of LVEF with a relatively smaller LV cavity. In contrast, LV-GLS practically offers a more sensitive measurement of subclinical LV myocardial systolic dysfunction, as myocardial strain describes the myocardial deformation and does not rely on a geometrical assumption.[34] In addition, previous studies reported that LV-GLS is associated with histopathologic features of myocardial hypertrophy, disarray, and fibrosis in patients with HCM.[35,36] Overall, LV-GLS could be a useful surrogate marker in identifying high-risk populations associated with myocardial fibrosis in patients with HCM and low-normal LVEF.

Role of LV-GLS in patients with HCM and low-normal LVEF

In a previous study, we demonstrated that LV-GLS played a significant role in addition to the established risk models in predicting SCD in patients with HCM.[24] Furthermore, we reported that patients with HCM and a low-normal LVEF of 50–60% have a worse long-term outcome than those with an LVEF ≥ 60% because of increased risks of hospitalizations for heart failure and cardiovascular death.[12] Therefore, it is critical to identify at-risk HCM patients early who have incipient overt LV dysfunction and are in the transition phase to end-stage HCM. One of

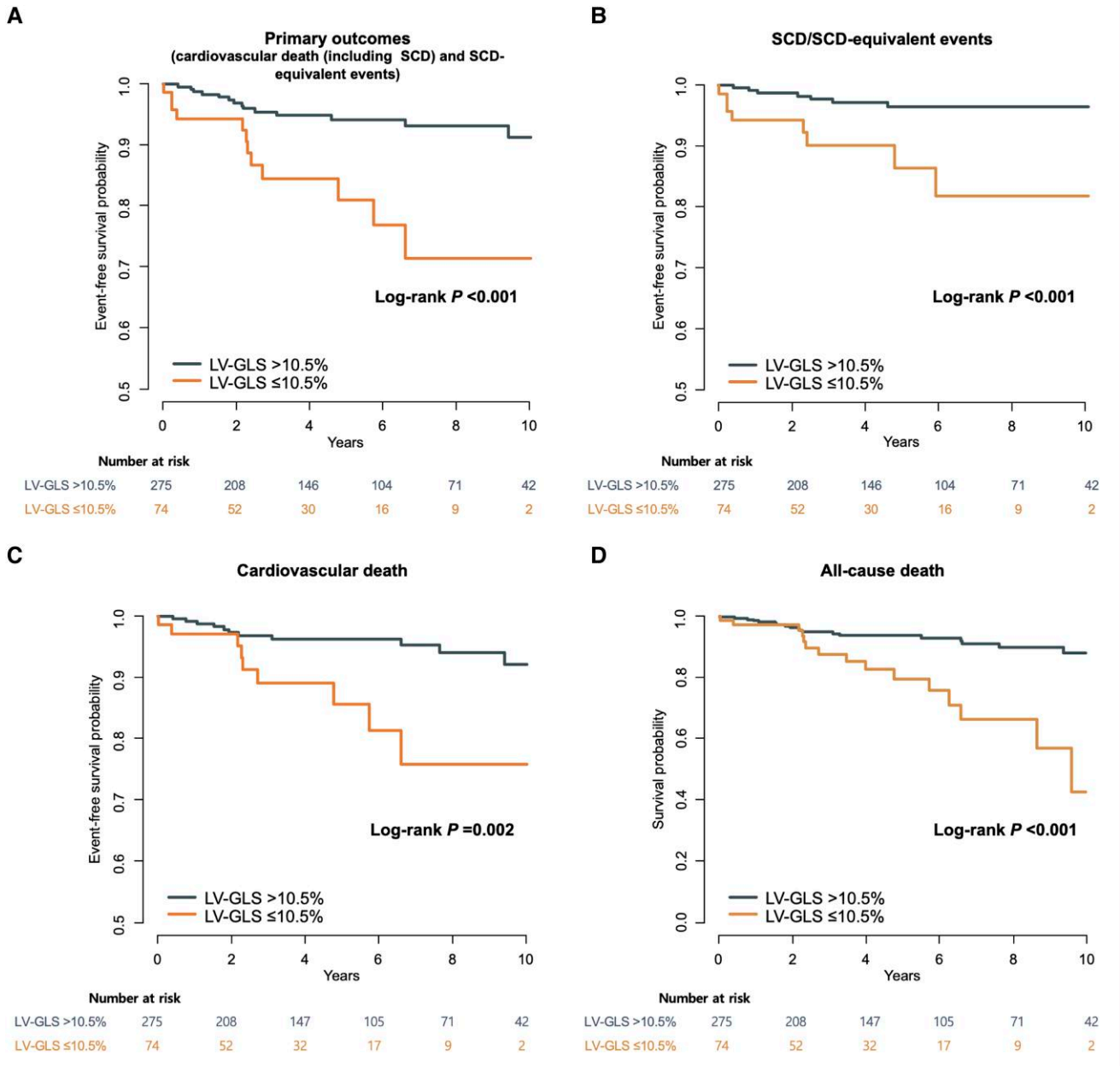


Figure 4 Kaplan–Meier curve of the primary and secondary outcome in patients with HCM. Kaplan–Meier curves demonstrate the event-free survival probability of (*A*) primary outcome encompassing cardiovascular death, including SCD and SCD-equivalent events, and secondary outcomes, including (*B*) SCD/SCD-equivalent events, (*C*) cardiovascular death, and (*D*) all-cause death, according to the absolute value of LV-GLS (i.e. >10.5% vs. ≤10.5%), in patients with HCM and low-normal LVEF of 50–60%. For abbreviations, see *Figures 1* and 2.

the key findings in the present study is that LV-GLS can be clinically used as an imaging surrogate marker to discern high-risk HCM patients among those with a low-normal LVEF. A previous study also partly supported the idea that some patients with HCM and an LVEF of 50–60% are at higher risk of further systolic function decline and progression to 'end-stage' HCM.[37] Our findings support the clinical significance of low-normal LVEF in patients with HCM while highlighting a new prognostic indicator for identifying a vulnerable subgroup among those with 'grey zone' LVEF (i.e. LVEF 50–60%).

LV-GLS is demonstrated to be a sensitive imaging marker reflecting comprehensive myocardial functional and histopathologic status in patients with HCM. It may be clinically useful in patients with HCM and a low-normal LVEF of 50–60%, among whom some patients are at risk of transitioning to the overt dysfunction stage or experiencing adverse cardiovascular events. However, LV-GLS is obviously missing from the list of features for ICD implantation indications for primary prevention aimed at improving the prognosis of patients with HCM.[11,17] This might be because LV-GLS usually varies with multiple conditions; therefore, defining an optimal cut-off is not straightforward. However, we proposed an optimal cut-off value of LV-GLS for outcome prediction that was relatively lower (i.e. 10.5%) than previous studies on LV-GLS in patients with HCM[33]; this is not surprising given that the study population already had low-normal LVEF. The LV-GLS cut-off values in our report have not been tested in other HCM populations;

Table 2 Cox proportional regression analysis

Variable	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	P	HR (95% CI)	P
Primary outcome				
|LV-GLS|, %	0.850 (0.769–0.940)	0.002	0.884 (0.789–0.991)	0.035
|LV-GLS| ≤ 10.5%	3.801 (1.750–8.257)	<0.001	2.517 (1.103–5.743)	0.028
SCD/SCD-equivalent events				
|LV-GLS|, %	0.851 (0.747–0.971)	0.016	0.891 (0.773–1.028)	0.114
|LV-GLS| ≤ 10.5%	4.800 (1.737–13.26)	0.002	3.072 (1.041–9.068)	0.042
Cardiovascular death				
|LV-GLS|, %	0.845 (0.753–0.948)	0.004	0.869 (0.761–0.993)	0.039
|LV-GLS| ≤ 10.5%	3.723 (1.532–9.051)	0.004	2.771 (1.074–7.149)	0.035
All-cause death				
|LV-GLS|, %	0.855 (0.782–0.934)	<0.001	0.869 (0.787–0.959)	0.005
|LV-GLS| ≤ 10.5%	3.741 (1.887–7.414)	<0.001	3.406 (1.574–7.369)	0.002

The primary outcome is a composite of cardiovascular death including SCD and SCD-equivalent events.
CI, confidence interval; HR, hazard ratio; LV, left ventricular; LV-GLS, LV global longitudinal strain; SCD, sudden cardiac death.
[a]Adjustment for variables with a $P < 0.01$ in the univariate analysis (refer to Supplementary data online, *Tables S1* and *S3*).

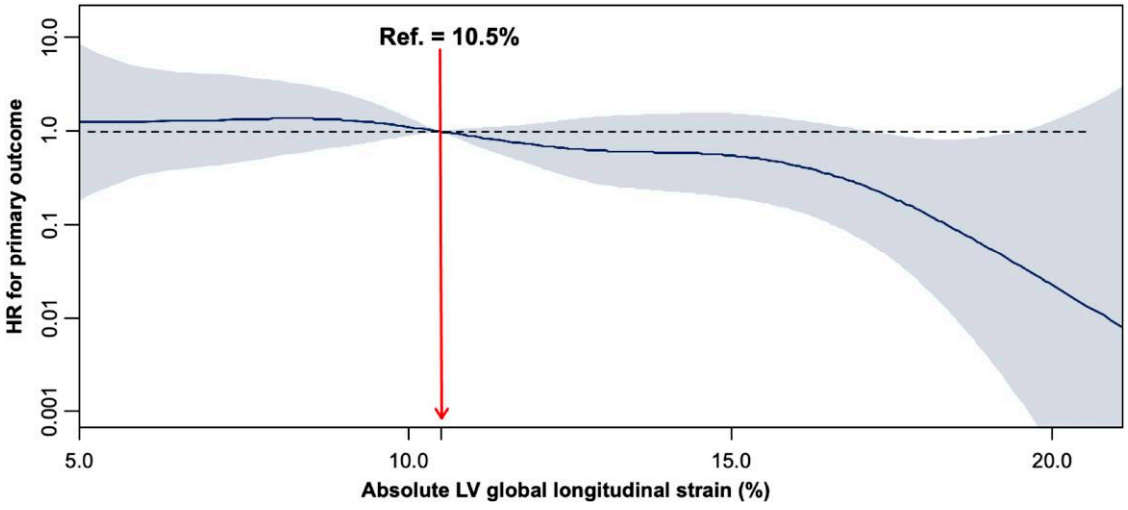


Figure 5 Spline-based hazard ratio (HR) curve for LV-GLS on the primary outcome. The solid line represents the relationship between LV-GLS and primary outcomes, including SCD-equivalent events and cardiovascular death, along with the corresponding 95% confidence limits in patients with HCM and low-normal LVEF of 50–60%. For abbreviations, see *Figures 1* and *2*.

therefore, additional studies are required to validate the LV-GLS cut-off value for clinical outcomes in patients with HCM and LVEF of 50–60% for external application.

Study limitations

First, this was a retrospective study, including the Korean population. Despite our efforts to account for confounding factors, it is important to acknowledge that some biases may still exist. Furthermore, one of the limitations of this study is the non-inclusion of individuals from diverse racial backgrounds. The sample size was relatively small, attributable to stringent inclusion criteria. Nonetheless, this is the first study to examine the prognostic implication of LV-GLS in identifying high-risk HCM populations with a low-normal LVEF with careful long-term follow-up. Second, there was no information on medical treatment for preventing the progression of heart failure. However, no medication has been proved to have clinical benefits for improving the prognosis of patients with HCM and low-normal LVEF. Third, we did not assess diastolic function in patients with HCM. Future studies should be considered incorporating comprehensive diastolic function assessment to obtain a more comprehensive understanding of the cardiac function profile in patients with HCM. Finally, the cut-off value for

LV-GLS for prognosis in this population may vary depending on the clinical outcome of interest and the strain analysis software used. Hence, large-scale external validation is required to confirm the optimal cut-off value of LV-GLS in patients with HCM and a low-normal LVEF. In addition, future investigations with larger sample sizes and diverse ethnicities are needed to confirm, extend, and strengthen the results presented in our study. Further, it would be better to incorporate patients with HCM across a broader spectrum of LVEF values to investigate the incremental value of LV-GLS.

Conclusion

In patients with HCM and a low-normal LVEF of 50–60%, LV-GLS was a prognosticator for long-term cardiovascular outcomes, such as cardiovascular death, including SCD and SCD-equivalent events. Furthermore, LV-GLS could predict SCD/SCD-equivalent events, cardiovascular death, and all-cause death. Therefore, LV-GLS assessment of LV systolic function can improve cardiovascular risk stratification in patients with HCM and a low-normal LVEF.

Supplementary data

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

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Conflict of interest: All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Data availability

All data are incorporated into the article and its online supplementary material.

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