J Cardiovasc Imaging. 2023 Apr;31(2):85-95
https://doi.org/10.4250/jcvi.2022.0053
pISSN 2586-7210·eISSN 2586-7296

Journal of Cardiovascular Imaging JCVI

Original Article

Check for updates

Role and Clinical Importance of Progressive Changes in Echocardiographic Parameters in Predicting Outcomes in Patients With Hypertrophic Cardiomyopathy

Kyehwan Kim, MD[1], Seung Do Lee, MD[1], Hyo Jin Lee, MD[1], Hangyul Kim, MD[1], Hye Ree Kim, MD[1], Yun Ho Cho, MD[2], Jeong Yoon Jang, MD[2], Min Gyu Kang, MD, PhD[1], Jin-Sin Koh, MD, PhD[1], Seok-Jae Hwang, MD, PhD[1], Jin-Yong Hwang, MD, PhD[1], and Jeong Rang Park, MD, PhD[1]

[1]Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital and Gyeongsang National University School of Medicine, Jinju, Korea
[2]Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Changwon Hospital and Gyeongsang National University School of Medicine, Changwon, Korea

OPEN ACCESS

Received: Apr 19, 2022
Revised: Nov 29, 2022
Accepted: Dec 11, 2022
Published online: Jan 13, 2023

Address for Correspondence:
Jeong Rang Park, MD, PhD
Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital and Gyeongsang National University School of Medicine, 79 Gangnam-ro, Jinju 52727, Korea.
Email: parkjrang@gmail.com

ABSTRACT

BACKGROUND: The prognostic utility of follow-up transthoracic echocardiography (FU-TTE) in patients with hypertrophic cardiomyopathy (HCM) is unclear, specifically in terms of whether changes in echocardiographic parameters in routine FU-TTE parameters are associated with cardiovascular outcomes.
METHODS: From 2010 to 2017, 162 patients with HCM were retrospectively enrolled in this study. Using echocardiography, HCM was diagnosed based on morphological criteria. Patients with other diseases that cause cardiac hypertrophy were excluded. TTE parameters at baseline and FU were analyzed. FU-TTE was designated as the last recorded value in patients who did not develop any cardiovascular event or the latest exam before event development. Clinical outcomes were acute heart failure, cardiac death, arrhythmia, ischemic stroke, and cardiogenic syncope.
RESULTS: Median interval between the baseline TTE and FU-TTE was 3.3 years. Median clinical FU duration was 4.7 years. Septal trans-mitral velocity/mitral annular tissue Doppler velocity (E/e'), tricuspid regurgitation velocity, left ventricular ejection fraction (LVEF), and left atrial volume index (LAVI) at baseline were recorded. LVEF, LAVI, and E/e' values were associated with poor outcomes. However, no delta values predicted HCM-related cardiovascular outcomes. Logistic regression models incorporating changes in TTE parameters had no significant findings. Baseline LAVI was the best predictor of a poor prognosis. In survival analysis, an already enlarged or increased size LAVI was associated with poorer clinical outcomes.
CONCLUSIONS: Changes in echocardiographic parameters extracted from TTE did not assist in predicting clinical outcomes. Cross-sectionally evaluated TTE parameters were superior to changes in TTE parameters between baseline and FU at predicting cardiovascular events.

Keywords: Cardiac arrhythmia; Hypertrophic cardiomyopathy; Ischemic stroke; Echocardiography

Journal of Cardiovascular Imaging JCVI

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common genetic disease in which the heart muscles become thickened. HCM is associated with mutations in genes encoding sarcomere proteins.[1)2)] Despite its characteristic manifestations, such as asymmetric myocardial thickness, the symptoms and signs of HCM are not fully understood based on simple categorization of thickened myocardium.[3-6)] Myocyte fibrosis, remodeling of small-sized vessels, and valvular dysfunction are common in HCM, resulting in a variety of clinical manifestations ranging from asymptomatic to heart failure, arrhythmia, sudden cardiac death, and end-stage HCM (ES-HCM).[1)2)7)] It is difficult to predict clinical outcomes in patients with HCM. Additionally, HCM is a progressive and dynamic disease in which thickening of the left ventricle (LV) walls affects LV diastolic dysfunction, leading to increases in LV filling pressure that in turn increases left atrium size and cause pulmonary hypertension.[8-10)] Furthermore, the ES phase of HCM, namely LV systolic dysfunction, occurs in some patients.[11-13)]

The American College of Cardiology (ACC)/American Heart Association (AHA) recently reported guidelines for patients with HCM. The ACC/AHA joint committees recommend performing comprehensive transthoracic echocardiography (TTE) for initial evaluation of patients with HCM.[2)14)] Furthermore, it is recommended that in asymptomatic patients with HCM, routine follow-up TTE (FU-TTE) be performed every 1–2 years to assess changes in LV systolic and diastolic function, wall thickness, chamber size, LV outflow tract (LVOT) obstruction (LVOTO), and valvular disease. Identifying HCM progression into LV systolic dysfunction, newly developed LVOTO, and significant valvular disease based on serial FU-TTE is important for dynamic management of patients with HCM. However, the appropriate FU interval for TTE and the ability of changes in echocardiographic parameters to predict clinical outcomes are still unclear.

The current study aimed to clarify the necessity of FU conventional TTE in patients with HCM and identify echocardiographic predictors of poor cardiovascular outcomes.

METHODS

Study population

The study population comprised patients diagnosed with HCM at Gyeongsang National University Hospital (Jinju, Korea) between January 2010 and December 2017. HCM was diagnosed as an unexplained myocardial disease with maximal LV wall thickness of ≥ 15 mm involving more than one segment or LV wall thickness > 13 mm with confirmed information about HCM and sudden cardiac death in first-degree relatives.[2)] Patients aged ≥ 18 years with at least 2 available TTEs were included in the study. There were 491 patients with HCM. We excluded patients without FU-TTE (n = 218), with an interval of less than one year between the initial and FU-TTE (n = 109), with severe aortic stenosis (n = 1), and those with previous surgical dual valve replacement (n = 1). A schematic diagram of the inclusion and exclusion criteria is provided in **Figure 1**. Data on cardiovascular risk factors including diabetes mellitus, hypertension, coronary artery disease, ischemic stroke and arrhythmia, laboratory test results, and history of taking a medicine for cardiovascular diseases were collected from medical records. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital, which waived the requirement for informed consent (IRB approval number: GNUH 2021-10-017).

Echocardiographic evaluation

All TTEs were performed according to American Society of Echocardiography (ASE) guidelines. [15-17)] Echocardiographic parameters were retrieved from a database of electronic medical records. LV dimensions at the tip of the mitral valves and level of the chordae tendineae were measured using the M-mode or 2D TTE in parasternal long- or short-axis views. After scanning whole LV segments, maximal LV wall thickness was selected and measured using M-mode or 2-dimensional TTE. Left atrial volume index (LAVI), left ventricular ejection fraction (LVEF), peak mitral inflow Doppler E-wave and A-wave velocities, mitral valve E/A ratio, mitral septal and lateral tissue Doppler e' velocities, a' velocities, and E to e' velocities (E/e') were determined. Tricuspid regurgitation (TR) peak velocity and right ventricular systolic pressure (RVSP, TR velocity, and right atrial pressure estimated by inferior vena cava size and plethora) were measured. Diastolic function was classified according to the 2016 ASE/European Association of Cardiovascular Imaging guidelines.[16)] LVOTO was defined as a peak pressure gradient of pulse-wave Doppler at the LVOT that exceeded 30 or more mmHg at rest or 50 or greater mmHg during the Valsalva maneuver in the absence of other obstructive or hemodynamic causes.

The first evaluation since 2010 using TTE in patients diagnosed with HCM was defined as the baseline TTE. The FU evaluation, which was performed at least one year after the baseline evaluation and before a defined cardiovascular event occurred in the current study, was defined as the FU-TTE (**Figure 1**). Changes in echocardiographic measurements were computed

 https://doi.org/10.4250/jcvi.2022.0053

Journal of Cardiovascular Imaging JCVI

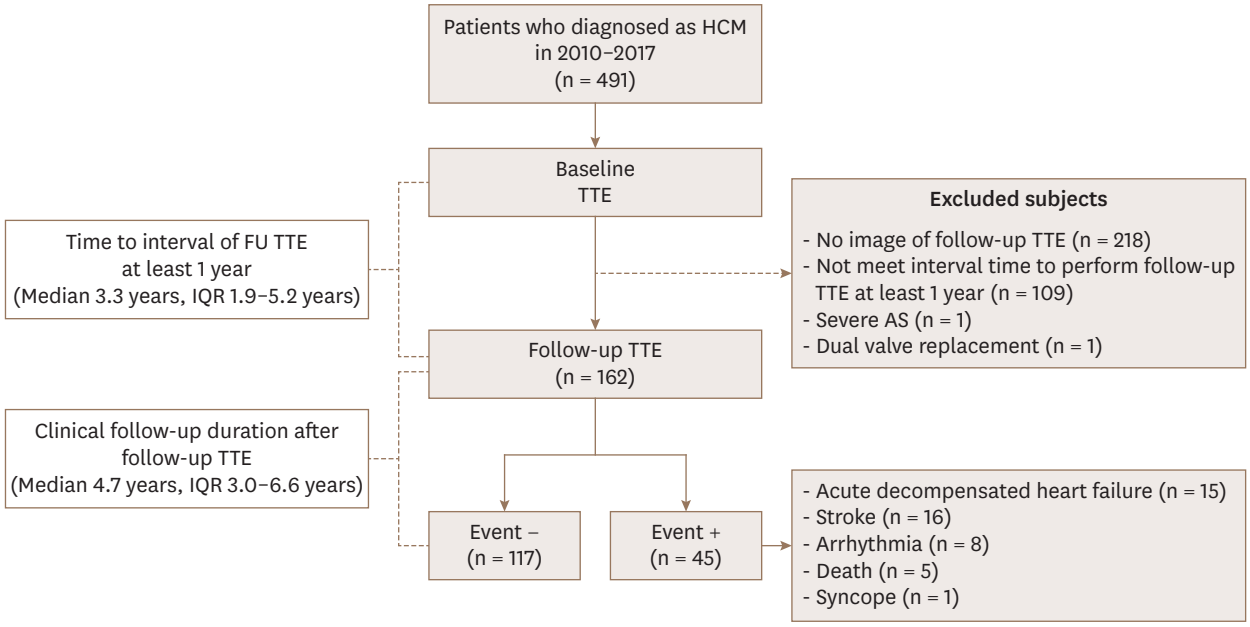


Figure 1. Schematic diagram of inclusion criteria and FU of patients with HCM.
AS: aortic stenosis, FU, follow-up, HCM: hypertrophic cardiomyopathy, IQR: interquartile range, TTE: transthoracic echocardiography.

by converting the different time intervals between the 2 examinations into change per year.

Clinical outcomes and FU

The following clinical outcomes were considered: (i) acute decompensated heart failure; (ii) cardiac death; (iii) fatal arrhythmia (ventricular fibrillation, ventricular tachycardia, and implantation of cardiac implantable electronic devices); (iv) ischemic stroke or transient ischemic attack; and (v) syncope. ES-HCM was defined as an LVEF of less than 50% at any time. Acute decompensated heart failure was defined as unscheduled admission and intravenous diuretic administration for symptoms and signs of congestive heart failure. The clinical FU duration after FU-TTE was calculated. Consequently, the interval between the 2 TTEs was not included in the FU period.

Statistical analysis

Continuous variables are presented as means ± standard deviations. After confirming the normality of data using the Kolmogorov-Smirnov test, Student's t-test or Mann-Whitney U test was performed. Categorical variables are expressed as numbers and percentages. Fisher's exact test was used to analyze categorical variables. Patients were assigned to event or no-event groups according to clinical outcomes. In addition, changed values between baseline and FU-TTE were expressed as changes per year to standardize the different times due to differences among patients in their baseline and FU-TTE dates. Wilcoxon signed-rank test or paired t-test was used to assess the significance of differences in baseline and FU echocardiographic parameters under non-parametric or parametric distributions, respectively. Logistic regression analysis of clinical and echocardiographic variables with $p < 0.05$ from the univariate analysis was performed to determine if any of these parameters predicted clinical outcomes. Model 1, which included statistically significant clinical factors and baseline echocardiography, was analyzed in the multivariate analysis. Model 2 included the clinical factors included in Model 1 and significant factors on FU-TTE to determine independent predictors. Changes in baseline and FU values were additionally included in regression Model 3. Age, hypertension, ischemic stroke, a history of acute decompensated heart failure, atrial fibrillation, estimated glomerular filtration rate, LVEF, LAVI, peak E velocity, E/e' and TR peak velocity were included as adjusting factors in the logistic regression models. Kaplan-Meier survival analysis with the strongest predictor was used. In survival analysis, LAVI was further refined and analyzed. Based on baseline values, we designated an increased-LAVI group that comprised patients with a size increase of 10% or more in LAVI during the indexed FU and a decreased-LAVI group that comprised patients with an LAVI that decreased in size by 10% or more. A change in LAVI size between –10% and 10% was considered to be within the error range and individuals who met this criterion were assigned to the static LAVI group. The significance level was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics (version 21.0; IBM Corp., Armonk, NY, USA), MedCalc Statistical Software version 19.2.5

https://doi.org/10.4250/jcvi.2022.0053

Journal of Cardiovascular Imaging JCVI

(MedCalc Software Ltd, Ostend, Belgium), and R-studio version 1.2.5033 (R Foundation, Vienna, Austria).

RESULTS

Study population

Between 2010 and 2017, 491 patients with HCM underwent TTE (**Figure 1**). After excluding patients who did not meet the inclusion criteria, data from 162 patients (64 women) were analyzed. Median FU duration of TTE was 3.3 years (interquartile range, 1.9–5.2 years), and median clinical FU duration was 4.7 years (interquartile range, 3.0–6.6 years). Baseline characteristics of the patients are presented in **Table 1**. Median age of the recruited patients was 67 years. Patients in the event group were older than those in the no-event group (70 vs. 66 years, p = 0.034). Apical-type HCM accounted for 32.1% (n = 52) of cases and was evenly distributed in both groups (p = 0.853). Compared with the no-event group, the prevalence of having a medical history of hypertension, stroke, acute decompensated heart failure, and atrial fibrillation was higher in the event group. The estimated glomerular filtration rate was lower in the event group than that in the no-event group. There was no difference in medication use between the 2 groups. None of the patients underwent surgical septal myectomy or alcohol septal ablation.

Changes in echocardiographic findings and correlations with clinical outcomes

Baseline TTE and FU-TTE parameter values and changes in values per year are shown in **Table 2**. There was no difference in LVEF and maximal LV wall thickness between the baseline and FU-TTE in any of the patients. ES-HCM was confirmed in 4 patients at baseline and 7 patients at FU. During the FU, LA anteroposterior diameter and LAVI increased significantly (LA anteroposterior diameter, 43 to 46 mm, p <0.001; LAVI, 50 to 57 mL/m^2, p <0.001). Mean increase in LAVI per year in the total cohort was 2.4 mL/m^2/year (p < 0.001). However, there was no difference in changes between the event and no-event groups. The proportion of patients with a severely enlarged LAVI (≥ 40 mL/m^2) increased from baseline to FU from 63.0% to 75.9%, respectively (**Table 3**). Among the 60 patients (37%) with an

Table 1. Baseline characteristics for the patients

Characteristics	Total (n = 162)	Event (n = 45)	No-event (n = 117)	p-value*
Female	64 (39.5)	18 (40)	46 (39.3)	1.000
Age (years)	67 (55–73)	70 (60–76)	66 (53–73)	0.034
HCM type				0.853
Apical	52 (32.1)	15 (33.3)	37 (31.6)	
Septal	110 (67.9)	30 (66.7)	80 (68.4)	
Diabetes mellitus	40 (24.7)	16 (35.6)	25 (21.4)	0.072
Hypertension	63 (38.9)	23 (51.5)	40 (34.2)	0.048
Stroke or TIA	19 (11.7)	10 (22.2)	9 (7.7)	0.013
Coronary artery disease	18 (11.1)	5 (11.1)	13 (11.1)	1.000
Heart failure	8 (4.9)	6 (13.3)	2 (1.7)	0.002
Atrial fibrillation	38 (23.5)	16 (35.6)	22 (18.8)	0.024
White blood cell (× 10^3/mm^3)	6.9 (5.5–8.7)	7.0 (5.7–8.7)	6.9 (5.4–8.7)	0.658
Hb (g/dL)	14.0 (12.3–15.2)	13.4 (11.5–15.0)	14.2 (12.4–15.4)	0.088
Serum creatinine (mg/dL)	0.9 (0.8–1.1)	1.0 (0.8–1.2)	0.9 (0.7–1.0)	0.010
eGFR (mL/min/1.73 m^2)	66 (51–88)	58 (41–76)	70 (55–95)	0.001
Medications				
Anti-platelets agents	65 (40.1)	19 (42.2)	46 (39.3)	0.735
Anti-coagulations	23 (14.2)	8 (17.8)	15 (12.8)	0.418
ACE inhibitor or ARB	63 (38.9)	20 (44.4)	43 (36.8)	0.368
CCB-DHP	27 (16.7)	8 (17.8)	19 (16.2)	0.814
CCB-NDHP	28 (17.3)	5 (11.1)	23 (19.7)	0.198
Beta-blocker	94 (58.0)	31 (68.9)	63 (53.8)	0.082
Amiodarone	15 (9.3)	3 (6.7)	12 (10.3)	0.480
Digitalis	8 (4.9)	1 (2.2)	7 (6.0)	0.322
Loop-diuretics	21 (13.0)	4 (8.9)	17 (14.5)	0.338
Spironolactone	9 (5.6)	0 (0.0)	9 (7.7)	0.056
Statin	50 (30.9)	16 (35.6)	34 (29.1)	0.423

Values are presented as number (%) or number (range).
ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, CCB: calcium channel blocker, DHP: dihydropyridine, eGFR: estimated glomerular filtration rate measured using the Cockcroft-Gault formulation, HCM: hypertrophic cardiomyopathy, Hb: hemoglobin, NDHP: non-dihydropyridine, TIA: transient ischemic attack.
*The p-value comparing the event group with the no-event group is displayed.

https://doi.org/10.4250/jcvi.2022.0053

Journal of Cardiovascular Imaging JCVI

LAVI of less than 40 mL/m^2 at baseline TTE, half had an increase at FU, and 93.1% of the patients with an already severely enlarged LAVI remained in the severe category. **Table 3** provides details regarding the changes in LAVI and categories of LAVI.

There were no significant changes in septal and lateral E/e' between baseline and FU. However, septal e' velocity at FU was increased compared with that at baseline. Estimated RVSP and peak TR velocity were significantly elevated at FU compared to baseline (RVSP, increase from 31 to 36 mmHg, p < 0.001 and peak TR velocity, increase from 2.4 to 2.6 m/s, p < 0.001). No patients with moderate or severe mitral regurgitation at baseline or FU examinations were identified. However, the amount of mitral regurgitation increased in 7 patients between baseline and FU (4.2%, p < 0.035). LV diastolic dysfunction of grade 2 or 3 was more frequently observed in the event group at baseline and FU compared with the no-event group.

Clinical events were observed in 45 patients during the FU period. There were 15 patients with acute decompensated heart failure; 5 with cardiac death; 8 with fatal arrhythmias, ventricular fibrillation, ventricular tachycardia, and implantation of a cardiac implantable electronic device; 16 with ischemic stroke or transient ischemic attack; and one with syncope. At baseline, the event group had a lower LVEF, larger LAVI, and higher peak E velocity, E/e', and TR velocity than did the no-event group (**Table 2**). The FU-TTE findings associated with clinical events were similar to those of the baseline TTE findings. However, the changes were not statistically significant. In particular, the LAVI in both groups increased during the FU. Mean change in LAVI tended to be numerically larger in the event group than in the no-event group. However, these changes were not statistically significant. (4.0 ± 9.7 mL/m^2 vs. 2.6 ± 5.3 mL/m^2, p = 0.342). No difference in average E/e' was observed (−0.06 ± 4.43 vs. 0.23 ± 2.10, p = 0.673). Additionally,

Table 2. Echocardiographic parameters, baseline, FU, and clinical event during FU

Parameters	Baseline TTE			FU-TTE			Changes per year		
	Event (n = 45)	No-event (n = 117)	p-value	Event (n = 45)	No-event (n = 117)	p-value	Event (n = 45)	No-event (n = 117)	p-value
IVSd (mm)	14 ± 4	15 ± 4	0.368	15 ± 5	15 ± 5	0.948	0.21 ± 1.48	−0.06 ± 2.45	0.255
LVIDd (mm)	49 ± 5	48 ± 6	0.277	48 ± 7	48 ± 6	0.770	−0.18 ± 2.56	0.08 ± 2.45	0.543
LVPWd (mm)	11 ± 2	10 ± 2	0.626	11 ± 3	10 ± 2	0.129	0.36 ± 1.09	−0.07 ± 1.17	0.034
Max wall thickness (mm)	17 ± 3	18 ± 3	0.638	17 ± 3	17 ± 3	0.729	−0.24 ± 2.29	−0.14 ± 1.21	0.728
LVEF (%)	59 ± 9	63 ± 5	0.010	58 ± 11	62 ± 7	0.022	−0.25 ± 3.63	−0.13 ± 3.21	0.831
LA AP diameter (mm)	46 ± 9	42 ± 7	0.007	49 ± 10	44 ± 9	0.002	1.27 ± 3.74	0.81 ± 2.68	0.388
LA volume index (mL/m^2)	64 ± 28	44 ± 15	0.000	73 ± 30	52 ± 19	0.000	4.04 ± 9.67	2.58 ± 5.31	0.342
Peak E velocity (m/s)	0.7 ± 0.3	0.6 ± 0.2	0.001	0.9 ± 1.6	0.6 ± 0.2	0.143	0.41 ± 2.72	0.02 ± 0.10	0.346
Peak A Velocity (m/s)	0.7 ± 0.3	0.6 ± 0.2	0.571	0.7 ± 0.3	0.7 ± 0.2	0.797	−0.02 ± 0.13	0.00 ± 0.09	0.473
E/A	1.2 ± 1.1	0.8 ± 0.3	0.025	1.3 ± 1.0	0.9 ± 0.5	0.084	0.18 ± 1.07	0.04 ± 0.24	0.548
DT (msec)	175 ± 56	209 ± 60	0.001	192 ± 77	221 ± 93	0.069	14.0 ± 57.4	1.15 ± 45.7	0.215
Septal e'	4.0 ± 1.4	4.4 ± 1.9	0.178	4.4 ± 1.3	4.6 ± 1.8	0.535	0.21 ± 0.96	0.07 ± 0.69	0.375
Septal E/e'	19 ± 11	14 ± 6	0.002	18 ± 9	14 ± 6	0.009	−0.17 ± 5.10	0.18 ± 2.62	0.674
Lateral e'	6 ± 2	6 ± 3	0.411	6 ± 3	6 ± 3	0.968	0.07 ± 1.34	0.06 ± 1.28	0.961
Lateral E/e'	13 ± 6	10 ± 5	0.000	13 ± 7	10 ± 5	0.029	0.36 ± 4.56	0.33 ± 2.11	0.968
Average E/e'	17 ± 11	12 ± 12	0.024	15 ± 8	12 ± 5	0.009	−0.06 ± 4.43	0.23 ± 2.10	0.673
RVSP (mmHg)	35 ± 13	29 ± 9	0.002	48 ± 14	34 ± 10	0.056	2.53 ± 7.01	1.43 ± 5.53	0.352
TR velocity (m/s)	2.6 ± 0.5	2.4 ± 0.4	0.002	2.8 ± 0.5	2.5 ± 0.4	0.003	0.06 ± 0.27	0.04 ± 0.22	0.722
LVOTO	7 (15.6)	23 (19.7)	0.547	7 (15.6)	18 (15.4)	0.978			
Mitral regurgitation			0.216			0.115			
No or Trivial	41 (91.1)	112 (95.7)		38 (84.4)	108 (92.3)				
Mild	4 (8.9)	5 (4.3)		7 (15.6)	9 (7.7)				
LV diastolic dysfunction			0.000			0.003			
Grade 1	19 (65.5)	94 (93.1)		15 (68.2)	85 (90.5)				
Grade 2	7 (24.1)	7 (6.9)		3 (13.6)	7 (7.4)				
Grade 3	3 (10.3)	0 (0.0)		4 (18.2)	2 (2.1)				
Undetermined									
Pericardial effusion	5 (11.1)	3 (2.6)	0.038	8 (17.8)	5 (4.3)	0.008			

The p-values demonstrate the measured values at the baseline and FU examinations (unchanged values). There were no significant changes in the baseline and FU echocardiographic parameters for cardiovascular outcomes. In addition, p-values regarding the changed values adjusting per year between the baseline and FU tests are not shown in this table (all variables were statistically insignificant).

DT: deceleration time, E/A: peak E velocity divided by peak A velocity in the trans-mitral valve, FU: follow-up, IVSd: interventricular septum in diastole, LA: left atrium, LA AP: left atrial anteroposterior diameter, LVIDd: left ventricular internal diameter in diastole, LVPWd: left ventricle posterior wall thickness in diastole, LV: left ventricle, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, RVSP: right ventricular systolic pressure, TR: tricuspid regurgitation.

https://doi.org/10.4250/jcvi.2022.0053

Journal of Cardiovascular Imaging JCVI

Table 3. Change of LA volume index during a median 3.3-year FU

Baseline		FU			
Category according to LAVI	Baseline	Category at FU	Change of categories	ΔLAVI (mL)	Overall changes in the category
Normal (≤ 28 mL/m²)	11.7% (n = 19)	Normal	5 (26.3)	4.2 ± 5.0	Δ −4.3% (n = 12, 7.4%)
		Mild	3 (15.8)		
		Moderate	4 (21.1)		
		Severe	7 (36.8)		
Mild (29–33 mL/m²)	8.0% (n = 13)	Normal	4 (30.8)	3.1 ± 6.1	Δ −2.4% (n = 9, 5.6%)
		Mild	0 (0.0)		
		Moderate	5 (38.5)		
		Severe	4 (30.8)		
Moderate (34–39 mL/m²)	17.3% (n = 28)	Normal	1 (3.6)	2.9 ± 3.7	Δ −6.2% (n = 18, 11.1%)
		Mild	2 (7.1)		
		Moderate	8 (28.6)		
		Severe	17 (60.7)		
Severe (≥ 40 mL/m²)	63.0% (n = 102)	Normal	2 (2.0)	2.9 ± 7.8	Δ +12.9% (n = 123, 75.9%)
		Mild	4 (3.9)		
		Moderate	1 (1.0)		
		Severe	95 (93.1)		

Values are presented as number (%) or mean ± standard deviation. ΔLAVI means the absolute difference between baseline and FU. (FU LAVI − Baseline LAVI). The overall category change reflects the absolute number and proportion of patients within the criteria based on each baseline category.
FU: follow-up, LA: left atrium, LAVI: left atrial volume index.

in 52 apical HCM patients, the LAVI of the baseline TTE was significantly greater in the event group than in no-event group (63 ± 34 vs. 42 ± 14, p = 0.046), but LVEF, Septal E', E/e', and TR were not significantly different between these 2 groups. In those patients with asymmetric septal HCM (n = 110), LAVI, mitral E velocity, E/e', and TR velocity were related to the occurrence of clinical events. However, the change in LAVI after a median of 3.3 years of FU was not significant (p = 0.665).

Prognostic role of echocardiographic and clinical variables

Logistic regression analysis to identify the independent predictors of clinical events revealed that LVEF and LAVI were independent factors in Model 1 (**Table 4**). When Model 2 was used, LAVI was the only independent significant factor. In Model 3, there were no significant predictors of clinical outcomes, including delta values. The Kaplan-Meier survival curve showed that a severely enlarged LAVI at baseline and FU-TTE was associated with higher cumulative events during FU (**Figure 2A**). When groups classified according to changes between baseline and FU-TTE LAVI were compared, the increased-LAVI and decreased-LAVI groups showed a poorer prognosis than the static LAVI-group (**Figure 2B**). In a subgroup analysis of patients with baseline LAVI < 40 mL/m², subjects with an LAVI greater than 10% had more frequent clinical events (**Figure 2C**). However, there was no statistically significant increase in clinical events in patients with a baseline LAVI ≥ 40 mL/m² (**Figure 2D**).

DISCUSSION

We found no association between changes per year in conventional TTE parameters and clinical outcomes in patients with HCM. Cross-sectionally measured values of LVEF, LAVI, E/e', and TR velocity were significantly associated with clinical outcomes. Among all echocardiographic parameters, the most powerful independent predictor was LAVI measured cross-sectionally at baseline and FU.

Phenotypic expression of HCM usually occurs during adolescence or young adulthood.[18][19] Most patients with "classic" HCM experience long periods of clinical stability. These patients may never experience significant degrees of adverse remodeling or disease progression during their lifetimes. Eriksson et al.[20] reported no interval change in LV wall thickness in participants with apical HCM during a FU of 9 years. However, several large-scale data registries[6][7][11][18][19] reported ES disease in approximately 5–10% of patients with HCM. Harris et al.[11] reported that 3.5% of patients had ES-HCM based on a multi-center registry. The authors retrospectively analyzed LV morphological and functional progression in ES-HCM patients. They showed a regression rate of 1.4 mm/year in LV septal thickness and 6.1%/year in LVEF. However, there were considerable gaps between evaluation and recognition of disease progression due to long stable periods: 9 ± 12 years from symptoms to initial evaluation and 5 ± 6 years from initial evaluation to ES recognition. Maron and Spirito reported that LV wall thickness regressed by approximately 25% at a rate

https://doi.org/10.4250/jcvi.2022.0053

Journal of Cardiovascular Imaging JCVI

Table 4. Logistic regression models to predict clinical events with baseline, FU, and changes in echocardiographic parameters

Variables with p < 0.05	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Model 1: Baseline TTE						
Age ≥ 65-year-old	12.6	1.652–95.669	0.001	0.4	0.127–1.137	0.065
Hypertension	2.0	1.001–4.046	0.037	2.2	0.897–5.187	0.086
Ischemic stroke or TIA	3.4	1.289–9.116	0.013	2.3	0.714–7.059	0.162
ADHF	8.8	1.714–45.649	0.006	1.6	0.215–11.696	0.652
Prior AF	2.4	1.107–5.128	0.037	1.4	0.558–3.703	0.452
eGFR < 60	3.7	1.782–7.517	0.001	4.4	1.543–12.620	0.006
LVEF < 60%	2.5	1.209–4.961	0.017	2.0	0.857–4.900	0.107
LAVI > 50 mL/m^2	5.8	2.707–12.287	0.000	4.7	1.904–11.823	0.001
E/e' avg. ≥ 14	3.5	1.687–7.200	0.001	1.7	0.658–4.553	0.266
TR peak velocity ≥ 2.8 m/s	2.2	0.992–4.925	0.055	1.8	0.612–5.168	0.290
Model 2: FU-TTE						
LVEF < 60%	2.5	1.209–4.961	0.017	1.9	0.824–4.222	0.135
LAVI > 56 mL/m^2	8.5	1.107–65.743	0.015	4.6	0.504–41.385	0.177
E/e' average ≥ 14	2.9	1.687–7.200	0.001	1.5	0.633–3.768	0.340
TR peak velocity ≥ 2.8 m/s	3.0	0.992–4.925	0.055	2.2	0.919–5.189	0.077
Model 3: Δ values						
Δ LVEF	2.5	1.209–4.961	0.017	1.1	0.952–1.193	0.272
Δ LAVI	8.5	1.107–65.743	0.015	1.0	0.946–1.066	0.883
Δ E/e' average	2.9	1.687–7.200	0.001	0.9	0.896–1.052	0.476
Δ TR peak velocity	3.0	0.992–4.925	0.055	1.1	0.491–2.263	0.892

Model 1: adjusted for all parameters of clinical factors and baseline echocardiography with p < 0.05 in the unadjusted model. Model 2: adjusted for all parameters of clinical factors and FU echocardiography with p < 0.05 in the unadjusted model. Model 3: Δ values (FU – Baseline parameters) were analyzed in logistic regression with clinical factors (age, hypertension, stroke, heart failure, atrial fibrillation, and eGFR). In the logistic regression analysis with enter method, variables with statistical significance are listed in the table. The Cox and Snell R-squared in models 1, 2, and 3 were 0.265, 0.224, and 0.181, respectively. ADHF: acute decompensated heart failure, AF: atrial fibrillation, CI: confidence interval, FU: follow-up, E/e': mitral inflow E of mitral annular tissue velocity e', eGFR: estimated glomerular filtration rate measured using the Cockcroft-Gault formulation (unit: mL/min/1.73 m^2), LVEF: left ventricular ejection fraction, LAVI: left atrial volume index, OR: odds ratio, TIA: transient ischemic attack, TR: tricuspid regurgitation, TTE: transthoracic echocardiography.

of 1.0 to 2.0 mm/year.[6] Moreover, they found that LV cavity dimension increased by approximately 20% at a rate of 1.0 to 1.5 mm/year, and up to 3 to 4 mm/year. The current study included 10 patients (6.1%) with ES-HCM, and the annual changes in LV maximal thickness and LVEF in these 10 individuals were 0.2 mm and 5.2%, respectively. However, there was no statistical difference between the 2 groups.

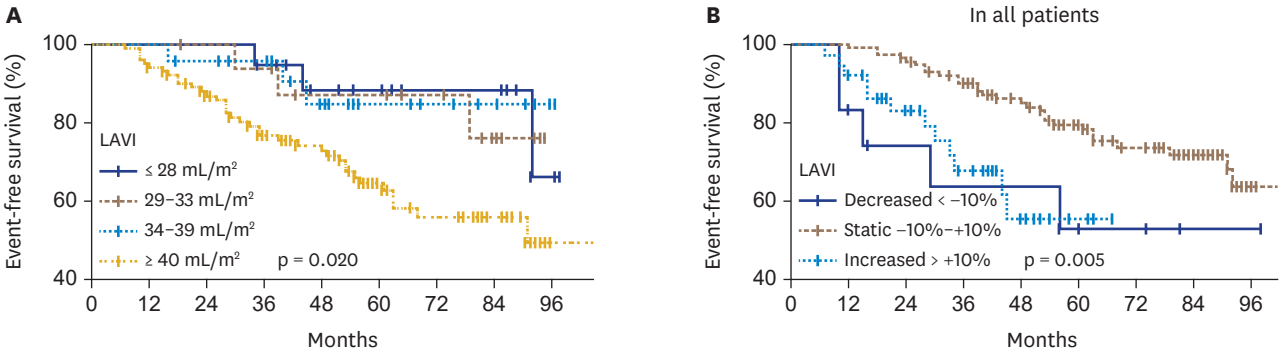
Increased LAVI and TR velocity are frequently observed in patients with HCM. Only 4 patients had a normal LAVI at FU in the current study. Losi et al.[21] demonstrated the clinical importance of changing LAVI in patients with HCM based on analysis of participants with a normal LAVI (27 mL/m^2) at baseline. However, in our cohort, patients already had enlarged LA at baseline (mean 50 mL/m^2 at baseline; 9% of patients had an LA of < 27 mL/m^2 at baseline, which was the criterion used in the Losi study). Pulmonary hypertension has been reported in patients with HCM.[8][10][22] Although a higher peak TR velocity indicates poor outcomes in patients with HCM, few studies have compared the relationship between changes in TTE parameters and clinical events. A small change in TR was observed in our cohort. Changes in TR velocities are likely due to several factors including LVOTO; primary valvular and systolic anterior motion-related mitral regurgitation; and natural aging.[5][23] Of note, in our study, there was no significant (≥ moderate) mitral regurgitation. In addition, only a small number of LVOTOs were found (18%). Therefore, the status of LAVI and TR velocity may be explained by LV diastolic dysfunction rather than by LVOTO as the main pathophysiology.

Changes in echocardiographic parameters were not significantly associated with clinical outcomes. Echocardiographic parameters for predicting progression towards ES disease and cardiovascular events are well established.[9][10][24] Cross-sectionally measured values (LVEF, LAVI, E/e', and TR velocity) were significantly useful for predicting the development of clinical events regardless of when the TTE study was performed (baseline or FU). Overall, LAVI was the most potent predictor of HCM-related morbidity in our study. Although changes within the heart might not be noticeable, it is worth paying attention to the causes of many clinical events affecting it.

The ESC HCM guideline that suggests evaluating maximal LV wall thickness to assess sudden death risk is based on only one study.[24] There have also been conflicting studies on the relationship between LV wall thickness and clinical outcomes.

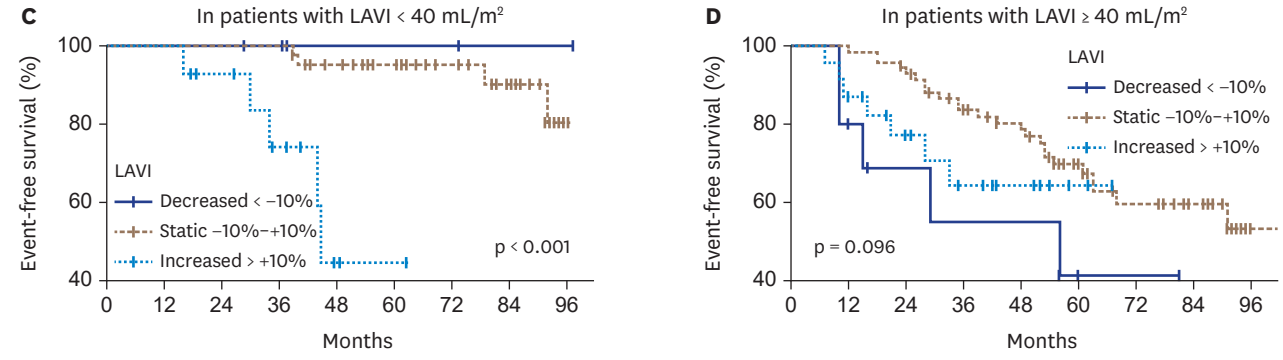
https://doi.org/10.4250/jcvi.2022.0053

Journal of Cardiovascular Imaging JCVI



No. at risk									
≤ 28 mL/m²	19	19	19	17	13	11	7	7	2
29–33 mL/m²	17	17	16	15	12	12	10	6	0
34–39 mL/m²	24	24	22	20	15	9	7	5	2
≥ 40 mL/m²	102	97	84	66	56	36	23	14	2

No. at risk									
Decreased < –10%	12	10	7	6	6	4	3	1	1
Static –10%–+10%	113	113	108	96	81	61	44	31	5
Increased > +10%	37	34	26	16	9	3	0	0	0



No. at risk									
Decreased < –10%	2	2	2	2	2	2	2	1	1
Static –10%–+10%	44	44	44	43	35	29	22	17	3
Increased > +10%	14	14	11	7	3	1	0	0	0

No. at risk									
Decreased < –10%	10	8	5	4	4	2	1	0	0
Static –10%–+10%	69	69	64	53	46	32	22	14	2
Increased > +10%	23	20	15	9	6	2	0	0	0

Figure 2. Kaplan-Meier survival analysis based on left atrial volume index. Kaplan-Meier curve analysis (A) demonstrated different clinical outcomes according to the grade of enlargement of LAVI (normal ≤ 28 mL/m²; 29 mL/m² ≤ mild ≤ 33 mL/m²; 34 mL/m² ≤ moderate ≤ 39 mL/m²; severe ≥ 40 mL/m²) at baseline. Kaplan-Meier curves based on trends in changes in LAVI are presented for all hypertrophic cardiomyopathy subjects (B), patients (n = 60) with LAVI < 40 mL/m² (C), and patients (n = 102) with a severely enlarged LAVI ≥ 40 mL/m² (D). The decreased LAVI group comprised individuals with a 10% or greater decrease in LAVI at FU compared to the baseline, whereas the increased group comprised individuals with a 10% or greater increase in LAVI at FU. The static group comprised individuals with no significant changes in LAVI (± 10%). Log-rank p-values are displayed in each figure.
FU: follow-up, LAVI: left atrial volume index.

Thaman et al.[24] showed that LV wall thickness was reduced by 0.6 mm/year. However, there were no significant differences in survival between patients with thinning walls ≤ 5 mm. No relationship between the pattern of hypertrophy and survival was observed in patients with a wall thickness < 30 mm.[2] Of note, only one patient in the current study had an MLVWT ≥ 30 mm. Although little change in myocardial thickness was noted in our study, the total rate of clinical events was 27.8%.

It has been reported that ES-HCM is associated with a 10-fold greater incidence of unfavorable outcomes than that in HCM patients with a preserved EF.[12] The incidence of ES-HCM is low and ES-HCM develops over a long period of time.[7][11] Other studies[11][25][26] reported the regression rate and risk factors for ES-HCM unrelated to clinical events. There was no significant change in LVEF during the FU in our study, and the change observed in LVEF did not help predict clinical events. Most patients with HCM have preserved LV systolic function. During the entire FU period, there were only 7 ES cases (5 patients at baseline). Only 6 participants (3.8%) with LVEF ≥ 50% at baseline experienced burn-out at FU. This might be related to the high proportion of patients with apical HCM (31.6%) in this study. The ability of changes in LVEF to predict clinical outcomes may have been limited in this study because of the

https://doi.org/10.4250/jcvi.2022.0053

Journal of Cardiovascular Imaging JCVI

small amount of change that did occur during the short-term FU and the mostly preserved LVEF at diagnosis. Tiny changes may have been missed or the changes may have fallen within the margin of error due to the short-term FU.

Variables related to diastolic dysfunction were strongly associated with poor outcomes in our cohort. Grade II or higher diastolic dysfunction was also more frequently observed in the event group than the non-event group. This pattern was maintained until FU. Rowin et al.[27] showed that the rate of elevated left ventricular end-diastolic pressure or pulmonary arterial wedge pressure in patients with HCM who were scheduled for heart transplantation reached 75%, and 40% had a restrictive inflow pattern. However, the rate of heart transplantation was 76.9% in patients with HCM with preserved EF ≥ 50%. These results highlight the importance of paying attention to diastolic dysfunction as an aggravating factor.

Some studies have reported that changes in echocardiographic parameters based on serial TTE studies are associated with poor clinical outcomes. Losi et al.[21] demonstrated that patients with an enlarged LA volume (> 27 mL/m^2) at baseline and with a fast dilating LA volume (> 3 mL/year) had a worse prognosis. The FU duration (mean, 5 years) was comparable to that in our study. However, the definition of LA volume and the number of enrolled patients with a normal LA size were different between our study and that of Losi and colleagues.[21] In our study, a larger proportion of our patient population had a severely enlarged LAVI. Therefore, progression in the patient cohort did not show a constant trend. Baseline LAVI ≥ 40 mL/m^2 was the most important predictor of clinical outcomes in our study, and progression in LAVI (> 10% increase compared to baseline) was also related to clinical events in patients with a smaller LAVI. We did not analyze patients with a smaller LAVI at baseline further because of the small number of these patients enrolled in the study.

The severity, number of hypertrophied segments, and diverse hemodynamic presentations of HCM differ from patient to patient. Therefore, the management approach and timing of FU-TTE should also vary among patients. However, to date, there are no established guidelines regarding the appropriate FU duration or essential TTE parameters to follow according to the diverse presentations of HCM. Recent HCM-related guidelines recommend routine FU-TTE every 1–2 years to assess changes in LV systolic and diastolic function, wall thickness, chamber size, LVOTO, and valvular disease even in asymptomatic patients with HCM (class I, level of evidence C).[2] Although the recognition of ES-HCM is crucial in predicting clinical outcomes and in changing management for heart failure, ES progression is generally slow and unpredictable.[18][25][27] Additionally, a few reports,[7][13][28] including the current report, have found that assessment of changes in LVEF has limited utility to predict clinical outcomes.

These findings suggest that clinicians should focus on cross-sectional measurements in patients with HCM with complicated hemodynamic responses. In patients with HCM without worsening symptoms and signs, clinicians should concentrate on hemodynamic aspects at the time of TTE. These aspects could include elevated LV filling pressure, systolic function, dilating cardiac chambers, and presence of pulmonary hypertension rather than simple comparison of FU-TTE parameters with those measured at baseline. The current study highlights the need for a large-scale prospective, longitudinal, multicenter study with scheduled FU-TTEs.

This was a small, single-center, retrospective study. Because there were few adverse clinical outcomes based on morphologic types of HCM, subgroup analysis could not be performed. Moreover, apical HCM accounted for 32.1% of cases in the present study. The better prognosis of apical HCM could have biased our study findings. Therefore, a large-scale prospective study is warranted. Second, the median duration of clinical FU was 4.7 years. We evaluated changes in echocardiographic parameters over a median of 3.3 years from baseline to just before clinical events. Given the retrospective nature of the study, the time to perform FU-TEE was inconsistent between subjects, which may have affected the predictive ability of changes in TEE parameters to predict clinical outcomes. However, we addressed this by converting the changes in TEE parameters to changes per year. A longer FU duration and regular check-ups should be evaluated in future studies.

In addition, we used only conventional echocardiographic data and not magnetic resonance imaging data or data acquired from 3-dimensional and/or speckle-tracking echocardiography. Cardiac magnetic resonance imaging has become a vital imaging modality for the precise measurement of LV mass and cardiac chamber sizes and predicting sudden cardiac death. However, serial cardiac magnetic resonance imaging FU is not recommended in current practice settings, and is not cost-effective. Therefore, the results of cardiac magnetic resonance imaging were not evaluated in this study. Even though 3-dimensional and strain echocardiography are important tools for precise measurement and risk stratification for HCM patients, we did not include data from these modalities in the current study. For precise evaluation of changes in the heart structures, more advanced imaging tools should be considered.

https://doi.org/10.4250/jcvi.2022.0053

In patients with HCM, changes in conventional TTE parameters were not significantly associated with clinical outcomes. Cross-sectionally measured echocardiographic parameters (LVEF, E/e', LAVI, and TR velocity) at the time of TTE were, however, related to clinical events. Among echocardiographic parameters, cross-sectionally measured LAVI at baseline or FU was the most reliable predictor of clinical outcomes in patients with HCM.

ACKNOWLEDGMENTS

We would like to thank S. Kim, a member of Medical Statistics Support Office of Gyeongsang National University Hospital, for advice on statistical analyses.

ORCID iDs

Kyehwan Kim
https://orcid.org/0000-0001-5234-1251
Seung Do Lee
https://orcid.org/0000-0002-9129-4248
Hyo Jin Lee
https://orcid.org/0000-0003-1746-7718
Hangyul Kim
https://orcid.org/0000-0003-0261-3962
Hye Ree Kim
https://orcid.org/0000-0001-5702-8950
Yun Ho Cho
https://orcid.org/0000-0002-7176-0491
Jeong Yoon Jang
https://orcid.org/0000-0002-5430-7679
Min Gyu Kang
https://orcid.org/0000-0002-9672-1798
Jin-Sin Koh
https://orcid.org/0000-0003-2920-7411
Seok-Jae Hwang
https://orcid.org/0000-0002-9467-9020
Jin-Yong Hwang
https://orcid.org/0000-0002-6632-7239
Jeong Rang Park
https://orcid.org/0000-0002-8330-2738

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kim K, Hwang JY; Data curation: Kim K, Lee SD, Lee HJ, Kim H; Formal analysis: Kim K, Kim H, Kim HR, Cho YH, Park JR; Investigation: Kim K, Lee SD, Lee HJ, Cho YH, Kang MG, Park JR; Methodology: Kim K, Kim H, Kim HR, Cho YH, Jang JY, Hwang JY, Park JR; Project administration: Hwang JY; Resources: Lee HJ, Cho YH, Park JR; Software: Kim K, Park JR; Supervision: Kim HR, Jang JY, Kang MG, Koh JS, Hwang SJ, Hwang JY, Park JR; Validation: Kim K, Cho YH, Hwang JY, Park JR; Visualization: Kim K, Kang MG, Park JR; Writing - original draft: Kim K, Park JR; Writing - review & editing: Kim K, Kim HR, Jang JY, Kang MG, Koh JS, Hwang JY, Park JR.

REFERENCES

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002;287:1308-20.
PUBMED | CROSSREF
2. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J* 2014;35:2733-79.
PUBMED | CROSSREF
3. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995;26:1699-708.
PUBMED | CROSSREF
4. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;357:420-4.
PUBMED | CROSSREF
5. Finocchiaro G, Haddad F, Pavlovic A, et al. How does morphology impact on diastolic function in hypertrophic cardiomyopathy? A single centre experience. *BMJ Open* 2014;4:e004814.
PUBMED | CROSSREF
6. Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. *Am J Cardiol* 1998;81:1339-44.
PUBMED | CROSSREF
7. Biagini E, Coccolo F, Ferlito M, et al. Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. *J Am Coll Cardiol* 2005;46:1543-50.
PUBMED | CROSSREF
8. Mitra A, Ghosh RK, Bandyopadhyay D, Ghosh GC, Kalra A, Lavie CJ. Significance of pulmonary hypertension in hypertrophic cardiomyopathy. *Curr Probl Cardiol* 2020;45:100398.
PUBMED | CROSSREF
9. Musumeci MB, Mastromarino V, Casenghi M, et al. Pulmonary hypertension and clinical correlates in hypertrophic cardiomyopathy. *Int J Cardiol* 2017;248:326-32.
PUBMED | CROSSREF
10. Ong KC, Geske JB, Hebl VB, et al. Pulmonary hypertension is associated with worse survival in hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2016;17:604-10.
PUBMED | CROSSREF
11. Harris KM, Spirito P, Maron MS, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation* 2006;114:216-25.
PUBMED | CROSSREF
12. Rowin EJ, Maron BJ, Carrick RT, et al. Outcomes in patients with hypertrophic cardiomyopathy and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2020;75:3033-43.
PUBMED | CROSSREF
13. Marstrand P, Han L, Day SM, et al. Hypertrophic cardiomyopathy with left ventricular systolic dysfunction: insights from the SHaRe Registry. *Circulation* 2020;141:1371-83.
PUBMED | CROSSREF
14. Nagueh SF, Bierig SM, Budoff MJ, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy: Endorsed by the American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, and Society of Cardiovascular

Journal of Cardiovascular Imaging JCVI

Computed Tomography. *J Am Soc Echocardiogr* 2011;24:473-98.
PUBMED | CROSSREF

15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39.e14.
PUBMED | CROSSREF
16. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277-314.
PUBMED | CROSSREF
17. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303-71.
PUBMED | CROSSREF
18. Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. *Circ Heart Fail* 2012;5:535-46.
PUBMED | CROSSREF
19. Olivotto I, Girolami F, Nistri S, et al. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice. *J Cardiovasc Transl Res* 2009;2:349-67.
PUBMED | CROSSREF
20. Eriksson MJ, Sonnenberg B, Woo A, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;39:638-45.
PUBMED | CROSSREF
21. Losi MA, Betocchi S, Barbati G, et al. Prognostic significance of left atrial volume dilatation in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2009;22:76-81.
PUBMED | CROSSREF
22. Covella M, Rowin EJ, Hill NS, et al. Mechanism of progressive heart failure and significance of pulmonary hypertension in obstructive hypertrophic cardiomyopathy. *Circ Heart Fail* 2017;10:e003689.
PUBMED | CROSSREF
23. Losi MA, Betocchi S, Grimaldi M, Spampinato N, Chiariello M. Heterogeneity of left ventricular filling dynamics in hypertrophic cardiomyopathy. *Am J Cardiol* 1994;73:987-90.
PUBMED | CROSSREF
24. Thaman R, Gimeno JR, Reith S, et al. Progressive left ventricular remodeling in patients with hypertrophic cardiomyopathy and severe left ventricular hypertrophy. *J Am Coll Cardiol* 2004;44:398-405.
PUBMED | CROSSREF
25. Melacini P, Basso C, Angelini A, et al. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. *Eur Heart J* 2010;31:2111-23.
PUBMED | CROSSREF
26. Hiemstra YL, Debonnaire P, van Zwet EW, et al. Development of and progression of overt heart failure in nonobstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2018;122:656-62.
PUBMED | CROSSREF
27. Rowin EJ, Maron BJ, Kiernan MS, et al. Advanced heart failure with preserved systolic function in nonobstructive hypertrophic cardiomyopathy: under-recognized subset of candidates for heart transplant. *Circ Heart Fail* 2014;7:967-75.
PUBMED | CROSSREF
28. Brinkley DM, Wells QS, Stevenson LW. Avoiding burnout from hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2020;75:3044-7.
PUBMED | CROSSREF

https://doi.org/10.4250/jcvi.2022.0053