Supplemental Material

Title: Prognosis of patients with hypertrophic cardiomyopathy and low-normal left ventricular ejection fraction

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Detailed Methods

Study population

This cohort study recruited 1936 consecutive patients diagnosed with hypertrophic cardiomyopathy (HCM) between 2008 and 2019 from two tertiary university hospitals. HCM was diagnosed by only experienced cardiologists who have more than 10 years of clinical and echocardiographic experience, based on the guidelines (1). All echocardiographic images were thoroughly reviewed and double-checked. In cases where HCM diagnosis was ambiguous, cardiac magnetic resonance imaging was performed in cooperation with cardiovascular radiologists. Additionally, in order to verify HCM diagnosis, we re-confirmed the diagnosis of HCM based on the morphology of left ventricular (LV) hypertrophy pattern (apical, asymmetrical septal hypertrophy, etc.), as well as the extent of blood pressure control.

We applied the following exclusion criteria: competitive sports and other causes of LV hypertrophy, such as Noonan syndrome, Fabry disease, glycogen storage disease, cardiac amyloidosis, and mitochondrial disease; and eligibility for secondary prevention of sudden cardiac death (SCD) (i.e., history of spontaneous ventricular tachycardia, ventricular fibrillation, or cardiac arrest) or ischemic cardiomyopathy (i.e., LV ejection fraction [LVEF] ≤ 40% with a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery). Based on these criteria, 22 patients were excluded because they were candidates for secondary prevention and four because they had combined ischemic cardiomyopathy. Additionally, 49 patients were excluded due to inadequate echocardiographic data and five due to lack of data for follow-up.

Risk factors for SCD and 5-year HCM Risk-SCD score

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All patients had undergone a comprehensive personal and family history and physical examination at baseline. The following factors were systematically assessed to determine the 5-year Risk-SCD scores (1); (i) age at initial evaluation, (ii) family history of SCD, defined as SCD in one or more first-degree relatives under 40 years of age or in a first-degree relative with confirmed HCM at any age, (iii) the history of unexplained syncope, (iv) non-sustained ventricular tachycardia, documented by 24-hour Holter monitoring or pacemaker/ICD recording, which was defined as ≥3 beats at a rate of ≥120 beats per minute, and lasting <30 seconds; and (v) echocardiographic parameters including maximal LV outflow tract pressure gradient (mmHg), maximal LV wall thickness (mm), and left atrial dimension (mm).

LV wall thickness was assessed at end-diastole using two-dimensional echocardiography, and maximal LV wall thickness was measured as the thickest segment of the LV wall (2). The left atrial anteroposterior dimension was measured at end-systole from the parasternal view. The maximal LV outflow tract pressure gradient was recorded as the largest value using continuous-wave Doppler at rest and/or during the Valsalva manoeuvre.

Definition of primary and secondary outcomes

The primary endpoint was a composite of SCD and equivalent events, including documented ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator (ICD) shocks, and aborted SCD. SCD was defined as an unexpected, witnessed arrest within hours of the patient being in a previously stable clinical condition or within 1 hour of a new onset of any symptom that could be interpreted as originating in the heart. Death occurring in bed overnight with no antecedent history of worsening symptoms was also considered SCD and aborted SCD was considered a successful resuscitation after cardiac arrest (3). An ICD shock was considered appropriate if the tachyarrhythmia had originated from the ventricle,

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documented by stored electrocardiographic data. Patients with an ICD were evaluated regularly by an experienced electrophysiologist (4). The secondary endpoints were hospitalization for heart failure (HHF), cardiovascular death, and all-cause death. HHF was defined as hospitalizing a patient with new or worsening symptoms and/or signs of heart failure requiring new heart failure medication or the addition of intravenous medications for improvement (5).

Deaths and their causes were ascertained using the National Death Registration Records of Korea and/or witness interviews in the case of death outside of the hospital and using hospital electrical medical records in the case of death in the hospital. Patients were censored when they underwent heart transplantation due to end-stage HCM.

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Reference

1. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.

2. 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 Computed Tomography. J Am Soc Echocardiogr 2011;24:473-98.

3. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212-8.

4. Choi YJ, Kim HK, Lee SC, et al. Validation of the hypertrophic cardiomyopathy risk-sudden cardiac death calculator in Asians. Heart 2019;105:1892-7.

5. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.

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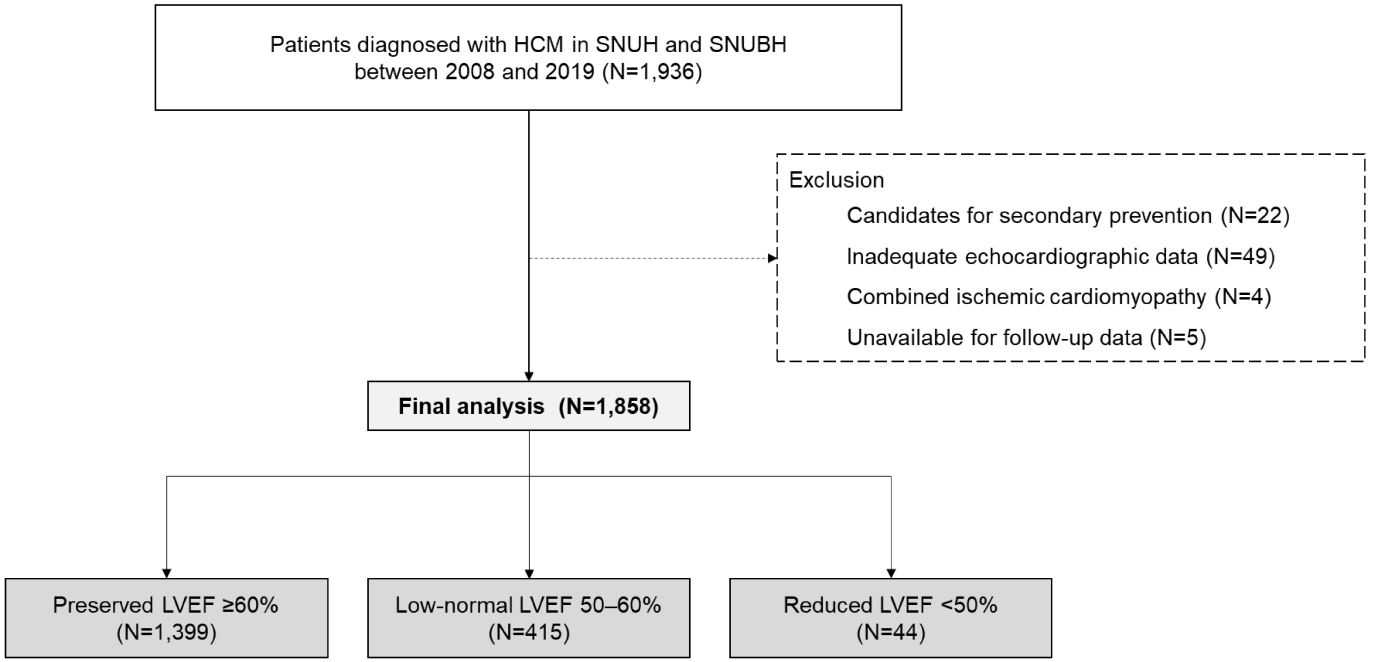
Supplemental Figures



Supplemental Figure 1. Flow chart of the study population

HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; SNUH, Seoul National University Hospital; SNUBH, Seoul National University Boondang Hospital.

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Supplemental Tables

Supplemental Table 1. Annualized event rate according to LVEF category

Outcomes	Annualized event rate (95% confidence interval)		
	Preserved LVEF ≥60%	**Low-normal LVEF 50–60%**	**Reduced LVEF <50%**
	N=1,399	N=415	N=44
Primary outcomes	0.41 (0.244–0.633)	0.87 (0.449–1.518)	0.56 (0.809–7.606)
Ventricular tachycardia/fibrillation	0.23 (0.117–0.420)	0.29 (0.079–0.742)	1.49 (0.180–5.365)
Appropriate ICD shock	0.02 (0.001–0.119)	0.22 (0.045–0.635)	0.00 (0.000–0.000)
Sudden cardiac death	0.15 (0.060–0.308)	0.36 (0.118–0.845)	1.49 (0.180–5.365)
Secondary outcomes			
Hospitalization for heart failure	0.67 (0.455–0.951)	1.79 (1.150–2.670)	5.31 (2.135–10.941)
Cardiovascular death	0.38 (0.227–0.604)	1.08 (0.603–1.776)	2.14 (0.442–6.258)
All-cause death	1.38 (1.066–1.760)	2.08 (1.394–2.990)	2.86 (0.778–7.310)

Abbreviations: LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.

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Supplemental Table 2. Univariate Cox proportional hazard regression analysis for primary and secondary outcomes

Variable	Univariate analysis		
	HR	**95% CI**	***P***
Primary outcomes (SCD/equivalent events)			
LVEF, % (*as a continuous variable*)	0.938	0.905–0.972	<0.001
Preserved LVEF ≥60%	1.000	(reference)	-
Low-normal LVEF 50–60%	2.148	1.043–4.425	0.038
Reduced LVEF <50%	7.295	2.479–21.467	<0.001
Age, years	0.976	0.953–0.999	0.041
Male	0.960	0.511–2.128	0.910
Atrial fibrillation	1.022	0.397–2.634	0.964
Family history of SCD	3.056	1.335–6.997	0.008
Unexplained syncope	3.718	1.785–7.740	<0.001
LA dimension, mm	1.053	1.013–1.095	0.009
LV-MWT, mm	1.025	0.940–1.117	0.578
LVOTmaxPG, mmHg	1.005	0.996–1.014	0.281
Hospitalization for HF			
LVEF, %	0.937	0.913–0.962	<0.001
Preserved LVEF ≥60%	1.000	(reference)	-
Low-normal LVEF 50–60%	2.688	1.577–4.580	<0.001
Reduced LVEF <50%	7.977	3.510–18.130	<0.001
Age, years	1.049	1.026–1.073	<0.001
Male, n (%)	0.382	0.232–0.630	<0.001
Atrial fibrillation	2.627	1.518–4.548	<0.001
Family history of SCD	1.049	0.421–2.618	0.918
Unexplained syncope	1.530	0.755–3.101	0.238
LA dimension, mm	1.092	1.062–1.122	<0.001
LV-MWT, mm	1.065	1.004–0.130	0.037
LVOTmaxPG, mmHg	1.000	0.991–1.009	0.976
Cardiovascular death			
LVEF, %	0.936	0.905–0.969	<0.001
Preserved LVEF ≥60%	1.000	(reference)	-
Low-normal LVEF 50–60%	2.799	1.411–5.555	0.003
Reduced LVEF <50%	5.542	1.632–18.826	0.006
Age, years	1.074	1.040–1.109	<0.001
Male, n (%)	0.477	0.248–0.916	0.026

Atrial fibrillation	2.059	0.969–4.379	0.061
Family history of SCD	0.696	0.167–2.899	0.619
Unexplained syncope	0.532	0.128–2.216	0.386
LA dimension, mm	1.076	1.037–1.116	<0.001
LV-MWT, mm	1.033	0.950–1.123	0.451
LVOTmaxPG, mmHg	1.006	0.998–1.015	0.121
All-cause death			
LVEF, %	0.975	0.947–1.003	0.079
Preserved LVEF ≥60%	1.000	(reference)	-
Low-normal LVEF 50–60%	1.510	0.975–2.339	0.065
Reduced LVEF <50%	2.040	0.743–5.600	0.167
Age, years	1.078	1.057–1.100	<0.001
Male, n (%)	0.635	0.426–0.947	0.026
Atrial fibrillation	2.004	1.265–3.176	0.003
Family history of SCD	0.374	0.118–1.179	0.093
Unexplained syncope	1.024	0.533–1.970	0.943
LA dimension, mm	1.056	1.031–1.080	<0.001
LV-MWT, mm	1.017	0.965–1.072	0.536
LVOTmaxPG, mmHg	1.005	0.995–1.010	0.073

The primary outcome was a composite of SCD and equivalent events, including documented ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator shocks, and aborted SCD. Abbreviations: CI, confidence interval; HR, hazard ratio; LA left atrium; LV, left ventricle; LVEF, LV ejection fraction; LVOTmaxPG, maximal LV outflow tract pressure gradient; LV-MWT, maximal LV wall thickness; SCD, sudden cardiac death.

Supplemental Table 3. Effect modification of age on primary and secondary outcomes

Variable	*P for interaction*
Primary outcomes (SCD/equivalent events)	
LVEF, %	0.586
Preserved LVEF ≥60%	-
Low-normal LVEF 50–60%	0.368
Reduced LVEF <50%	0.678
Hospitalization for HF	
LVEF, %	0.688
Preserved LVEF ≥60%	
Low-normal LVEF 50–60%	0.681
Reduced LVEF <50%	0.079
Cardiovascular death	
LVEF, %	0.718
Preserved LVEF ≥60%	
Low-normal LVEF 50–60%	0.878
Reduced LVEF <50%	0.178
All-cause death	
LVEF, %	0.233
Preserved LVEF ≥60%	
Low-normal LVEF 50–60%	0.341
Reduced LVEF <50%	0.662

Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

Supplemental Table 4. Cox proportional regression analysis for hospitalization for heart failure with mortality considered as a competing risk

Variable	Univariate analysis			Multivariate analysis [a]		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Categorical variable						
LVEF category [b]	2.740	1.890–3.990	<0.001	2.538	1.639–3.930	0.001
Continuous variable						
LVEF, %	0.937	0.912–0.963	<0.001	0.941	0.910–0.972	0.001

[a] Adjusted for age, gender, atrial fibrillation, left atrial size, and maximal wall thickness.

[b] LVEF category was LVEF ≥60%, LVEF 50–60%, and LVEF <50%

Abbreviations: CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

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Supplemental Table 5. The 5-year HCM Risk-SCD score stratified based on LVEF in 897 HCM patients with a complete dataset of seven risk factors

Variable	LV systolic function			*P*
	Preserved LVEF ≥60%	Low-normal LVEF 50–60%	Reduced LVEF <50%	
	N=681	N=194	N=22	
HCM Risk-SCD score, % [a]	2.05 [1.40–3.35]	2.37 [1.52–3.73]	2.55 [1.82–3.52]	0.019
HCM Risk-SCD category				0.109
Low-risk (<4%)	557 (81.8)	147 (75.8)	18 (81.8)	
Intermediate-risk (4–6%)	80 (11.7)	25 (12.9)	1 (4.5)	
High-risk (≥6%)	44 (6.5)	22 (2.5)	3 (13.6)	

Continuous variables were presented as median [interquartile range], and categorical variables were presented as frequencies (percentages).

Abbreviations: HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

[a] Risk score was calculated by the 5-year HCM Risk-SCD model endorsed by the 2014 European Society of Cardiology guidelines on diagnosis and management of HCM.

Supplemental Table 6. Net reclassification index and integrated discrimination index for SCD/equivalent events [a]

Variable	Model 1			Model 2			Model 3		
	Value	**95% CI**	***P***	**Value**	**95% CI**	***P***	**Value**	**95% CI**	***P***
HCM Risk-SCD category [b] plus LVEF (%)									
Net reclassification improvement	0.576	0.161–0.991	0.007	0.322	0.276–0.369	<0.001	0.249	0.201–0.297	<0.001
Integrated discrimination improvement	0.041	0.004–0.078	0.029	0.018	0.001–0.037	0.049	0.009	-0.005–0.019	0.064
HCM Risk-SCD category[b] plus LVEF category [c]									
Net reclassification improvement	0.625	0.205–1.045	0.004	0.531	0.489–0.573	<0.001	0.531	0.489–0.579	<0.001
Integrated discrimination improvement	0.042	0.003–0.081	0.035	0.021	0.001–0.042	0.040	0.013	0.007–0.025	0.038

Abbreviations: CI, confidence interval; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

Model 1 included 897 patients for whom all seven risk factors can be identified.

Model 2 included 1,614 patients without information on the presence or absence of NSVT. In this model, we put the missing value on NSVT as negative.

Model 3 included 1,614 patients without information on the presence or absence of NSVT. In this model, we put the missing value on NSVT as positive.

[a] SCD-equivalent events included documented ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator shocks, and aborted SCD.

[b] HCM Risk-SCD category according to 2014 European Society of Cardiology guidelines; low risk (<4%), intermediate risk (4–6%), or high risk (≥6%).

[c] LVEF was classified into three categories; preserved LVEF (≥60%), low-normal LVEF (50–60%), and reduced LVEF (<50%).

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