

Clinical Characteristics and Prognosis of End-stage Hypertrophic Cardiomyopathy

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Abstract

Background: End-stage hypertrophic cardiomyopathy (HCM) is complicated by substantial adverse events. However, few studies have focused on electrocardiographic features and their prognostic values in HCM. This study aimed to evaluate the clinical manifestations and prognostic value of electrocardiography in patients with end-stage HCM.

Methods: End-stage HCM patients were enrolled from a total of 1844 consecutive HCM patients from April 2002 to November 2013 at Fuwai Hospital. Clinical data, including medical history, electrocardiography, and echocardiography, were analyzed. Cox hazards regression analysis was used to assess the risk factors for cardiovascular mortality.

Results: End-stage HCM was identified in 99 (5.4%) patients, averaged at 52 ± 16 years old at entry. Atrial fibrillation was observed in 53 patients and mural thrombus in 19 patients. During 3.9 ± 3.0 years of follow-up, embolic stroke, refractory heart failure, and death or transplantation were observed in 20, 39, and 51 patients, respectively. The incidence of annual mortality was 13.2%. Multivariate Cox hazards regression analysis identified New York Heart Association Class (NYHA) III/IV at entry (hazard ratio [HR]: 1.99; 95% confidence interval [CI]: 1.05–3.80; $P = 0.036$), left bundle branch block (LBBB) (HR: 2.80; 95% CI: 1.47–5.31; $P = 0.002$), and an abnormal Q wave (HR: 2.21; 95% CI: 1.16–4.23; $P = 0.016$) as independent predictors of cardiovascular death, in accordance with all-cause death and heart failure-related death.

Conclusions: LBBB and an abnormal Q wave are risk factors of cardiovascular mortality in end-stage HCM and provide new evidence for early intervention. Susceptibility of end-stage HCM patients to mural thrombus and embolic events warrants further attention.

Key words: End-stage; Hypertrophic Cardiomyopathy; Left Bundle Branch Block; Prognosis; Q wave

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common genetic disease that is characterized by a hypertrophied, nondilated, left ventricular (LV) cavity with normal or supernormal systolic function.^[1] However, a small number of HCM patients progress to LV remodeling and systolic dysfunction.^[2] Such a condition is referred to as end-stage HCM,^[3] which has attracted considerable interest because of its high risk of substantial cardiovascular mortality. The reported prevalence of end-stage HCM varies from 2.4% to 15.7% in different series.^[4–8] Despite recent progress in the differential diagnosis of dilated cardiomyopathy and underlying mechanisms,^[9–11] research focusing on end-stage HCM has been sparse, and the sample size of most studies was small. In addition, risk factors for cardiovascular mortality and the strategies for management of end-stage

HCM remain obscure. Accordingly, the prognostic factors of end-stage HCM patients need to be clarified to target early management. Therefore, the purpose of this study was to evaluate the clinical characteristics, prognosis, and risk factors in Chinese end-stage HCM patients.

METHODS

Study patients

This retrospective study included 1844 consecutively enrolled HCM patients from April 2002 to November 2013 at Fuwai Hospital in Beijing. HCM was diagnosed as documentation of a hypertrophied or nondilated LV (maximum LV wall thickness [MLVWT] ≥ 15 mm in adults and the equivalent relative to body surface area in children), at some point during the patients' clinical course, in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy by echocardiography or cardiac magnetic resonance imaging.^[12] End-stage HCM was defined

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by the detection of a LV ejection fraction (LVEF) <50% on echocardiography during follow-up.^[6] Patients were excluded for the following reasons: A history of surgical or ablative septal reduction therapy; a history of coronary artery disease or documented coronary arterial narrowing ($\geq 50\%$ stenosis of at least one major artery by angiography). Echocardiography was performed using commercially available ultrasound equipment. The magnitude of LV hypertrophy was assessed from two-dimensional images in accordance with the recommendation of the American Society of Echocardiography.^[13] LVEF was calculated using a modified Simpson's rule.

Initial data regarding medical history, electrocardiograms, and echocardiograms at the diagnosis of end-stage HCM were collected. The follow-up data were obtained during serial clinical visits or by interview by telephone. The study was performed according to the principles of the *Declaration of Helsinki*. All of the patients provided their informed consent to participate in this research, which was approved by the Ethics Committee of Fuwai Hospital.

Follow-up

The primary endpoint was the occurrence of cardiovascular or noncardiovascular death. Cardiovascular death was defined as follows: (1) Sudden cardiac death (SCD), unexpected sudden collapse occurring within 1 h from the onset of symptoms in patients with a previously stable or uneventful clinical course; (2) Heart failure-related death, occurring in the context of progressive cardiac decompensation ≥ 1 year before death and proceeded by signs and symptoms of heart failure or cardiogenic shock; (3) Stroke-related death that occurred as a result of probable or proven embolic stroke; (4) Heart transplantation, which was considered equivalent to heart failure-related death; and (5) Aborted cardiac arrest or appropriate discharge of an implantable cardioverter-defibrillator (ICD) for ventricular fibrillation that was regarded as surrogate SCD.

Conventional risk factors for sudden death, including a family history of sudden death, MLVWT ≥ 30 mm at the initial diagnosis of HCM, syncope, and nonsustained ventricular tachycardia at the diagnosis of end-stage HCM, were calculated for survival analysis.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). All of the data were expressed as mean \pm standard deviation (SD) or frequency. Comparisons of characteristics between groups were made with the Student's *t*-test, Wilcoxon rank-sum test, Chi-square test, or Fisher's exact test as appropriate. The Kaplan-Meier method was used to calculate the rate of survival free from the primary survival curves among different patient groups. Multivariate Cox proportional hazards analysis was applied to evaluate the influence of possible predictors. All reported *P* values were two-sided, and a *P* < 0.05 was considered as statistically significant.

RESULTS

Baseline characteristics

End-stage HCM patients were identified in 99 of 1844 (5.4%) patients [Table 1], during a follow-up period of 12 ± 9 years after the diagnosis of HCM. The annual incidence of end-stage HCM was 0.45%. The mean age was 44 ± 16 years old (range, 4–80 years) at initial diagnosis of HCM and 52 ± 16 years old (range, 14–82 years) at the diagnosis of end-stage HCM. Of them, 58 (59%) patients had a LV end-diastolic diameter (LVEDD) ≥ 55 mm, whereas the remaining 41 (41%) patients had a LVEDD <55 mm. Left atrial thrombus, and LV mural thrombus were observed in 5 (5%) and 14 (14%) patients, respectively. Patients with a Q wave ($n = 55$) had a larger LVEDD (59 ± 13 mm vs. 53 ± 9 mm, *P* = 0.018) and a lower LVEF (42 ± 7 mm vs. 38 ± 7 mm, *P* = 0.007) compared with patients without a Q wave ($n = 44$). Patients with a Q wave had a higher frequency of severe symptomatic heart failure (New York Heart Association [NYHA] Class III/IV, 67% vs. 43%, *P* = 0.016), sustained ventricular tachycardia/ventricular fibrillation (56% vs. 9%, *P* = 0.036), and use of amiodarone (55% vs. 44%, *P* = 0.045) than patients without a Q wave.

Clinical outcomes

During a follow-up period of 3.9 ± 3.0 years, all-cause death occurred in 51 (52%) of 99 patients. Among the death events, heart failure-related death was the most common cause ($n = 26$, including an ICDs), followed by SCD ($n = 17$), heart transplantation ($n = 4$), ICDs ($n = 2$), stroke-related death ($n = 1$), and noncardiovascular death ($n = 1$, lung cancer). The annual mortality rate was 13.2%. Figure 1 showed freedom from all-cause death in the entire cohort.

In addition, 61 patients were NYHA Class III/IV at the last evaluation and 39 patients developed refractory heart failure. Embolic stroke was observed in 20 patients and peripheral artery thrombus in two patients. Cardiac resynchronization therapy (CRT) with or without a defibrillator was implanted in three and two patients, respectively.

Prognostic factors

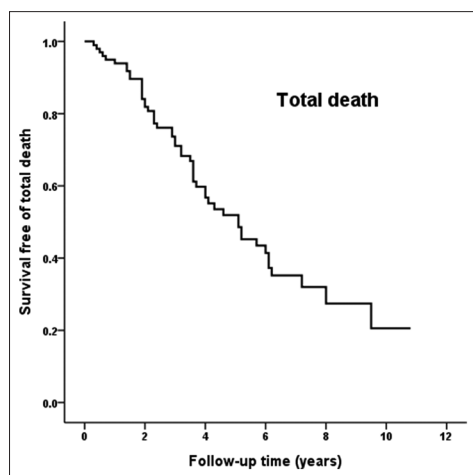
To evaluate the possible predictors of cardiovascular death for end-stage HCM patients, we divided patients into the cardiovascular death group and the survivor group [Table 1]. Kaplan-Meier analysis showed that a higher probability of cardiovascular death was observed in patients with NYHA Class III/IV (*P* = 0.018), those with severe systolic dysfunction (LVEF $\leq 35\%$) (*P* = 0.045), and those with the presence of left bundle branch block (LBBB) (*P* = 0.002) and an abnormal Q wave (*P* = 0.001, Figure 2).

Univariate Cox regression analysis showed that the predictors of cardiovascular death included NYHA Class III/IV (hazard ratio [HR]: 2.08; 95% confidence interval [CI]: 1.12–3.87; *P* = 0.02), and the presence of LBBB (HR: 2.36; 95% CI: 1.32–4.22; *P* = 0.004) and a Q wave (HR: 2.68; 95% CI: 1.42–5.04; *P* = 0.002). In

Table 1: Baseline characteristics of patients at the diagnosis of end-stage HCM

Variables	Overall (n = 99)	Survival (n = 48)	Cardiovascular death (n = 50)	P
Male (n (%))	71 (72)	35 (73)	35 (70)	0.749
Age (mean ± SD, years)	52 ± 16	52 ± 15	51 ± 17	0.750
Family history of HCM (n (%))	45 (45)	22 (46)	22 (44)	0.855
Family history of sudden death (n (%))	27 (27)	14 (29)	12 (24)	0.563
NYHA class III/IV (n (%))	56 (57)	20 (42)	36 (72)	0.002
Unexplained syncope (n (%))	27 (27)	13 (27)	14 (28)	0.919
Electrocardiography (n (%))				
Q wave	55 (56)	17 (35)	37 (74)	0.000
LBBB	22 (22)	4 (8)	18 (36)	0.001
RBBB	8 (8)	6 (13)	2 (4)	0.243
Atrial fibrillation	53 (54)	28 (58)	24 (48)	0.306
Nonsustained VT	48 (48)	20 (42)	28 (56)	0.156
Sustained VT or VF	18 (18)	8 (17)	10 (20)	0.670
Echocardiography				
LAD (mean ± SD, mm)	48 ± 9	46 ± 6	49 ± 10	0.141
LVEDD (mean ± SD, mm)	56 ± 12	55 ± 11	58 ± 13	0.151
IVS (mean ± SD, mm)	15 ± 5	15 ± 5	14 ± 5	0.418
MLVWT (mean ± SD, mm)	16 ± 5	17 ± 5	16 ± 5	0.269
PW (mean ± SD, mm)	11 ± 3	11 ± 3	11 ± 3	0.416
LVEF (mean ± SD, %)	40 ± 7	42 ± 7	39 ± 8	0.065
Intracavitary thrombus (n (%))	19 (19)	7 (15)	12 (24)	0.238
Apical aneurysm (n (%))	11 (11)	6 (13)	5 (10)	0.695
Therapy (n (%))				
ACEI/ARB	54 (55)	24 (50)	29 (58)	0.427
β-blocker	87 (88)	42 (88)	44 (88)	0.940
Amiodarone	33 (33)	11 (23)	22 (44)	0.027
Digoxin	28 (28)	13 (27)	14 (28)	0.919
Warfarin	36 (36)	16 (33)	20 (40)	0.494
Spironolactone	57 (58)	20 (42)	36 (72)	0.002
Pacemaker	21 (21)	9 (19)	11 (22)	0.690
ICD	10 (10)	4 (8)	6 (12)	0.790
≥2 risk factors for sudden death (n (%))	40 (41)	18 (38)	22 (44)	0.770
ASH/CON/AP/MVO/LVO-HCM (n)	70/4/3/13/9	32/2/1/9/4	37/2/2/4/5	0.513

ARB: Angiotensin receptor blocker; HCM: Hypertrophic cardiomyopathy; NYHA: New York Heart Association; LBBB/RBBB: Left/right bundle branch block; VT: Ventricular tachycardia; VF: Ventricular fibrillation; LAD: Left atrial diameter; LVEDD: Left ventricular end-diastolic diameter; MLVWT: Maximum left ventricular wall thickness; IVS: Intraventricular septal thickness; PW: Posterior wall thickness; LVEF: Left ventricular ejection fraction; ASH: Asymmetric septal hypertrophic; CON: Concentric; AP: Apical hypertrophic; LVO: Left ventricular obstructive; MVO: Midventricular obstructive; ACEI: Angiotensin converting enzyme inhibitor; ICD: Implantable cardioverter-defibrillator; SD: Standard deviation.

**Figure 1:** Freedom from all-cause death in the entire cohort.

the multivariate model, after adjusting for confounding factors, NYHA Class III/IV at the diagnosis of end-stage HCM ($HR: 1.99$; $95\% CI: 1.05-3.80$; $P = 0.036$), the presence of a Q wave ($HR: 2.21$; $95\% CI: 1.16-4.23$; $P = 0.016$), and LBBB ($HR: 2.80$; $95\% CI: 1.47-5.31$; $P = 0.002$) were identified as independent predictors of cardiovascular death. Similar results were obtained for sudden death, all-cause death, and heart failure-related death [Table 2].

DISCUSSION

The present study showed that the morphological features of end-stage HCM appeared to be more diverse than previously thought. The phase of end-stage HCM showed a varied prognosis, but overall, proved to be largely unfavorable. In addition, NYHA functional class at entry and the

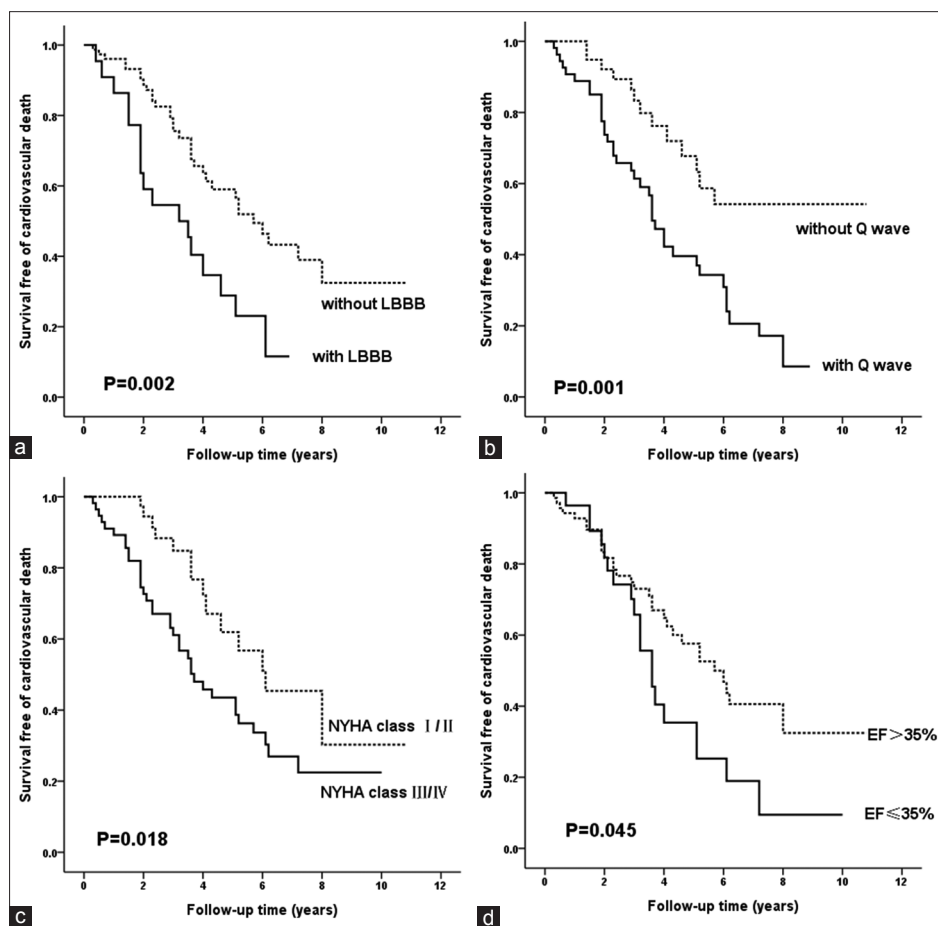


Figure 2: Kaplan-Meier analyses of significant variables on the probability of cardiovascular death in patients with end-stage hypertrophic cardiomyopathy. (a) Comparison of survival free of cardiovascular death with or without left bundle branch block; (b) Abnormal Q wave; (c) New York Heart Association functional (NYHA) Class III/IV; (d) Left ventricular ejection fraction $\leq 35\%$.

presence of LBBB and a Q wave in electrocardiography were independent predictors of cardiovascular mortality in end-stage HCM.

In accordance with our result, the reported incidence of end-stage HCM is relatively uniform, ranging from 0.5% to 1.5% of patients with HCM per year.^[4-7] Also, restrictive-hypokinetic morphological end-stage HCM was comparable with the dilated-hypokinetic subtype.^[6,7] In addition, we found that midventricular obstructive HCM was a main subtype of evolution into the end-stage phase, secondary to asymmetric septal hypertrophy. As previously shown,^[14] midventricular obstructive HCM is disposed to develop systolic dysfunction, especially with apical aneurysms. In addition, LV mural thrombus was present in 14% of patients without ischemic or dilated cardiomyopathy. This finding suggested that the dyskinetic or akinetic walls provide a substrate for ventricular mural thrombus formation in end-stage HCM.^[15]

Our results also suggested that a simple electrocardiogram could be a reliable prognostic predictor of end-stage HCM. Abnormal Q waves were considered as an electrocardiographic characteristic of HCM.^[16] The

presence of abnormal Q waves was also closely related to ventricular enlargement and systolic dysfunction in HCM patients,^[17] in accordance with our results. In addition, our study indicated that an abnormal Q wave was a risk factor for mortality in end-stage HCM. To date, there are two underlying mechanisms of abnormal Q waves in HCM: Loss of electrical forces due to transmural myocardial fibrosis, and an altered direction of the resultant initial QRS vector due to increased electrical forces of disproportionate hypertrophy.^[18] However, a relationship between the location and severity of LV hypertrophy and the presence of abnormal Q waves is controversial.^[19,20] Recently, an increasing amount of studies have identified late gadolinium enhancement (equal to myocardial fibrosis) by CMR as a risk factor for sudden death and development of the end-stage phase in patients with HCM.^[10,21] In addition, Papavassiliu *et al.*^[22] found that the segmental and transmural extent of late gadolinium enhancement rather than the mere presence of myocardial late gadolinium enhancement is the underlying mechanism of abnormal Q waves in HCM. Therefore, abnormal Q waves are associated with an unfavorable prognosis in end-stage HCM, probably by extensive myocardial fibrosis. Further studies on this issue are required.

Table 2: Results of univariate and multivariate Cox proportional-Hazards analyses of the relation between baseline clinical variables and outcome

Variables	Cardiovascular death univariate analysis		All-cause death multivariate analysis		Cardiovascular death multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Male sex	1.02 (0.56–1.88)	0.941	0.96 (0.50–1.84)	0.899	0.95 (0.49–1.82)	0.873
Age (per 10 years increase)	1.00 (0.84–1.19)	0.978	0.99 (0.81–1.20)	0.884	0.98 (0.81–1.19)	0.832
NYHA class III/IV	2.08 (1.12–3.87)	0.020	1.92 (1.02–3.62)	0.045	1.99 (1.05–3.80)	0.036
Atrial fibrillation	0.74 (0.42–1.29)	0.288	0.58 (0.30–1.13)	0.109	0.56 (0.29–1.10)	0.090
LVEF (per 10% decrease)	0.83 (0.58–1.20)	0.320	1.08 (1.26–4.60)	0.720	1.07 (0.71–1.60)	0.760
LBBB	2.36 (1.32–4.22)	0.004	2.78 (1.47–5.28)	0.002	2.80 (1.47–5.31)	0.002
Abnormal Q wave	2.68 (1.42–5.04)	0.002	2.40 (1.26–4.60)	0.008	2.21 (1.16–4.23)	0.016
≥ 2 risk factors for sudden death	1.14 (0.65–2.00)	0.842	1.01 (0.55–1.83)	0.984	1.02 (0.56–1.86)	0.955

Variables	Heart failure-related death multivariate analysis		Sudden cardiac death multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Male sex	0.96 (0.37–2.49)	0.934	0.94 (0.31–2.82)	0.910
Age (per 10 years increase)	1.03 (0.79–1.34)	0.832	0.88 (0.63–1.22)	0.438
NYHA class III/IV	3.95 (1.42–10.96)	0.008	1.10 (0.35–3.48)	0.874
Atrial fibrillation	0.49 (0.17–1.41)	0.186	0.39 (0.13–1.17)	0.092
LVEF (per 10% decrease)	0.77 (0.43–1.38)	0.372	1.43 (0.65–3.15)	0.378
LBBB	4.24 (1.44–12.46)	0.009	4.24 (1.44–12.43)	0.009
Abnormal Q wave	2.89 (1.20–6.96)	0.018	2.69 (0.98–7.36)	0.054
≥ 2 risk factors for sudden death	1.02 (0.43–2.43)	0.959	0.63 (0.22–1.82)	0.398

NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; LBBB: Left bundle branch block; HR: Hazard ratio; CI: Confidence interval.

In our study, we observed that the presence of LBBB was associated with a poorer prognosis in multivariate analysis, supporting the prognostic importance of LBBB in HCM patients from a national study in Japan.^[23] LBBB is defined as a marker of unfavorable prognosis in chronic heart failure, mainly due to contractive asynchrony.^[24–26] In HCM, inter- and intra-ventricular asynchrony is aggravated by regional heterogeneity of contraction and relaxation with asymmetric hypertrophy.^[27] Additionally, LBBB is associated with more marked LV dilation, depressed LVEF, and mitral valve regurgitation in patients with heart failure.^[25] Therefore, we hypothesized that LBBB is a new marker for LV systolic dysfunction with a poor prognosis in end-stage HCM. Recently, biventricular pacing was reported to improve heart failure symptoms and reverse remodeling in end-stage HCM patients with LBBB in case reports and a series report.^[28–30] In view of these findings, CRT is considered for HCM patients with refractory symptoms, LVEF <50%, and LBBB in the newly enacted European Society of Cardiology guideline (Class IIb, level C).^[31] In addition, our study showed that the risk of mortality of mild systolic dysfunction was equal to that of severe systolic dysfunction by echocardiography, which strengthened the importance of early CRT management, even in mild systolic dysfunction. Therefore, the presence of LBBB in an electrocardiogram is an indicator of routine CRT implantation in end-stage HCM for an early management of refractory heart failure.

Previous studies have indicated direct correlations of conventional risk factors (left ventricular wall thickness and

syncope) with cardiovascular death in end-stage HCM.^[4,7] However, our data did not support these findings. Our results supported recent findings that these risk factors might not necessarily be predictors for sudden death or cardiovascular death and that they should not be considered as isolated risk factors for cardiovascular mortality in patients with HCM.^[21,32] As proposed by Olivetto *et al.*,^[33] MLVWT may be a risk factor for sudden death only in patients diagnosed with HCM at a young age. A high proportion of included pediatric patients (39%) can explain the difference between a previous study^[4] and our study. In addition, the different definitions of endpoint and length of follow-up could change the composition of mortality.^[7] A longer follow-up period would be better for evaluation of risk.

Patients in end-stage HCM are at higher risk of atrial fibrillation (54%) than in general HCM (20–30%).^[34] LV hypertrophy aggravated the incidence of left atrial thrombus in atrial tachyarrhythmia^[35] and additional frequent mural thrombus complicates embolic events, even in sinus rhythm. Atrial fibrillation is still a strong risk factor for embolic stroke in HCM.^[34] Because of left atrial enlargement is a marker of susceptibility for atrial fibrillation,^[36] we strongly recommended anticoagulants for each patient with end-stage HCM. Unfortunately, only 36% of our patients regularly took anticoagulants. In addition, the ICD was not effectively implanted as required for primary prevention in most patients. It to some extent represents a natural course of end-stage HCM. This indicated that strong interventions will be effective for improving the prognosis of end-stage HCM.

These interventions include health education, financial support, intensive surveillance, ICD or CRT implantation, and heart transplantation.

This study has several limitations. First, our study was performed in a referral hospital, and selective bias was inevitable. Second, genetic analysis was not undertaken in this cohort despite the increasing value of genetic testing in HCM.^[37] Third, late enhancement analysis by cardiac magnetic resonance imaging was not available in our study, and its prognostic significance was overlooked. Finally, the follow-up time was relatively short. Therefore, more detailed data on a larger multicenter scale are encouraged to evaluate the detailed risk factors related to end-stage HCM.

In conclusion, in end-stage HCM, atrial fibrillation, mural thrombus, and thromboembolic events are fairly frequent incidents. Heart failure-related death and sudden death are the major outcomes in end-stage HCM. Patients with LBBB and an abnormal Q wave have a high probability of cardiovascular death and need early targeted management for mild systolic dysfunction.

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