

Very long-term prognosis in patients with hypertrophic cardiomyopathy: a longitudinal study with a period of 20 years

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Abstract

Aims We aim to clarify the prognosis on patients with hypertrophic cardiomyopathy (HCM) for a follow-up period of more than 10 years.

Methods and results We retrospectively analysed 102 consecutive patients with HCM diagnosed by 31 December 2000. Complete and detailed clinical records were obtained for 93 (91%) of the 102 patients. Sixty-three (68%) of the 93 patients were men, and the mean age of the patients at the initial evaluation was 51.5 ± 13.0 years. During the mean follow-up period of 19.6 ± 8.1 years (median 20.1 years), HCM-related deaths occurred in 20 patients (21% [1.1%/year]). HCM-related adverse events (including HCM-related deaths and nonfatal HCM-related events: hospitalization for heart failure, embolic stroke admission, and sustained ventricular tachycardia with haemodynamic instability or appropriate implantable cardioverter-defibrillator discharge) occurred in 45 patients (48%). The first HCM-related adverse events occurred in approximately 20% of the patients in every decade, the first decade to the third decade, from the initial evaluation. Forty-seven patients (51%) had documentation of atrial fibrillation at the last follow-up. There were seven patients in the end-stage HCM group at the initial evaluation, and 22 patients (24%) had progression to end-stage HCM during the follow-up period.

Conclusions In our cohort of patients, HCM-related mortality was relatively favourable. However, approximately half of the patients suffered from HCM-related adverse events during the follow-up period of 20 years. It is important for HCM patients to be carefully followed up over the long-term because HCM is a lifelong disease.

Keywords Hypertrophic cardiomyopathy; Lifelong disease; Long-term prognosis

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Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with a heterogeneous clinical presentation and a heterogeneous course.^{1,2} The disease is now recognized as a lifelong disease with its phenotype itself being a slowly progressive disorder that manifests remarkable evolution of clinical features throughout life.^{3,4} Treatment strategies for better management of HCM have been established, and recent studies have suggested that the prognosis has become better than that shown in previous studies and HCM is

generally associated with mild disability and normal life expectancy if sudden death can be prevented.^{5–8} However, most of the studies on the clinical outcomes of HCM had a follow-up period of less than 10 years and there have been few studies on the long-term clinical course of HCM.^{9,10} Because HCM is a lifelong disease, it is important to clarify the very long-term prognosis of the disease over a period of more than 10 years.

The purpose of this study was to determine the clinical courses in patients with HCM during a follow-up period of approximately 20 years.

Methods

Study population

We retrospectively studied 102 consecutive HCM patients who were diagnosed by 31 December 2000 at Kochi Medical School Hospital. The diagnosis of HCM was based on echocardiographic demonstration of left ventricular hypertrophy (LVH), that is, maximum LV wall thickness ≥ 15 mm, in the absence of other cardiac diseases that could produce hypertrophy of such magnitude (e.g. arterial hypertension, aortic stenosis, or storage disease). Information on the most recent clinical assessments was obtained for patients who visited our institution or related facilities up to 31 December 2017.

The study was approved by the Ethics Committee on Medical Research of Kochi Medical School and followed the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation.

Clinical evaluation

Evaluation of the patients included medical history, clinical examination, 12-lead electrocardiography, and echocardiography. LV wall thickness was measured in the parasternal short-axis views (2D or M-mode) at the mitral valve, papillary muscles, and apical levels at end diastole. LV end-diastolic diameter (LVEDd) and end-systolic diameter (LVESd) were measured from M-mode and 2D images obtained from parasternal long-axis views for calculation of fractional shortening (%FS = (LVEDd – LVESd)/LVEDd \times 100). LV outflow tract and mid ventricular gradients were calculated from continuous-wave Doppler using the simplified Bernoulli equation.

Based on morphologic and haemodynamic assessments by echocardiography, we divided the patients into five groups: (i) hypertrophic obstructive cardiomyopathy (HOCM), defined as the presence of basal LV outflow tract obstruction (gradient >30 mmHg); (ii) mid-ventricular obstruction (MVO), defined as the presence of systolic LV cavity obliteration at the mid ventricle, creating MVO with a peak systolic gradient >30 mmHg; (iii) end-stage HCM, defined as LV systolic dysfunction of the global ejection fraction (EF) $< 50\%$ (Global EF was determined from apical 2- and 4-chamber views; concomitant coronary artery disease was excluded by coronary artery angiography and/or myocardial scintigraphy.); (iv) apical HCM, defined as hypertrophy confined to the LV apex below the papillary muscle level; and (v) hypertrophic non-obstructive cardiomyopathy (HNOCM) (non-obstructive HCM other than end-stage HCM and apical HCM).

Hypertrophic cardiomyopathy-related deaths were defined as three types of death: (i) sudden cardiac death (SCD), in which unexpected sudden collapse occurred in patients with a relatively stable or uneventful clinical course; (ii) heart failure (HF) death, which was in the context of progressive car-

diac decompensation; and (iii) embolic death, which occurred as a result of probable or proven embolic stroke. HCM-related adverse events were defined as follows: (i) SCD-relevant events including SCD and spontaneous sustained ventricular tachycardia (VT) associated with haemodynamic instability or appropriate discharges of implantable cardioverter defibrillator (ICD); (ii) composite HF events including HF death and hospitalization for HF; and (iii) composite embolic stroke events including embolic stroke deaths and hospitalization for embolic stroke.

Data analysis

Statistical analysis was performed using SPSS (version 21.0.0.0) statistical software (SPSS Inc, Chicago, IL USA). All data are displayed as means \pm SD (ranges) for continuous variables. The significance of differences between the two groups was assessed using the unpaired *t*-test for continuous variables and the χ^2 test for categorical variables. Cumulative event-free estimates curves were obtained by using the Kaplan–Meier method.

Results

Baseline clinical characteristics

Complete and detailed clinical information at the last follow-up was obtained for 93 (91%) of the 102 patients. *Table 1* shows clinical characteristics of the 93 patients with HCM at the initial evaluation in our hospital. The ages at initial evaluation and at diagnosis were 51.5 ± 13.0 years (range: 16–78 years) and 50.8 ± 13.7 years (range: 14–78 years), respectively. Sixty-three (68%) of the patients were men. Fifty patients (54%) were diagnosed because of their symptoms, and the other 43 patients (46%) were diagnosed due to incidental findings such as ECG abnormalities and systolic murmur or family screening. Forty patients (43%) had proven familial HCM and 25 patients (27%) had a family history of SCD. Eighty-nine patients (96%) had New York Heart Association (NYHA) functional class I or II and 9 patients (10%) had a history of unexplained syncope at the initial evaluation. Eleven patients (12%) had documented paroxysmal or permanent atrial fibrillation (AF) at the initial evaluation. Of the 93 patients, there were 7 patients (8%) in the HOCM group, 3 patients (3%) in the MVO group, 18 patients (19%) in the apical HCM group, 7 patients (8%) in the end-stage HCM group, and 58 patients (62%) in the HNOCM group. All patients in HOCM and MVO group demonstrated NYHA functional classes I and II at the initial evaluation. The data of medical therapies at the initial evaluation were available in 89 patients. Beta-blockers were most frequently prescribed. The mean follow-up period for the 93 patients was 19.6 ± 8.1 years

Table 1 Clinical characteristics of the 93 HCM patients at the initial evaluation

Age at initial evaluation, years	51.5 ± 13.0
Gender: men, n (%)	63 (68)
Reason for diagnosis	
Symptoms, n (%)	50 (54)
ECG or auscultation abnormality, n (%)	28 (30)
Family screening, n (%)	15 (16)
Family history of HCM, n (%)	40 (43)
Family history of SCD, n (%)	25 (27)
Presence of symptoms at initial evaluation, n (%)	
NYHA functional class I	57 (61)
NYHA functional class II	32 (34)
NYHA functional class III	3 (3)
NYHA functional class IV	1 (1)
Atrial fibrillation at initial evaluation, n (%)	11 (12)
Echocardiographic data at initial evaluation	
Subtype, n (%)	
HOCM	7 (8)
MVO	3 (3)
End-stage HCM	7 (8)
Apical HCM	18 (19)
HNCM	58 (62)
Maximum LV wall thickness, mm	19.5 ± 4.2
LV end-diastolic diameter, mm	44.6 ± 6.7
Fractional shortening, %	40.9 ± 10.0
Left atrial diameter, mm	38.9 ± 7.3
Medical therapies, n = 89	
Beta-blockers, n (%)	31 (35)
Calcium antagonists, n (%)	20 (22)
Disopyramide, n (%)	12 (13)
ACEI/ARB, n (%)	9 (10)
Warfarin, n (%)	10 (11)

HCM, hypertrophic cardiomyopathy; ECG, electrocardiogram; SCD, sudden cardiac death; NYHA, New York Heart Association; HOCM, hypertrophic obstructive cardiomyopathy; MVO, mid ventricular obstruction; HNCM, hypertrophic non-obstructive cardiomyopathy; LV, left ventricular; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers.

(median 20.1 years). None of the patients underwent cardiac transplantation or myectomy. Ten patients (11%) received ICD implantations and one patient had alcohol septal ablation.

Hypertrophic cardiomyopathy-related deaths

Clinical outcomes are shown in *Figure 1*. During the follow-up period, 47 patients (51%) died. HCM-related deaths occurred in 20 of those 47 patients: SCDs in 5 patients, HF deaths in 11 patients, and embolic deaths in 4 patients. The HCM-related annual mortality rate was 1.1% per year and the HCM-related 20-year survival rate was 81%. In the group analysis for the study population, the mean age at HCM-related deaths was 70.7 ± 9.1 years (range, 49–84 years): mean age of 67.4 ± 13.8 years (range, 49–84 years) for SCD, mean age of 72.1 ± 6.3 years (range, 62–81 years) for HF death, and mean age of 70.7 ± 6.8 years (range, 61–80 years) for embolic stroke death. HCM-related deaths tended to occur at a younger age than the age at which non-HCM-related deaths occurred (70.7 ± 9.1 vs. 75.5 ± 12.3 years, $P = 0.145$).

Table 2 shows clinical characteristics at the initial evaluation of patients with and without HCM-related death. Patients with HCM-related death were significantly older (57.8 ± 10.0 years vs. 49.7 ± 13.3 years, $P = 0.005$) and had a significantly higher rate of presence of symptoms and AF. Regarding echocardiographic findings, LVEDd and left atrial diameter were larger and FS was lower in patients with HCM-related death than in the patients without HCM-related adverse events.

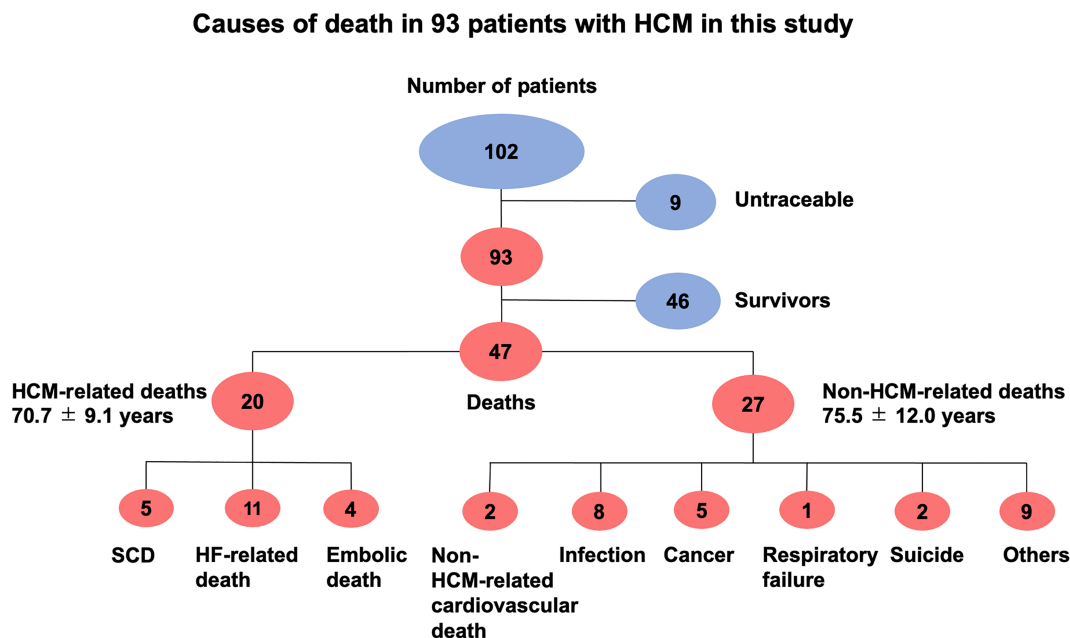
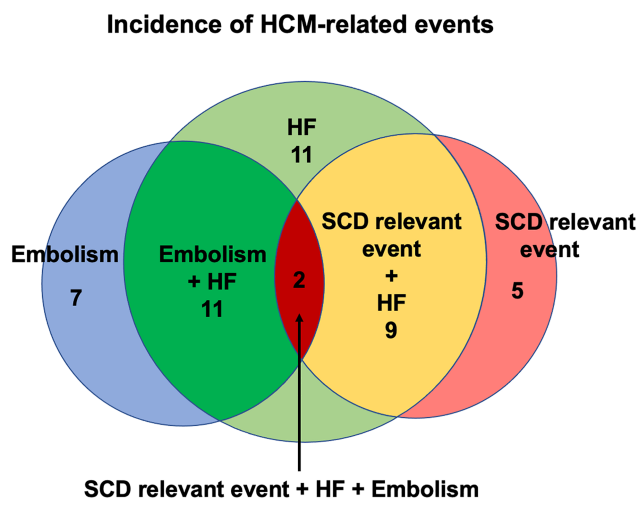
Figure 1 Causes of death in 93 patients with HCM in this study. HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; HF, heart failure.

Table 2 Clinical characteristics at the initial evaluation of patients with and those without HCM-related death

	HCM-related death (+), n = 20	HCM-related death (-), n = 73	P value
Age at initial evaluation, years	57.8 ± 10.0	49.7 ± 13.3	0.005
Gender: men, n (%)	13 (65)	50 (68)	0.767
Family history of HCM, n (%)	10 (50)	30 (41)	0.476
Family history of SCD, n (%)	6(30)	19 (26)	0.723
Symptoms at initial evaluation, n (%)	16 (80)	39 (54)	0.016
Chest pain at initial evaluation, n (%)	7 (35)	27 (37)	0.870
Palpitation at initial evaluation, n (%)	9 (45)	12 (16)	0.013
Syncope at initial evaluation, n (%)	1 (5)	8 (11)	0.678
NYHA functional class III or IV, n (%)	4 (20)	0 (0)	0.002
Atrial fibrillation at initial evaluation, n (%)	8 (40)	3 (4)	<0.001
HOCM, n (%)	1 (5)	6 (8)	1.000
End-stage HCM, n (%)	6 (30%)	1 (1%)	<0.001
Maximum LV wall thickness, mm	18.3 ± 3.0	20.0 ± 4.6	0.127
LV end-diastolic diameter, mm	48.1 ± 7.9	43.7 ± 6.2	0.010
Fractional shortening, %	33.1 ± 11.1	43.1 ± 8.7	<0.001
Left atrial diameter, mm	45.0 ± 6.3	37.3 ± 6.8	<0.001

HCM, hypertrophic cardiomyopathy; ECG, electrocardiogram; SCD, sudden cardiac death; NYHA, New York Heart Association; HOCM, hypertrophic obstructive cardiomyopathy; MVO, mid ventricular obstruction; HNCM, hypertrophic non-obstructive cardiomyopathy; LV, left ventricular; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers.

Figure 2 Details of the incidence of HCM-related events. Sixty-nine cardiovascular events occurred in 45 patients. HF, heart failure; SCD, sudden cardiac death.



Hypertrophic cardiomyopathy-related adverse events

During the follow-up period, a total of 69 HCM-related adverse events in 45 patients (48%) occurred: SCD relevant events in 16 patients, composite HF events in 33 patients, and composite embolic stroke events in 20 patients. Multiple events occurred in 22 patients (*Figure 2*).

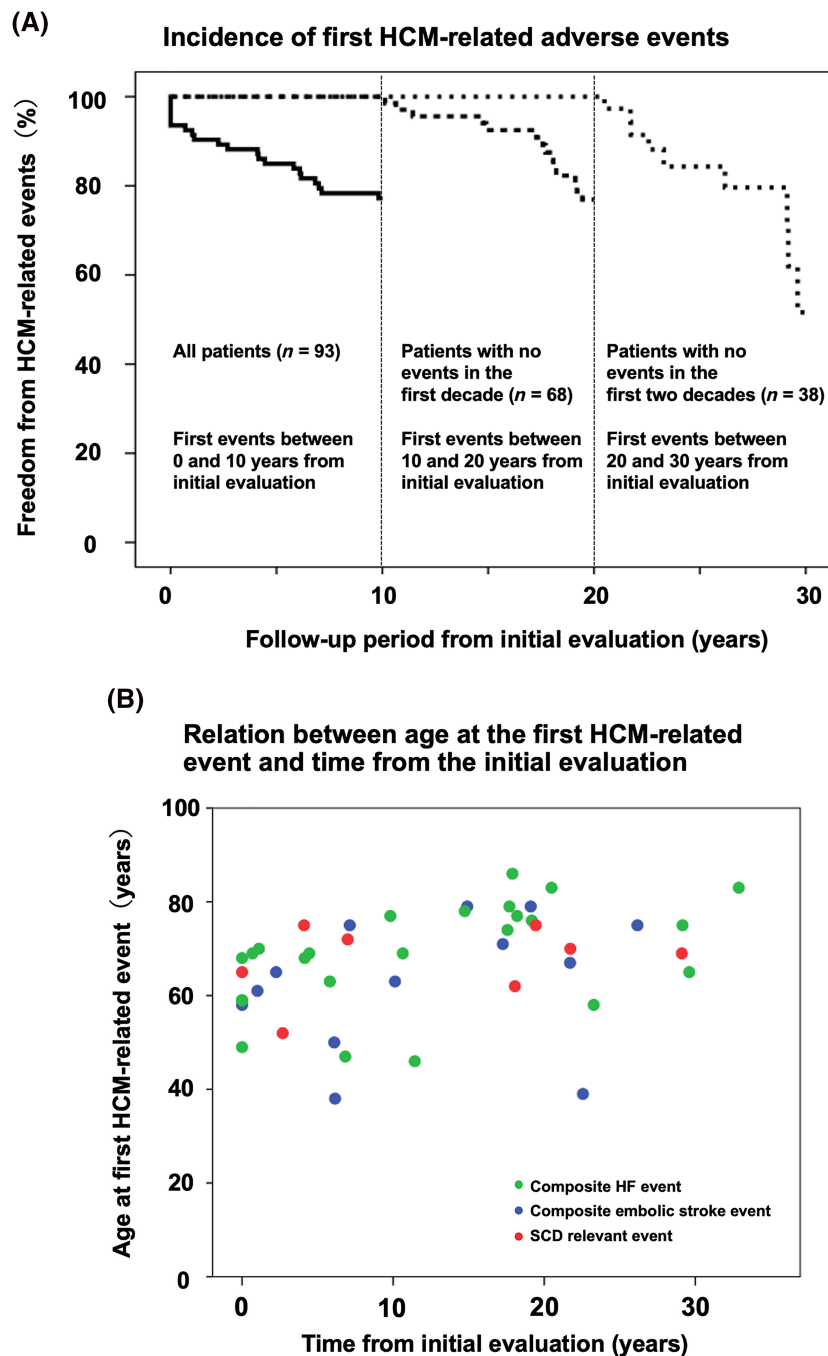
Figure 3A shows the cumulative first HCM-related adverse event-free rate. First HCM-related adverse events occurred in approximately 20% of all patients in the first decade from the initial evaluation. In the next decade, first

HCM-related adverse events similarly occurred in approximately 20% of the patients who did not suffer from HCM-related adverse events or have non-HCM-related deaths in the first decade. Similar results were also obtained in the third decade. *Figure 3B* shows the relation between age at the first HCM-related adverse event and time from the initial evaluation. First HCM-related adverse events occurred most frequently in patients from the ages of 60 to 80 years. On the other hand, a few first HCM-related adverse events occurred in patients under 60 years of age, even after more than 10 years had passed since the initial evaluation.

Figure 4 shows the relationship of the 20 patients with embolic events and the timing of receiving anticoagulation therapy. Of these patients, 11 had anticoagulation therapy using warfarin prior to the embolic events. One patient without anticoagulation therapy died from the embolic event. In the remaining eight patients, AF was detected after events in six patients and LV thrombus was detected in two patients.

Table 3 shows clinical characteristics at the initial evaluation of patients with HCM-related adverse events that occurred in the first decade from the initial evaluation and with HCM-related adverse events that occurred after the first decade versus those without HCM-related adverse events. Patients with HCM-related adverse events in the first decade were significantly older, more symptomatic, and had a significantly higher rate of AF. Regarding echocardiographic findings, LVEDd and left atrial diameter were larger and FS was lower in patients with HCM-related adverse events in the first decade than in patients without HCM-related adverse events. On the other hand, there were no significant differences between patients with HCM-related adverse events after the first decade and patients without HCM-related adverse events.

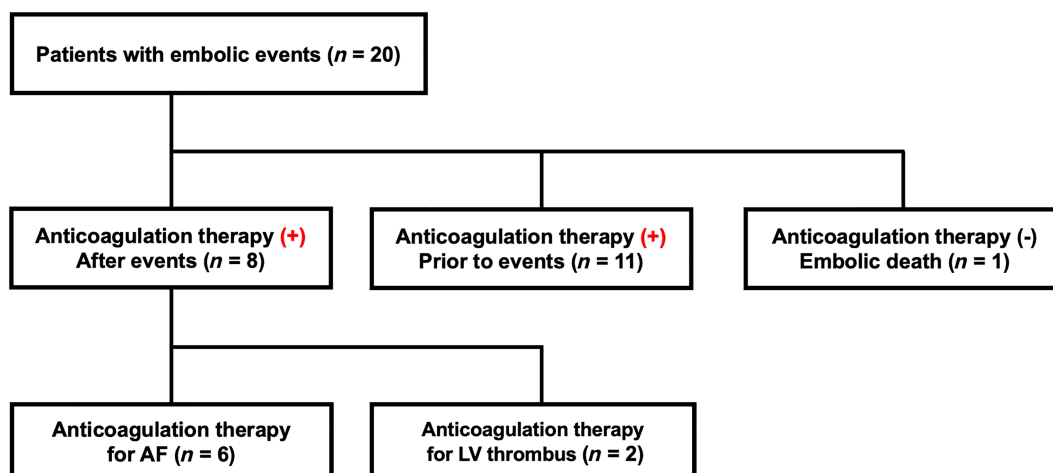
Figure 3 (A) Incidence of HCM-related adverse cardiovascular events per decade. (B) Relation between age at the first HCM-related event and time from the initial evaluation. HF, heart failure; SCD, sudden cardiac death.



Atrial fibrillation and left ventricular remodelling

During the follow-up period, 36 patients (39%) developed new onset of AF. Finally, 47 patients (51%) were diagnosed with paroxysmal or permanent AF, and 43 (91%) of them had received anticoagulation therapy by the end of the

follow-up. Moreover, of the 47 patients with documentation of AF, 74% of the patients suffered from HCM-related adverse events. As for the subtypes, seven patients were diagnosed with end-stage HCM at the initial evaluation. In addition to them, 22 patients (24%) developed new end-stage HCM during the course of this study. Finally, 29 patients

Figure 4 The relationship of the patients with embolic events and timing of receiving anticoagulation therapy. AF, atrial fibrillation; LV, left ventricle.**Table 3** Baseline characteristics at the initial evaluation of patients with HCM-related adverse events that occurred in the first decade from initial evaluation and with HCM-related adverse events that occurred after the first decade versus those without HCM-related adverse events

	HCM-related events (-), n = 48	HCM-related events (+) in the first decade, n = 21	P value	HCM-related events (+) after the first decade, n = 24	P value ^a
Age at initial evaluation, years	49.2 ± 13.8	57.5 ± 10.7	0.016	50.8 ± 12.1	0.634
Gender: men, n (%)	35 (73)	14 (67)	0.599	14 (58)	0.211
Family history of HCM, n (%)	19 (40)	9 (43)	0.799	12 (50)	0.400
Family history of SCD, n (%)	13 (27)	6 (29)	0.899	6 (25)	0.850
Reason for diagnosis: Symptoms, n (%)	24 (50)	17 (81)	0.016	14 (58)	0.504
Chest pain at initial evaluation, n (%)	17 (35)	7 (33)	1.000	10 (42)	0.616
Palpitation at initial evaluation, n (%)	8 (17)	9 (43)	0.020	4 (17)	1.000
Syncope at initial evaluation, n (%)	7 (15)	1 (5)	0.419	1 (4)	0.255
NYHA functional class III or IV	0 (0)	4 (19)	0.007	0 (0)	NA
Atrial fibrillation at initial evaluation, n (%)	2 (4)	7 (33)	0.002	2 (8)	0.597
HOCM, n (%)	4 (8)	1 (5)	1.000	2 (8)	1.000
End-stage HCM, n (%)	0 (0)	7 (33)	<0.001	0 (0)	NA
Maximum LV wall thickness, mm	19.7 ± 4.7	18.1 ± 2.8	0.112	20.4 ± 4.1	0.557
LV end-diastolic diameter, mm	43.2 ± 6.3	48.5 ± 7.6	0.004	43.7 ± 5.4	0.739
Fractional shortening, %	43.3 ± 8.1	32.8 ± 12.7	0.002	43.5 ± 7.0	0.898
Left atrial diameter, mm	36.8 ± 7.4	45.4 ± 6.4	<0.001	37.9 ± 5.2	0.500

HCM, hypertrophic cardiomyopathy; ECG, electrocardiogram; SCD, sudden cardiac death; NYHA, New York Heart Association; HOCM, hypertrophic obstructive cardiomyopathy; MVO, mid ventricular obstruction; HNCM, hypertrophic non-obstructive cardiomyopathy; LV, left ventricular; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers.

^aHCM-related events (-) vs. HCM-related events (+) after the first decade.

(31%) had end-stage HCM at the last evaluation. Of the 29 patients with end-stage HCM, 86% of the patients suffered from HCM-related adverse events.

Discussion

From the viewpoint of a lifelong disease, we revealed the clinical courses of HCM in patients with a mean follow-up period of 20 years in the study. Although HCM mortality was

favourable with an HCM mortality rate of only 1.1% per year in our study, about half of the patients suffered from serious HCM-related adverse events. Some patients had HCM-related adverse events for the first time even more than 20 years after diagnosis. Furthermore, a considerable number of the patients progressed to onset of AF and/or end-stage HCM, and AF and end-stage HCM were strongly associated with HCM-related adverse events. These results indicate that the disease requires lifelong management.

In our study, the mean age of the patients at the initial evaluation was 51.5 ± 13.0 years and 67% of the patients

were men. Although half of the patients were diagnosed with HCM because of cardiac symptoms (54%), there were few patients with NYHA functional class III or IV. Documented AF was observed in 12% of the patients. Characteristics of these patients were in accordance with the previously reported data obtained from HCM populations in Western countries.^{5,11,12}

With regard to mortality, our investigation showed a favourable prognosis with an HCM-related annual mortality rate of only 1.1%. This is probably due to the fact that our patient cohort was not a tertiary centre population but a community-based cohort. Furthermore, as shown in previous studies, the prognosis of patients with HCM has been improved by new treatment strategies for HCM patients including the use of implantable defibrillators, administration of a novel oral anticoagulant, septal reduction therapy, and heart transplantation.^{5–8}

Although HCM mortality was favourable, the present study showed that half of the patients with HCM had HCM-related adverse events. Furthermore, about half of the patients with adverse events suffered from multiple events. Clinically serious HCM-related adverse events are likely to significantly diminish the patient's quality of life. First HCM-related adverse events occurred most frequently in patients from the ages of 60 to 80 years, although several events occurred in patients under 60 years of age. We also found that first HCM-related events occurred in some patients even after more than 20 years had passed since the initial evaluation. Our results therefore indicated that HCM patients should be carefully followed up at all ages.

Based on results shown in *Table 3*, HCM-related adverse events that occurred within 10 years from the first visit were associated with worse clinical profiles including more advanced age, more symptomatic, presence of AF, and more advanced LV and left atrial remodelling at the initial evaluation. Therefore, these advanced clinical profiles are predictors of HCM-related adverse events occurring within a short period. On the other hand, there were no significant differences among the clinical profiles in patients with HCM-related events after the first decade and patients without HCM-related events. These results suggest that there are no predictors of HCM-related adverse events more than 10 years after the initial evaluation. In this study, we focused on new-onset AF and progression to end-stage HCM. Several studies have shown that the incidence of AF in HCM patients was approximately 10–30%.^{5–7,11–14} Although the prevalence of AF at diagnosis was 12% in our study, 51% of the patients finally had documentation of AF at the last follow-up. As for end-stage HCM, 24% of the patients progressed to end-stage HCM during the follow-up period of 20 years. In short, about 1% of patients per year progressed to end-stage HCM. Finally, 31% of the patients had end-stage HCM at the last evaluation. Although the time course of LV remodelling is heterogeneous, LV remodelling often occurs

gradually over the years.^{15,16} Previous studies have shown that AF and end-stage HCM are associated with worse clinical outcomes,^{13,17–20} and 74% of the patients with AF and 86% of the patients with end-stage HCM in the present study suffered from HCM-related adverse events. Based on these facts, it is expected that the longer the follow-up period is, the higher will be the frequency of development of AF and end-stage HCM. It is therefore important to monitor the long-term course of patients with HCM. Ongoing monitoring over a long period could lead to early intervention with contemporary treatment strategies, which might improve the outcomes of HCM patients.

Limitations

This study has several limitations. First, the size of the cohort was relatively small and the design was retrospective. However, to the best of our knowledge, this is the largest HCM cohort for a 20-year follow-up period. Second, management for patients might have influenced the clinical outcomes. Only one patient underwent septal reduction therapy for LV outflow tract obstruction. There were some reasons for the undertreatment of patients with HOCM. Firstly, in this study, patients had been diagnosed as HCM by 2000. Although the number of patients undergoing septal reduction therapies has been gradually increasing in recent years in Japan, the institutions performing septal reduction therapies were not centralized at that time. Therefore, those therapies had infrequently been performed around 2000. In addition, this study was conducted in the Kochi prefecture, a rural area in Japan. The patients might have difficulties of access to experienced centres. Secondly, all patients with HOCM or MVO were asymptomatic or mildly symptomatic in our cohort at initial evaluation. Only a small number of them underwent septal reduction therapy because of their mild symptoms. However, the fact that septal reduction therapy was performed only in one patient might influence on the prognosis of the patients with HOCM.

Conclusions

In our cohort, HCM mortality was relatively favourable. However, half of the patients suffered from HCM-related adverse events during the follow-up period of 20 years. HCM patients should be carefully followed up because HCM is a lifelong disease.

Conflict of interest

None of the authors have conflict of interest to disclose.

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