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Clinical scenarios of hypertrophic cardiomyopathy-related mortality: Relevance of age and stage of disease at presentation

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ABSTRACT

The evolving epidemiology of hypertrophic cardiomyopathy (HCM) has progressively changed our perception of HCM-related mortality. However, recent studies detailing individual causes of death based on age and clinical setting are lacking. Thus, the present study aimed to describe the modes of death in a consecutive cohort of HCM patients based on presenting clinical features and stage of disease.

Methods: By retrospective analysis of a large HCM cohort, we identified 161 patients with >1 year follow-up who died between 2000 and 2020 and thoroughly investigated their modes of death. HCM stage at presentation was defined as "classic", "adverse remodeling" or "overt dysfunction".

Results: Of the 161 patients, 103 (64%) died of HCM-related causes, whereas 58 (36%) died of non-HCM-related causes. Patients who died of HCM-related causes were younger than those who died of non-HCM related causes. The most common cause of death was heart failure (HF). Sudden cardiac death (SCD) ranked third, after non cardiovascular death, and mostly occurred in young individuals. The proportion of HF related death and SCD per stage of disease was 14% and 27% in "classic", 38% and 21% in "adverse remodeling" and 74% and 10% in "overt dysfunction".

Conclusions: Most HCM patients die due to complications of their own disease, mainly in the context of HF. While SCD tends to be juvenile, HF related deaths often occur in age groups no longer amenable to cardiac transplant. Modes of death vary with the stage of disease, with SCD becoming less prevalent in more advanced phases, when competitive risk of HF becomes overwhelming.

Hypertrophic cardiomyopathy (HCM) has long been considered a malignant disease of the young, with no or limited therapeutic options. In the early days, the outcome was thought to be heavily influenced by the arrhythmic propensity, with sudden cardiac death (SCD) reported as the leading cause of death [1–4].

Subsequently, the evolving epidemiology of the disease has radically changed our perception of HCM-related mortality [5,6]. Recognition of milder HCM phenotypes, due to increased awareness, genetic cascade screening and easier access to cardiac imaging, coupled with advances in management, have all contributed to determine a different scenario [5–7]. Contemporary descriptions of HCM report low mortality rates, largely due to heart failure-related complications (HF), while SCD rates are consistently low [8–10]. Ageing with HCM is not uncommon and competing risk of acquired cardiovascular (CV) and non-CV diseases

Abbreviations: AF, Atrial fibrillation; CMR, Cardiac magnetic resonance; COPD, Chronic obstructive pulmonary disease; CV, Cardiovascular; EF, Ejection fraction; HCM, Hypertrophic cardiomyopathy; HF, Heart failure; ICD, Implantable cardiac defibrillator; LV, Left ventricle; LVOTO, Left ventricular outflow tract obstruction; SCD, Sudden cardiac death; TIA, Transient ischemic attack.

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becomes relevant over time, influencing individual outcome.

While there is general agreement on the labelling of sudden versus HF-related mortality, a detailed and up to date characterization of the modes of death in HCM patients is lacking. Specifically, individual circumstances remain poorly described, as fine details are unavoidably lost in large registries and retrospective series. Yet, discerning these aspects might be relevant to our understanding of disease behaviour and may potentially improve event prevention and patient management. Based on these premises, the present study aimed to describe the clinical features, disease stage at presentation and the modes of death in a cohort of consecutive HCM patients followed at a national referral centre over the last two decades.

1. Methods

We conducted a retrospective analysis of our centralized database and identified 1491 HCM patients with at least >1 year of follow-up between January 2000 and December 2020, 191 of whom died in the same period. The cause of death could not be ascertained in 30 of the 191 patients, all aged >70 years. The remaining 161 constituted our study cohort (Fig. 1). For each, baseline features, clinical characteristics, disease staging and modes of death were assessed in detail. The study was approved by the local ethics committee.

1.1. HCM diagnosis

HCM was defined by a wall thickness ≥ 15 mm in one or more left ventricular (LV) myocardial segments -as measured by echocardiography and/or cardiac magnetic resonance (CMR) imaging- that was not explained by abnormal loading conditions. The clinical diagnosis of HCM in first-degree relatives of patients with unequivocal disease was based on the presence of otherwise unexplained increased LV wall thickness ≥ 13 mm in one or more LV myocardial segments [11]. Patients known to have inherited metabolic diseases, syndromic causes of HCM, amyloidosis and other phenocopies have been excluded [12].

At presentation, all patients underwent clinical assessment, genetic counselling, physical examination, resting electrocardiography, and transthoracic echocardiography.

Family history of SCD was defined as a history of SCD in 1 or more first-degree relatives younger than 40 years with or without a diagnosis of HCM, or when SCD occurred in a first-degree relative with confirmed HCM at any age [11].

1.2. Echocardiographic evaluation

The LV ejection fraction was calculated using the Simpson's method. The left atrial diameter was determined by M-mode or 2-dimensional echocardiography in the parasternal long-axis plane [13]. LV outflow tract obstruction (LVOTO) was defined as an instantaneous peak Doppler LV outflow tract pressure gradient ≥ 30 mmHg at rest or during Valsalva manoeuvre or during exercise. The peak instantaneous LV outflow tract gradient was measured with continuous-wave Doppler [14]. In all patients at diagnosis with a LVOTO < 50 mmHg and in those patients who developed symptoms suggestive of exercise inducible LVOTO during follow-up we offered exercise echocardiography. Exercise echocardiography was performed on a dedicated station with a semi-supine bicycle and a dedicated echocardiographer with specific training on stress echocardiography.

1.3. Genetic test

Routine genetic testing for HCM patients was introduced at our center in 1998 using Sanger sequencing and targeting the first three genes associated with HCM: MYH7, MYBPC3, and TNNT2. The set of targeted genes was expanded in 2005 to include the other five sarcomeric genes irrefutably associated with HCM (TPM1, MYL2, MYL3, TNNI3, and ACTC1). Sanger sequencing was replaced with the next-generation sequencing (NGS) at our center in early 2013, analyzing 111 genes and subsequently implemented to the current panel of 174 genes in 2018. The current NGS panel include genes for different

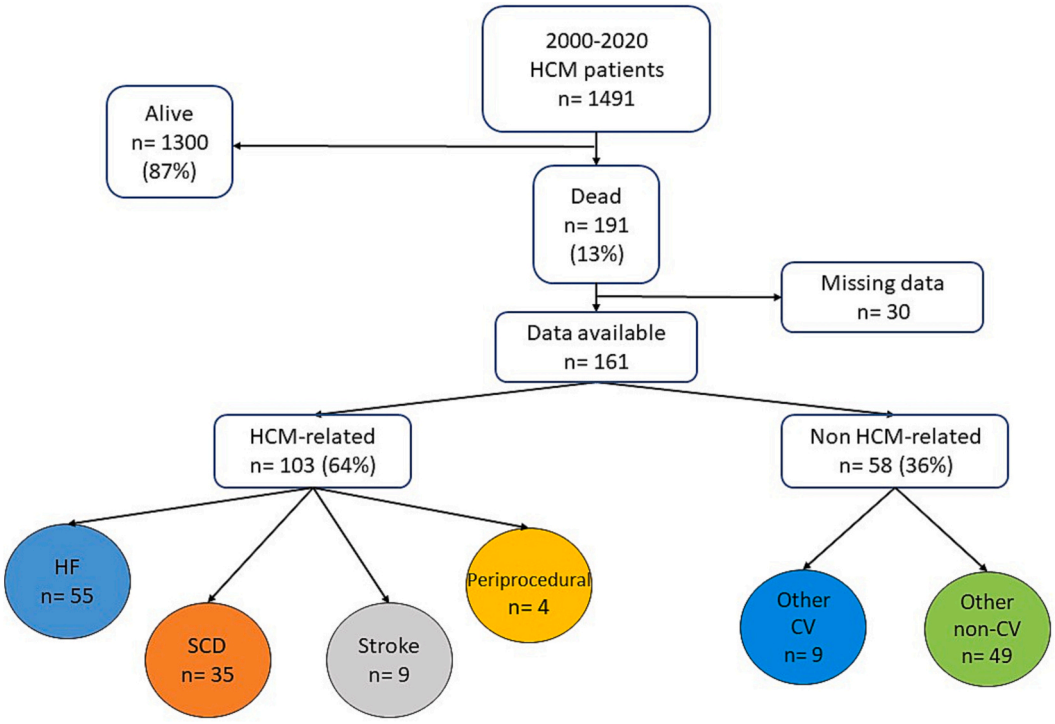

Fig. 1. Patients selection and modes of death.
The figure represents the selection process from our centralized database, the patients included in the final study cohort and the causes of death.
Abbreviations: HCM = hypertrophic cardiomyopathy, HF = heart failure, SCD = sudden cardiac death, CV = cardiovascular.

cardiomyopathies and channelopathies and specifically 16 genes for HCM.

1.4. Stages of disease at presentation

Stages of disease were defined -as previously published [15]- as follows:

1) "*Classic HCM phenotype*" characterized by overt hypertrophic phenotype, the LV is hyperdynamic (defined by a LV ejection fraction (EF) >65%), the diastolic pattern is generally normal or only mildly abnormal, whereas more severe degrees of diastolic impairment are less common and generally occur in patients with severe LV outflow obstruction or massive LV hypertrophy and restrictive pathophysiology.
2) "*Adverse remodeling*" *characterized* by the presence of unfavourable structural modifications, superimposed to the "classic HCM phenotype", translating into worsening contractile function (i.e. a LVEF in the low-normal range, between 50% and 65%), commonly associated with moderate to severe diastolic dysfunction and marked atrial dilatation.
3) "*Overt dysfunction*" is the end-stage clinical evolution of HCM, characterized by severe functional deterioration of LV systolic function (defined by a LVEF <50%).

1.5. Modes of death

Modes of death were classified into HCM-related mortality and non-HCM-related mortality as follows:

1.5.1. HCM-related mortality

Four modes of death were defined for HCM related mortality:

1) HF-related death was defined as occurring in the context of cardiac decompensation and progressive HF-related disease course, particularly if complicated by pulmonary oedema or evolution to the end-stage phase and/or requiring hospitalization for HF.
   Patients with advanced refractory HF who successfully underwent heart transplants were not considered equivalent to HF mortality in this analysis.
2) SCD was defined as unexpected sudden collapse occurring within 1 h from the onset of symptoms in patients who had previously experienced a relatively stable or uneventful clinical course [16]. Patients who either were successfully resuscitated from cardiac arrest (with documented ventricular tachycardia) or received appropriate shocks from an implantable cardiac defibrillator (ICD) were not regarded as equivalents of SCD in the present data analysis.
3) Ischemic stroke-related death was judged to be a direct consequence of permanent neurologic impairment and disability due to an ischemic cerebral thromboembolic event. However, episodes of transient cerebral ischemia with symptoms lasting <24 h were regarded as transient ischemic attacks (TIA) and were not considered as a cause of death.
4) Perioperative mortality was defined as all causes of death not included in the previous definitions and were likely related to HCM-specific perioperative treatments and their possible complications.

1.5.2. Non-HCM-related mortality

Two modes of death were defined for non-HCM-related mortality:

1) Other cardiovascular (CV) deaths were defined as all causes of death related to CV events but not directly related to HCM; these were largely due to common conditions such as coronary artery disease. Coronary artery disease related HF was included in this group.
2) Other non-CV deaths were defined as all causes of death not related to HCM and without a CV aetiology.

2. Statistical analysis

Variables are expressed as mean and standard deviation, median and interquartile range, or counts and percentages, as appropriate.

Differences among means were analyzed with 1-way ANOVA with the least significant difference for post hoc group comparisons. Differences among median values were assessed statistically by use of the student *t*-test or the nonparametric Kruskal-Wallis test, as appropriate. Comparison of nominal variables expressed as proportions were performed by use of the Pearson x^2 test.

3. Results

Of the 161 patients who died, 103 (64%) died due to HCM-related causes, whereas 58 (36%) died largely from non-HCM-related causes such as coronary artery disease (other CV) or other non CV causes (Fig. 1). Of the 103 patients with HCM-related mortality, 66 (64%) were males, median age at diagnosis was 44 (26–58) years, median age at death was 66 (46–73) years (Table 1). Half of these 103 ($n = 55$; 53%) died of HF, 35 (34%) died of SCD, 9 (9%) died of ischemic stroke and 4 (4%) died of periprocedural complications following myectomy or alcohol septal ablation (Fig. 1, Table 1).

Of the 58 patients with non-HCM-related mortality, 36 (62%) were males, median age at diagnosis 59 (46–71) years, median age at death 74 (63–81) years, 9 (16%) died of CV causes and 49 (84%) of non-CV causes (Fig. 1, Table 1).

3.1. Age at diagnosis and death

Patients with HCM-related mortality were younger at diagnosis and at the time of death compared to those with non-HCM-related death (all $p < 0.0001$, Table 1, Fig. 2).

HCM-related mortality was the main cause of death through all age groups ≤ 75 years and was the only cause of death in patients aged < 36 years (Supplementary material Fig. 1).

According to the age at HCM diagnosis (Fig. 2, left panel) patients presented different patterns. Most patients who were diagnosed with HCM < 40 years died of SCD followed by HF and of other causes in a minority of cases. Patients who were diagnosed between their 40s and 60s died mainly of HF and other non-CV death and to a less extent of SCD. Patients diagnosed after 60 died mainly of other non-CV death.

According to the age at death (Fig. 2, right panel and Supplementary materials Fig. 1), the 2 main modes in HCM related mortality, HF and SCD, showed 2 prevalent distributions, occurring at 70 and 44 years of age, respectively. Other non-CV death showed the oldest median age for both diagnosis and death, respectively 60 (49–71) and 74 (63–82) years old.

3.2. Modes of death per stage of disease

3.2.1. Classic HCM phenotype

Fifty-six (35%) patients presented with a "classic" HCM phenotype at diagnosis, 29 (52%) of them presented LVOTO (Supplementary materials Fig. 2). Half of patients with classic HCM phenotype died of HCM-related causes ($n = 30$; 54%), versus 45% of non-HCM-related death. Differently from the other two stages, the single most common cause of death was "other non-CV related" mortality, in 43%. Among HCM-related causes, SCD prevailed ($n = 15$; 27%) while HF-related events were only 8 (14%), Fig. 3.

3.2.2. Adverse remodeling

Of the 86 (53%) patients with "adverse remodeling" at diagnosis, more than half died of HCM-related causes ($n = 57$, 66%), largely due to HF ($n = 33$, 38%); SCD occurred in 18 (21%) individuals. This stage included the highest percentage of patients who died of stroke ($n = 6$; 7%), Fig. 3.

Table 1
Demographic, clinical, electrocardiographic and echocardiographic characteristics of the 161 patients with HCM who died between 2000 and 2020. An extended version of the table is available in the supplementary materials.

	HCM related *n* = 103/161 (64%)	HF n = 55/103 (53%)	SCD n = 35/103 (34%)	Ischemic Stroke n = 9/103 (9%)	Perioperative n = 4/103 (4%)	Non-HCM related *n* = 58/161 (36%)	Other CV *n* = 9/58 (16%)	Other non CV *n* = 49/58 (84%)	*p*-value
Baseline evaluation									
Males, n (%)	**66 (64%)**	35 (64%)	26 (74%)	3 (33%)	2 (50%)	**36 (62%)**	7 (78%)	29 (59%)	0.238
Age at diagnosis (yrs)	**44 (26–58)**	48 (32–58)	31 (10–53)	41 (30–67)	36 (24–66)	**59 (46–71)**	49 (33–66)	60 (49–71)	<0.001
Gene mutation LP, P, n (%)*	**54 (52%)**	34 (62%)	16 (45%)	3 (33%)	1 (25%)	**21 (36%)**	5 (56%)	16 (32%)	0.059
NYHA									0.056
I, n (%)	**44 (43%)**	21 (38%)	17 (49%)	4 (44%)	2 (50%)	**25 (43%)**	6 (67%)	19 (39%)	
II, n (%)	**47 (45%)**	25 (46%)	17 (49%)	4 (44%)	1 (25%)	**24 (41%)**	3 (33%)	21 (43%)	
III-IV, n (%)	**12 (12%)**	9 (16%)	1 (3%)	1 (11%)	1 (25%)	**9 (16%)**	0	9 (18%)	
Max LV WT (mm)	**21 ± 6**	21 ± 5	21 ± 6	23 ± 5	20 ± 17	**20 ± 5**	21 ± 5	20 ± 5	0.852
LVEDD (mm)	**44 ± 6**	46 ± 6	44 ± 7	42 ± 5	39 ± 4	**45 ± 6**	46 ± 5	45 ± 7	0.340
EF (%)	**59 ± 12**	55 ± 12	64 ± 10	57 ± 7	76 ± 7	**63 ± 8**	62 ± 6	64 ± 8	<0.0001
<50%, n (%)	**(16%)**	14 (25%)	2 (6%)	0	0	**3 (5%)**	0	3 (6%)	
≥50%, n (%)	**(84%)**	41 (75%)	33 (94%)	9 (100%)	4 (100%)	**55 (95%)**	9 (100%)	46 (94%)	
Obstructive HCM, n (%)	**39 (38%)**	22 (40%)	10 (29%)	3 (33%)	4 (100%)	**27 (47%)**	3 (33%)	24 (49%)	0.083
LA diameter (mm)	**45 ± 9**	48 ± 8	41 ± 11	46 ± 4	42 ± 12	**45 ± 9**	43 ± 6	45 ± 7	0.009
Diastolic function									0.366
Normal/grade I disf, n (%)	**64 (62%)**	31 (56%)	23 (65%)	7 (78%)	3 (75%)	**40 (69%)**	7 (78%)	33 (67%)	
Grade II dysf., n (%)	**19 (18%)**	8 (15%)	9 (26%)	1 (11%)	1 (25%)	**8 (14%)**	0	8 (16%)	
Grade III dysf., n (%)	**20 (19%)**	16 (29%)	3 (9%)	1 (11%)	0	**10 (17%)**	2 (22%)	8 (16%)	
Variables assessed during all follow up									
Follow up (yrs)	**17 ± 11**	21 ± 11	13 ± 10	18 ± 12	11 ± 12	**14 ± 10**	15 ± 13	14 ± 10	0.006
Total AF, n (%)*	**56 (54%)**	39 (70%)	8 (22%)	8 (89%)	1 (25%)	**34 (58%)**	4 (44%)	30 (62%)	<0.0001
Age at death (yrs)	**66 (46–73)**	70 (58–74)	43 (25–66)	70 (47–79)	58 (30–73)	74 (63–81)	72 (53–75)	74 (63–82)	<0.001

Abbreviations: AF = atrial fibrillation, CV = cardio-vascular, Dysf. = dysfunction, EF = ejection fraction, HCM = hypertrophic cardiomyopathy, HF = heart failure, LA = left atrium, LP = likely pathogenetic variant, LV = left ventricle, LVEDD = left ventricular end diastolic diameter, NYHA = New York Heart Association, P = pathogenetic variant, SCD = sudden cardiac death, WT = wall thickness.
Columns in bold: "HCM-related mortality" and "Non-HCM-related mortality" represent the two main category of death causes. Each bold colum is followed by multiple columns representing the differnt modes of death underlying the main category.

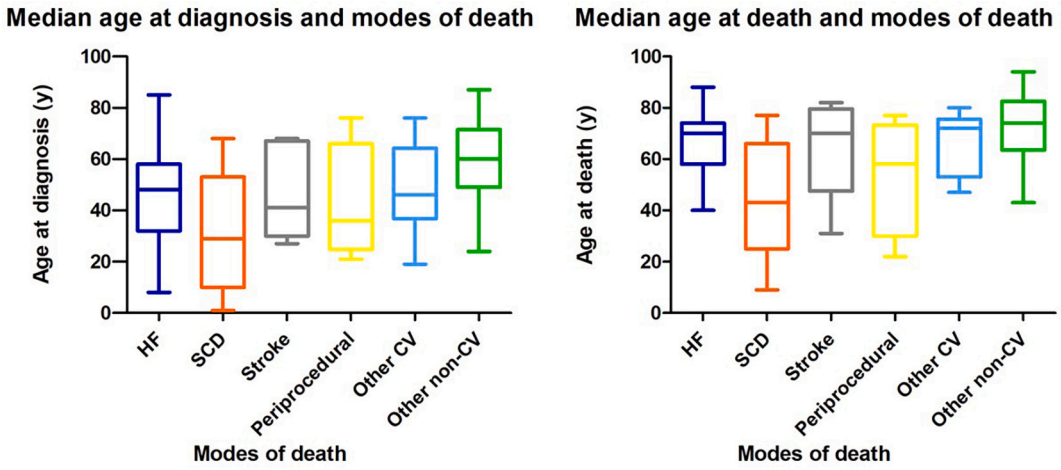

Fig. 2. Median age at diagnosis (left) and at death (right) per modes of death.
Abbreviations: HF = heart failure, SCD = sudden cardiac death, CV = cardiovascular.

3.2.3. *Overt dysfunction*

Of the 19 (12%) patients in "overt dysfunction" at diagnosis, HF represented the cause of demise in almost three quarters (*n* = 14, 74%); SCD and non-HCM causes accounted for only 10% and 16% respectively, Fig. 3.

3.3. *Clinical scenarios*

3.3.1. *Heart failure death*

HF was the most prevalent mode of death overall (Fig. 1). Patients who died of HF were mainly males (*n* = 35, 64%), median age at diagnosis 48 (32–58) years (higher than for the other HCM-related modes, Table 1, Fig. 2). HF-death occurred most frequently in midlife and beyond (Supplementary material Fig. 1) and largely in the "adverse

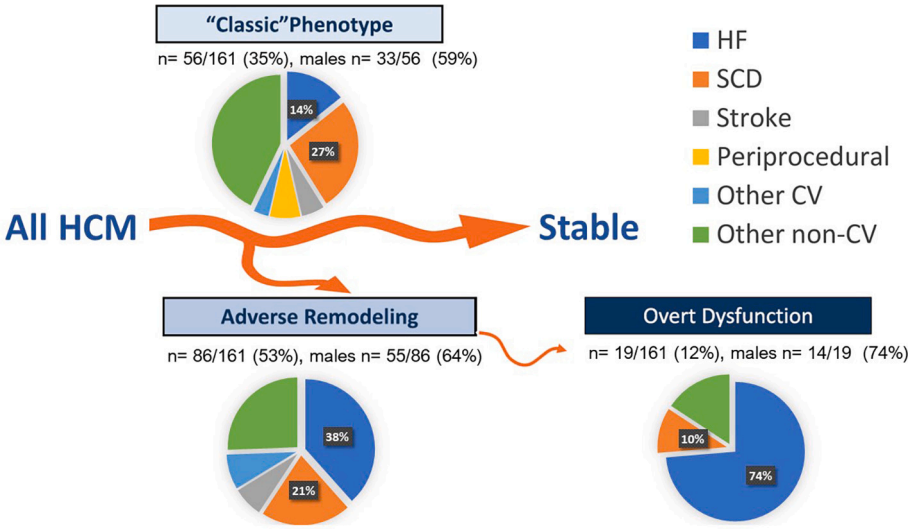

Fig. 3. Modes of death based on the stage of HCM at diagnosis.
Stages of hypertrophic cardiomyopathy. Thickness of the orange lines reflects prevalence of each stage in HCM cohorts. "Classic HCM phenotype" is characterized by LVEF >65%, "adverse remodeling" is characterized by LVEF between 50% and 65%, "overt dysfunction" is the end-stage clinical evolution of HCM, characterized by LVEF <50%.
Abbreviations: CV = cardiovascular, HCM = hypertrophic cardiomyopathy, HF = heart failure, LVEF = left ventricular ejection fraction, SCD = sudden cardiac death,

remodeling" and "overt dysfunction" stages (Fig. 3), after a prolonged clinical course (on average 21 ± 11 years after HCM diagnosis) despite close follow-up and treatment.

At the time of diagnosis, a reduced LVEF (<50%) was present in 14 (25%) patients and grade II or III diastolic dysfunction was present in 24 (44%) (Table 1). Pathogenic sarcomere mutations were more prevalent (62%) among patients who died of HF, including 3 patients with multiple pathogenic variants.

Comorbidities in patients who died of HF included chronic kidney disease and chronic obstructive pulmonary disease (COPD) in over a quarter of patients and hypertension in 25 (46%) patients (Supplementary materials Table 1). During follow up, 39 (70%) patients had developed atrial fibrillation (AF), severe atrial enlargement was common in this group and over one quarter developed non-fatal ischemic stroke or TIA, classified as cardioembolic after comprehensive neurological evaluation. In this group, life-threatening arrhythmias interrupted by appropriate ICD shocks or resuscitated out-of-hospital cardiac arrest occurred in 10 (18%) patients and 2 of them experienced appropriate ICD shocks in secondary prevention. Notably, most HF deaths (n = 37, 67%) occurred >65 years of age (Supplementary material Fig. 1), i.e. after the limit generally considered for transplant eligibility.

3.3.2. Sudden cardiac death

SCD was the third most frequent cause of mortality overall and the second most frequent among HCM related mortality (Fig. 1). Patients who died suddenly were mainly males (n = 26, 74%), median age at diagnosis and death were respectively 31 (10–53) and 43 (25–66) years (Table 1, Supplementary material Fig. 1). SCD occurred in all age groups and represented the most prevalent mode in younger individuals (≤ 45 years of age) but had limited prevalence >46 years (Supplementary material Fig. 1). Overall, 45% of patients who died of SCD carried pathogenic sarcomere gene mutations. Comorbidities were uncommon (Supplementary materials Table 1).

Overall, 35 (21.7%) patients implanted an ICD, 9 of them implanted a cardiac resynchronization therapy (CRT) defibrillator and 9 patients received an appropriate ICD shock during follow-up. Most of the patients who received an ICD died of HF (n = 25) and in a minority of cases of stroke, other cardiovascular related causes, other non cardiovascular related causes.

3.3.3. Stroke death

Ischemic strokes accounted for a minority of HCM related deaths, n = 9 (9%) (Fig. 1). Stroke related death was rare but did occur even among young patients, with a couple of events in the group aged 26–45 years old and 2 to 3 deaths per age group above 55 years (Supplementary material Fig. 1).

Of the 9 patients who died of ischemic stroke, 6 (67%) were women and most were in the adverse remodeling stage (Fig. 2). AF was documented in all but one and left atrial diameter was >40 mm in 8 (89%) patients. Three patients experienced recurrent strokes during their follow-up, despite warfarin or direct oral anticoagulants. None of the study patients experienced hemorrhagic stroke because of anticoagulation therapy.

3.3.4. Periprocedural death

Four patients died of periprocedural complications related to septal reduction therapy over 2 decades (Fig. 1), including 2 (50%) males and 2 females, at a median age of 58 (30–73) years. Three patients died due to complications following surgical septal myectomy and one in the setting of an alcohol septal ablation procedure.

One patient, aged 62, died because of acute cardiac failure after weaning from extracorporeal circulatory support; one patient, aged 77, with multiple comorbidities (smoker, diabetes, arterial hypertension, coronary artery disease, chronic obstructive pulmonary disease), died of sepsis after surgical myectomy; one patient, aged 30, died, at another centre, due to refractory heart failure, one-week post-operatively and one patient (aged 54) died of electromechanical dissociation during coronary angiography, before intracoronary alcohol injection, in the setting of an alcohol septal ablation procedure; autopsy showed extensive acute microvascular ischemia.

3.3.5. Other CV death

Other CV death represented a residual cause of death among non HCM related mortality (n = 9, 16%; Fig. 1). Mortality related to CV death occurred in patients aged 45 and beyond (Supplementary material Fig. 1), median age at diagnosis was 49 (33–66) years old, median age at death was 72 (53–75) years old and 7 (78%) patients were males. The main causes of death were myocardial infarction, aortic dissection, cerebral aneurism rupture. Other CV related mortality mainly affected patients in the "adverse remodeling" stage (Fig. 3). Among this mode of death, patients reported a high prevalence of CV risk factors ranging from 11% for COPD to 78% for arterial hypertension, 78% were defined as smokers or previous smokers and notably, 2 (22%) patients previously underwent coronary artery angioplasty (Supplementary materials Table 1).

3.3.6. Other non-CV death

This mode of death mainly affected older groups of age and showed

the oldest median age for both diagnosis and death, respectively 60 (49–71) and 74 (63–82) years old, Fig. 2. Patients died of non-CV causes i.e. cancers, infective diseases, suicide, neurological diseases, car accidents, immunological disorders, etc. No patient died of other non-CV death before 36 years of age, whereas it represented the most common cause of death in the age group >75 years (Supplementary materials Fig. 1).

4. Discussion

In the present study, we aimed to provide a detailed characterization of the modes of death in HCM patients based on age at presentation, stage of disease and clinical setting. We found that HCM-related mortality accounts for two-thirds of all deaths (64%) and is largely due to HF (Fig. 1). Sudden cardiac death accounts for 34% of HCM-related mortality and 22% of all deaths, occurring at any age but mostly in younger patients (Supplementary materials Fig. 1). In patients who are in the stable, "classic" HCM stage at presentation, HF-related death was uncommon compared to those presenting with adverse remodeling or overt dysfunction (Fig. 3). Conversely, SCD was progressively less represented with increasing stage severity. Competing, non-HCM-related CV causes of death accounted for 44% in the classic HCM stage versus 16% in the overt dysfunction stage, with adverse remodeling patients showing an intermediate pattern (Fig. 3). The prevalence of CV risk factors was significant in the adverse cardiac remodeling stage (Supplementary materials Table 1), suggesting a potential role as promotors of the HCM progression process in older patients [17,18]. Finally, median age of patients who died of HCM-related causes was 66 years of age, i.e. 8 years younger than those with non-HCM-related death. Among HCM related causes, there was a > 25 years difference in age distribution between SCD death occurring at a median age of 44 years, and HF death occurring at a median of 70, Fig. 2.

While consistent with the existing literature [8,19], these findings provide novel insight, emphasizing the considerable burden of HCM on individual longevity despite available management options. With regard to SCD, the ICD has offered an effective opportunity for prevention and has shown a major impact on sudden mortality [10,20]. However, risk stratification tools are still imperfect as events may occur in patients perceived to be at low or moderate risk after clinical work-up [21,22]. While ICD implantation rates and policies might vary considerably by region, a quota of patients dying suddenly persists and seems little affected by local practices [23]. Conversely, HF progression is a more predictable and usually slow process [15,24,25]; however, standard HF drugs often fail to prevent progression, particularly in the presence of widespread LV fibrosis [26–29]. Furthermore, clinical demise tends to cluster in the 60–70-year age-span, thus limiting the opportunity of cardiac transplant referral. Despite promising progresses in drug development [30], none of the available treatments has shown yet the disease-modifying potential required to interfere with this process.

Notably, the present study lends support to the clinical HCM staging system proposed in 2012 [15]. Stage classification may have important clinical implications in the understanding of the disease, gauging competing risks and setting individualized goals of management. In an era of drug discovery, staging is instrumental to trial design and enrollment. Finally, understanding the stage of the disease is essential to counsel patients and lead shared decision-making discussions. For patients in the "classic HCM" stage, emphasis should be placed on the prevention of disease progression (including early relief of LV outflow obstruction) and prophylaxis for SCD. A pivotal role is represented by clinical scrutiny for signs of disease progression, prevention of cardiac comorbidity, and control of conventional CV risk factors such as sedentary lifestyle, hypertension, dyslipidemia, and diabetes [31,32].

HCM patients with "adverse cardiac remodeling" should be considered at risk of further progression toward overt dysfunction and HF-related death [15]. Because such progression may occur over very extended periods of time [33] close clinical surveillance with CMR, cardiopulmonary testing, and serial NTproBNP may prove valuable, potentially allowing for preventive treatment. At present, it is plausible to consider timely implementation of treatments that have proven effective in other causes of LV dysfunction [34]. In addition, aggressive management of AF is likely to play an important role in preventing functional and clinical deterioration in HCM patients as well as stroke occurrence. Indeed, the prevalence of AF in our cohort was overall predictably very high in the stroke group but was also represented in the other groups due to the elevated median age.

Overt dysfunction is a challenging stage in which clinical severity is evident and management.

necessarily aggressive, based on standard guidelines for HF [34]. Patients eligible for heart transplant or mechanical circulatory support should be referred for advance HF treatment evaluation, ideally before approaching this stage [32].

5. Limitations

This is a retrospective study and presents common limitations to retrospective data collection. Data on the cause of death was not available in 30 of the 191 consecutive patients, therefore were excluded from the final analysis. The period of the study covers 2 decades and, during this time span, we assisted to an evolution in the diagnostic process and technological development, risk stratification and treatments, that could have had an influence on the results of the study. For instance, CMR was introduced in our centre in 2004. As a result, we lack of systematic CMR data and particularly LGE quantification was not standardised.

6. Conclusions

Most HCM patients die due to complications of their own disease, mainly in the context of HF: the vast majority of these events are premature. However, while SCD tends to occur in younger patients, HF-related deaths often affect age groups no longer amenable to cardiac transplant albeit well in advance of average lifespan. Modes of death vary with the stage of disease, with SCD becoming less prevalent in more advanced phases of progression, when competitive risks of HF-related events become overwhelming. These data highlight an unmet medical need in the prevention of disease progression associated with HCM.

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Declaration of Competing Interest

None declared.

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