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Relationship between aetiology and left ventricular systolic
dysfunction in hypertrophic cardiomyopathy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common cardiac disease caused by a number of genetic and acquired disorders.[1] Mutations in genes coding for cardiac sarcomere proteins account for the majority of cases, but other diseases including inherited disorders of metabolism, myocardial infiltration, neuromuscular disorders and malformation syndromes can present with a similar phenotype. In many cases, obvious clinical features suggest the diagnosis of these less common disorders, but in some patients they may be overlooked or misdiagnosed if the index of clinical suspicion is low.

Severe left ventricular (LV) systolic dysfunction, commonly referred to as end-stage disease or the “burnt-out phase”, is an uncommon but important evolution of HCM.[2-4] In tertiary referral centres, end-stage disease has a prevalence of 2-5% and an incidence of 0.5-1 cases per 100 patient/years, and is associated with a poor prognosis due to high rates of refractory heart failure and sudden arrhythmic death.[3-6] Small observational series suggest that patients with rarer phenocopies are more likely to develop systolic impairment than those with disease caused by sarcomere protein gene mutations [7-12] and current ESC guidelines suggest that LV systolic dysfunction is one of several clinical features (‘red flags’) that assists in the differential diagnosis of HCM.[13]

Hypertrophic cardiomyopathy (HCM)

HCM is a common inherited heart disease with a prevalence in the general population of 1 over 500 subjects. It is inherited in an autosomal pattern and mutations in the genes encoding beta-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) account for the majority of cases; less commonly affected genes include cardiac troponin I and T (TNNI3, TNNT2), tropomyosin alpha-1 chain (TPM1) and myosin light chain 3 (MYL3). In general, patients with a sarcomere protein mutation present earlier and report a higher prevalence of family history of HCM and sudden cardiac death than those without a mutation.[14, 15] Moreover they also tend to have more severe hypertrophy, microvascular

dysfunction and myocardial fibrosis.[16] A minority of patients with HCM evolves towards severe systolic dysfunction, commonly referred to as end-stage disease or the “burnt-out phase”. [2-4] In tertiary referral centres, end-stage disease has a prevalence of 2-5% and an incidence of 0.5-1 cases per 100 patient/years, and carries an ominous prognosis due to high rates of refractory heart failure and sudden arrhythmic death, representing the sole indication for heart transplantation in HCM.[3-6]

Light chain amyloidosis (AL amyloidosis)

Acquired monoclonal immunoglobulin light chain amyloidosis (AL) is characterized by clonal plasma cells in the bone marrow that produce the immunoglobulin lights chain that circulate in the blood and break down to form amyloid deposits in various tissues of the body.[17] AL amyloidosis usually involves more than one organ and without appropriate treatment, it may progress rapidly. Cardiac involvement is characterised by LV hypertrophy, usually in a minor degree compared to transthyretin-related (TTR) amyloidosis, but a more frequent and rapid progression towards heart failure [12], plausibly due to the well-documented direct toxicity of the immunoglobulin circulating light chains. [18, 19] In all the three forms of amyloidosis, myocardial involvement is frequent and has major clinical implications, warranting chemotherapy when in relation to AL. [20, 21]

Hereditary transthyretin type amyloidosis (TTR)

Hereditary TTR amyloidosis is due deposition of transthyretin, a small molecule mainly produced by the liver.[17] The hereditary form is caused by mutations in the transthyretin gene that are inherited in an autosomal pattern. More than 100 mutations have so far been identified. The manifestation of the disease mainly depends on the specific genetic abnormality in the TTR molecule. Some patients with hereditary TTR amyloidosis mainly present with neuropathy, cardiac involvement or a combination of both.[17] Hereditary TTR amyloidosis is a more slowly progressive disease than AL amyloidosis, it is characterised by a higher degree of LV hypertrophy but shows a less frequent evolution to heart failure and a less severe prognosis.[12]

Wild-type or senile systemic amyloidosis (SSA)

Wild-type or SSA results from deposition of amyloid derived from wild-type transthyretin (ie, transthyretin with a normal amino acid constitution).[17] It is a slowly progressive disease that affects almost exclusively men in their seventies or eighties.[12] The clinical manifestations of SSA are quite similar among patients and progression towards heart failure is an inexorable event. The median survival from the onset of heart failure is 7.5 years compared with 15 months in patients with AL amyloidosis and a similar degree of LV thickening.[12]

Anderson-Fabry Disease (AFD)

Anderson-Fabry Disease (AFD) is an X-linked lysosomal storage disorder caused by mutations in the α -galactosidase A gene (GLA) that results in deficiency of the enzyme and the accumulation of glycosphingolipid throughout the body. It is the second commonest X-linked lysosomal storage disorder (after Gaucher's disease) with a population prevalence of 1 in 40,000–117,000 live births for males.[22] In its classic form, AFD is a multisystem disease with cutaneous, renal, cerebral and cardiac manifestations that causes progressive debilitating symptoms and premature death [22, 23]. Over 400 mutations have been identified in the GLA gene, most of which are associated with the classical phenotype. A group of mutations are associated with a phenotype characterised by prominent and, in some cases, exclusive cardiac involvement, mainly LV hypertrophy, diastolic dysfunction, valvular and conduction disease. Cardiac management comprises symptomatic control with anti-anginal therapies, and treatment of heart failure and arrhythmia. Therapy with recombinant enzyme improves cardiac function, LV hypertrophy, milder forms of renal disease and possibly cerebrovascular complications. [24] Heart failure is a frequent manifestation in AFD with a recent study describing a prevalence of 10.6% and incidence of 1.62 per 100 person-years of patients developing severe heart failure symptoms either prior or during follow up. [25] Also it has been previously demonstrated that LV systolic function progressively deteriorates in untreated patients with AFD suggesting that systolic performance should be monitored in patients with the condition, and that systolic function may be a useful surrogate marker of response to enzyme replacement therapy. [11]

Mitochondrial diseases

Primary mitochondrial respiratory chain diseases are systemic disorders caused by sporadic or inherited mutations in nuclear or mitochondrial DNA.[26, 27] Mitochondrial DNA mutations are inherited in the maternal line, but nuclear mutations may be transmitted as autosomal dominant, autosomal recessive, and X-linked traits. All mutations result in impaired respiratory chain function with consequent reduction in ATP production and an increase in free radical formation.[27, 28] The clinical presentation of mitochondrial diseases is variable in age at onset, symptoms, and the range and severity of organ involvement. [26-28] Cardiac involvement is a frequent manifestation in children and adults with mitochondrial disorders. [29-32] In a recent study on adult patients with six different phenotypes of mitochondrial disease, 81% had evidence for cardiac involvement, more frequently ECG abnormalities (69%) and hypertrophic cardiomyopathy (19%). [32]

Glycogen storage disorders (GSD)

GSD are the result of defects in the processing of glycogen synthesis or breakdown within muscles, liver, and other cell types. The inherited forms are caused by inborn error of metabolism (genetically defective enzymes) involved in these processes. There are more than 14 types of metabolic GSD that mainly affect the liver and muscle with an overall prevalence varying between 1: 20,000 and 43,000. GSD confined to the liver are associated with hepatomegaly and hypoglycaemia, whereas those that affect muscle glycogen metabolism present with muscle cramps, weakness, exercise intolerance and cardiomyopathy.[33]

Danon disease is an extremely rare X-linked GSD caused by mutations in the lysosomal-associated membrane protein-2 (LAMP-2) leading to glycogen accumulation in lysosomes with normal maltase activity.[34, 35] Clinical features include muscle weakness, severe LV hypertrophy and learning disability.[7, 36] The diagnosis is suggested by normal acid maltase levels, vacuolation and glycogen deposition on muscle. There is no specific treatment but some patients with progressive heart failure require cardiac transplantation.[37]

Mutations in the gene for the γ 2 subunit (PRKAG2) of adenosine monophosphate (AMP)-activated protein kinase (AMPK) may cause LV hypertrophy mimicking HCM with

electrophysiologic abnormalities (including Wolff-Parkinson-White syndrome and atrioventricular blocks).[38-41] AMP kinase acts as an enzymatic modulator of adenosine triphosphate (ATP) sensitivity to cellular energy requirements. PRKAG2 mutations produce a distinctive cardiac histopathology characterized by enlarged myocytes with vacuoles containing glycogen derivatives; notably, myocyte disarray is absent and interstitial fibrosis is minimal.[40] Clinical features include extracardiac manifestations such as a skeletal myopathy, consistent with a systemic metabolic storage disease. Treatment require pacing for progressive conduction disease in up to thirty-eight percent of patients by the age of 40 years and syncope and sudden death is reported. [41] Cardiac hypertrophy, typically in association with LV systolic dysfunction has been detected by echocardiography in 30% to 50% of affected patients. The degree of hypertrophy and LV dysfunction may range from mild to severe and in severe cases may require cardiac transplantation.[42]

Noonan syndrome and LEOPARD syndrome

Both syndromes are due to specific mutations in the PTPN11 gene and are part of the so called “RASopathies”, which are caused by germline mutations in components of the RAS-MAPK (mitogen-activated protein kinases) signal transduction pathway. Most are diagnosed in childhood, but some milder forms (particularly Noonan syndrome) escape early detection and are identified later in life.

Noonan syndrome is an autosomal dominant disorder with multisystem involvement including distinctive dysmorphic facial features (most commonly hypertelorism, ptosis, low-set ears, and short webbed neck), short stature, skeletal anomalies (in particular, sternal deformities and cubitus valgus), and intellectual and developmental disabilities. [43] The majority, 80–90%, have cardiovascular involvement that can include a broad range of congenital heart defects, most prevalently pulmonary valve stenosis, and/or early-onset LV hypertrophy in approximately 20% of cases. Noonan syndrome is mainly diagnosed in children and the presence of LV hypertrophy affects outcomes with heart failure being the more frequent complication and primary cause of death in these patients.[44, 45]

LEOPARD syndrome is a rare inherited disease characterized by a spectrum of somatic abnormalities described in the acronym (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retardation of growth, deafness).

Friedreich's ataxia

Friedreich's ataxia is a degenerative neuromuscular disease with an autosomal recessive inheritance. It is caused by a mutation that consists of an unstable expansion of GAA trinucleotide expansion in the first intron of the gene encoding frataxin on chromosome 9 (9q13).[46] The loss of frataxin results in deficiency of a Krebs cycle enzyme, aconitase, and of three mitochondrial respiratory chain complexes (I–III) resulting in iron overload and oxidative stress.[47] Friedreich's ataxia is characterized by spinocerebellar degeneration which is associated often to heart disease and diabetes mellitus. Cardiac involvement is mainly represented by LV hypertrophy. [48] Therapy with idebenone, a short chain quinone acting as antioxidant, has been shown to protect heart muscle against oxidative stress.[49]

Carnitine palmitoyltransferase II (CPT II) deficiency

The carnitine cycle consists of three enzymes that transport long chain fatty acids into mitochondria. Defects of this system [carnitine transporter defects (CTD), carnitine-palmitoyl transferase 1 and 2 deficiencies (CPT-1 and 2), and carnitine acylcarnitine translocate deficiency (CACT)] are associated with cardio-metabolic disease.[50] CPT II deficiency presents most frequently in adolescents and young adults with predominant muscular involvement. It is characterised by muscle pain with or without myoglobinuria with elevation of serum creatinine kinase precipitated by strenuous exercise, cold, fever or prolonged fasting.

Four and a half LIM domain protein I (FHL1)

FHL1 is a protein with 3 isoforms (FHL1A, FHL1B, and FHL1C). FHL1A is the predominantly expressed striated and cardiac muscle isoform and plays a role in sarcomere synthesis and integrity, by interacting with myosin binding protein C. [51] Around 25 distinct mutations in FHL1 have been described, in association with four myopathic conditions: reducing body myopathy, X-linked myopathy with postural muscle atrophy, scapulooperoneal myopathy and Emery Dreifuss muscular dystrophy. [52] Cardiac involvement is characterised more frequently by dilated cardiomyopathy but also LV hypertrophy can be present. [53, 54]

AIMS OF THE STUDY

The aims of this study were:

1. To assess the prevalence of the different aetiologies underlying the hypertrophic phenotype cardiomyopathy.
2. To assess the prevalence of the different aetiologies underlying the hypertrophic phenotype cardiomyopathy associated with systolic dysfunction.
3. To assess whether this phenotype characterised by LV hypertrophy and systolic dysfunction is more frequent among sarcomere or non-sarcomere forms and if it could be an age-specific “red flag” for differential diagnosis.
4. To compare the long-term survival of patients with hypertrophic phenotype cardiomyopathy due to different aetiologies.

METHODS

Study design and setting

This is a retrospective, longitudinal cohort study involving patients from 2 cardiomyopathy European tertiary referral centres: The Heart Hospital, University College London, U.K. (a regional referral centre for AFD) and Sant'Orsola Bologna University Hospital, Italy (a regional referral centre for cardiac amyloidosis).

Study population and patient assessment

Patients were identified by systematically searching hospital records and clinical databases. All patients were ≥ 16 years of age and had a maximum LV wall (MWT) thickness ≥ 13 mm in any segment. All patients were evaluated for specific aetiologies using medical history, pedigree analysis, physical examination, ECG and cardiac imaging and laboratory testing. In selected patients, skeletal muscle and endomyocardial biopsy and molecular genetic testing were considered. The following conditions were included: AFD, mitochondrial disease, cardiac amyloidosis, specifically light chain amyloidosis (AL), hereditary transthyretin type amyloidosis (ATTR) and wild-type or senile systemic amyloidosis (SSA), Noonan syndrome, LEOPARD syndrome, carnitine palmitoyltransferase II (CPT II) deficiency, four and a half LIM domain protein I (FHL1), Friedreich's ataxia and glycogen storage disease (GSD). HCM was diagnosed when the LV was non-dilated with a MWT > 15 mm or MWT 13-14mm with a family history of unequivocal disease in a first degree relative. [55]

HCM patients from S. Orsola Bologna University Hospital were assessed in between 1980 and 2013, and some of these patients have been included in other recently published studies [56-59]. The HCM study population at the Heart Hospital was based on 874 unrelated patients who were consecutively genetically tested for sarcomere protein gene mutations using high-throughput sequencing between 2011 and 2013. The genotype-phenotype associations for this cohort have recently been published by Lopes et al [60]. Patients with MWT <13 mm, diagnosed with HCM on the basis of familial criteria [55] were excluded from this analysis. Patients with phenocopies and MWT ≥ 13 mm were evaluated between 1986 and 2013 at S. Orsola Bologna University Hospital and between 1991 and

2014 at The Heart Hospital and some of those patients have previously been described in other studies [25, 53, 61]

Data collection

Data were collected independently at each participating centre using uniform methodology. Clinical characteristics were assessed at first (baseline) evaluation. LV systolic dysfunction was defined as a resting LV ejection fraction <50% measured using 2D echocardiography and the biplane Simpson method [3].

Study outcomes

The primary study outcome was all-cause mortality or cardiac transplantation for end-stage heart failure.

Secondary study outcomes: sudden cardiac death, heart failure-related death or heart transplantation, stroke related death, non-cardiovascular death. When the cause of death was not known, the death was considered non-cardiac. [62] Sudden cardiac death was defined as natural death due to cardiac causes, occurring within 1 hour of the onset of acute symptoms. Death was also classified as sudden if it occurred unexpectedly but was unwitnessed, such as in bed overnight. Aborted cardiac death due to successful cardiac resuscitation or appropriate internal cardioverter defibrillator (ICD) intervention for ventricular fibrillation or ventricular tachycardia were considered equivalent of sudden death. Heart failure-related death was defined as death occurring in the context of long-standing cardiac failure, with severe clinical deterioration usually requiring hospitalization within the year before death.

The cause of death was ascertained at each centre using hospital and primary health care records, death certificates, post-mortem reports, and interviews with witnesses.

Statistical analysis

Data are reported as median and IQR for continuous variables or frequencies (percentage) for categorical variables. Comparison of clinical and laboratory variables in patients with

HCM and phenocopies was performed with 2-sample t Test for continuous parametric variables and Mann–Whitney U test for all continuous non-parametric variables. Comparison of multiple groups of continuous non-parametric data were performed using Kruskal Wallis test. Categorical variables were compared using Chi-square test for parametric data and Fisher's exact test for non-parametric data.

The follow-up time for each patient was calculated from the date of their first evaluation to the date of reaching the primary end-point, or death from another cause, or to the date of their most recent evaluation. The cumulative probability for the occurrence of an outcome was estimated using the Kaplan-Meier method and log-rank test from the first clinical evaluation at the referral centre.

All p-values were two-sided and the results were considered statistically significant if < 0.05 . SPSS (Version 22.0) was used for all statistical analyses.

RESULTS

The combined study population consisted in 1697 adult patients followed-up at The Heart Hospital, London, UK and at S Orsola University Hospital, Bologna, Italy.

1288 patients (76%) had a diagnosis of HCM and 409 (24%) of phenocopies.

Figure 1 explains the patient population selection process and in Table 1 is summarized the final overall population and according to each centre.

Clinical characteristics at first evaluation of patients with HCM and phenocopies

Demographic and clinical features of patients with HCM and phenocopies at first evaluation at the referral centres are described in Table 2.

Patients with a diagnosis of phenocopies were more often diagnosed with HCM due to non-cardiac symptoms [140 (34%) versus 0 (0%), $p < 0.001$] and were more symptomatic at first evaluation [NYHA functional class III-IV 144 (11%) versus 97 (24%), $p = 0.01$].

Compared to HCM, phenocopies had a higher prevalence of atrial fibrillation/atrial flutter [50 (12%) vs 74 (6%), $p < 0.001$]. Patients with HCM showed greater values of maximal LV wall thickness compared to phenocopies [18 (16-22)mm vs 16 (14-19)mm, $p < 0.001$]. No significant differences were present in relation to LV end-diastolic diameter and left atrial diameter.

Prevalence of LV systolic impairment in hypertrophic phenotype cardiomyopathy

In the overall population systolic impairment, defined as 2D echocardiographic documentation of LV ejection fraction $< 50\%$, was present in 145 patients (9%). The prevalence of systolic impairment was significantly higher in patients with rarer phenocopies compared to patients with HCM [105/409 (26%) versus 40/1288 (3%), respectively ($p < 0.0001$)].

Among phenocopies, the prevalence of systolic dysfunction was higher in patients with AL amyloidosis (40%, 46/115 pts) followed by those with SSA (38%, 18/48 pts), GSD (31%, 5/16), hereditary TTR amyloidosis (28%, 24/86 pts), Friedreich's ataxia (18%, 2/11), mitochondrial disease (13%, 3/23 pts) and AFD (8%, 7/85). None of the patients with a

diagnosis of Noonan's syndrome, LEOPARD syndrome, FHL1 and CPT II deficiency showed LV systolic impairment at first evaluation. Only one patient with HCM had previous septal myectomy and none had previous alcohol septal ablation.

Considering each specific aetiology, among patients with hypertrophic phenotype and systolic impairment, the most frequent aetiology was represented by AL amyloidosis (32%, 46/145), followed by HCM (28%, 40/145), hereditary TTR amyloidosis (17%, 24/145), SSA (12%, 18/145), AFD (5%, 7/145). GSD, mitochondrial diseases and Friedreich's ataxia represented overall less than 7% of cases (Figure 2).

Age at first evaluation according to aetiologies in the overall population and in the subgroup with LV systolic impairment

HCM was the most frequent diagnosis for each age decade, as shown in Figure 3. Other conditions were distributed among all the decades with a prevalence for syndromic and metabolic diseases during the youngest decades of life while cardiac amyloidosis were characteristic of older age groups. Patients with mitochondrial diseases and HCM presented mainly in their 40ies-60ies for first evaluation at the referral centre.

In the overall population with hypertrophic phenotype cardiomyopathy, median age at first evaluation was younger in patients with Friedreich's ataxia, LEOPARD syndrome, Noonan syndrome and GSD [24 (20-32) years old] compared to patients affected by mitochondrial disease, HCM, AFD [51 (41-61) years old], respectively, and to patients with hereditary TTR amyloidosis, AL amyloidosis and wild-type or SSA [64 (55-73) years old, respectively ($p < 0.001$)] (Fig.4).

Patients with Friedreich's ataxia were the youngest at first evaluation at the referral centre [20 (17-23) year old] while patients with senile systemic amyloidosis the oldest [78 (73-81) year old] (Table 2, Fig. 5).

The onset of systolic dysfunction occurred earlier in patients with Friedreich's ataxia and GSD, precisely in the 2nd and 3rd decade of life, while the development of LV impairment was a later occurrence in patients with mitochondrial disease, AFD and wild-type or SSA, involving the older ages (6th decade onwards) as shown in Figure 6.

Rare causes of hypertrophic phenotype cardiomyopathy in the adult

Rarer causes of hypertrophic cardiomyopathy were related to FHL1 and CPT II deficiency. The two patients with FHL1 were both males and not family related. Age at first evaluation was 19 and 31 years old and both were diagnosed in the context of family screening. Both had a MWT of 16mm with normal LV systolic function at first evaluation and were in NYHA functional class I. The sole patient with CPT II deficiency was male and was diagnosed due to non-cardiac symptoms. Age at first evaluation was 35 year, MWT was 16mm and systolic function was normal.

Long-term prognosis in the overall population with hypertrophic phenotype cardiomyopathy and in the subgroup of patients with LV systolic impairment

Median duration of follow-up from first evaluation was 3.7 (IQR 1.6-7.2) years. In the overall population, 250 (15%) patients experienced all-cause mortality/heart transplantation (HTx) (Table 3). All-cause mortality/HTx was significantly more frequent in phenocopies compared to HCM occurring in 129 (32%) and 121 (9%), respectively ($p < 0.001$) (Figure 7). 5 patients in the phenocopies subgroup underwent heart transplantation and died afterwards, 2 due to non-cardiac causes and 3 of unknown cause. In the overall population, 160 (9%) patients experienced confirmed CV death/HTx, including sudden death and equivalents, heart failure (HF) and stroke related death. Similarly this was significantly more frequent among phenocopies than in HCM, 71 (17%) vs 89 (7%), respectively ($p < 0.001$). When considering specifically HF related-death this

was more frequent among phenocopies compared to HCM [34 (8%) vs 21 (2%), respectively, $p < 0.001$] (Figure 8).

HTx occurred overall in 33 (2%) patients, 18 (1%) in the HCM population and 15 (4%) among phenocopies ($p = 0.003$).

When considering specific aetiology, prognosis was worst in patients affected by cardiac amyloidosis. Patients with AL amyloidosis showed the worst prognosis due to all-cause mortality/HTx as well as HF-related death, followed by hereditary TTR amyloidosis and wild-type or SSA amyloidosis. Patients with HCM had the less severe prognosis as well as AFD and other aetiologies (Figure 9 and 10). No HF-related death occurred in pts with other aetiologies than cardiac amyloidosis, HCM and AFD.

When considering prognosis according to the presence of systolic dysfunction, this was considerably worst in patients with HCM and phenocopies and systolic impairment compared to those with preserved systolic function (Figure 11 and 12).

In the overall population 58 patients were assessed only at first evaluation therefore they have not been included in the outcome analysis.

DISCUSSION

The present study assessed the prevalence of LV systolic dysfunction in the largest cohort of adult patients with hypertrophic cardiomyopathy caused by different aetiologies as well as the long term prognosis in relation to the each specific aetiology.

In a population of 1700 patients, HCM due to documented or presumed mutations in sarcomere protein genes was the most frequent aetiology responsible for the phenotype accounting for 75% of cases. Nevertheless a quarter of patients assessed had a diagnosis of phenocopies as cause of LV hypertrophy showing that what usually thought to be less common conditions represents indeed a significant portion of the spectrum of the disease and therefore addressing the need for a correct diagnosis for management and treatment [1].

It is known that systolic dysfunction and evolution towards HF is a frequent complication of several conditions. A study on 18 patients with AL amyloidosis and 18 with SSA showed that despite SSA presenting with greater LV wall thickness and at an older age, the severity of heart failure was higher in the AL group and the median survival was much shorter. [12] Similarly, a recent study on a large population of patients with AFD has documented a prevalence of 10.6% and incidence of 1.62 per 100 person-years of severe heart failure symptoms either prior or during follow up. [22] Also it has been previously demonstrated that LV systolic function progressively deteriorates in untreated patients with AFD suggesting that systolic performance should be monitored in patients with the condition, and that systolic function may be a useful surrogate marker of response to enzyme replacement therapy. [11] Finally, several studies have described the so called end-stage disease or “burnt-out phase” of sarcomere HCM reporting a prevalence of 2-5% and an incidence of 0.5-1 cases per 100 patient/years and showing a poor prognosis associated with this evolution due to high rates of refractory heart failure and sudden arrhythmic death. [3-6]

The real prevalence of the combined phenotype of HCM and systolic dysfunction has not yet been investigated in large cohorts of patients with different aetiologies. In order to help the clinician in the correct diagnostic process, we have therefore investigated the prevalence of systolic dysfunction among the different aetiologies and related this evolution to age at first evaluation as possible “red-flag” for differential diagnosis. The prevalence of LV impairment resulted to be significantly higher among phenocopies. When the combination of LV hypertrophy, systolic dysfunction and age at presentation was

considered, patients with Friedreich's ataxia and GSD showed an earlier presentation of the combined phenotype compared to patients with HCM, hereditary TTR and AL amyloidosis, while in patients with mitochondrial disease, AFD and wild-type or SSA evolution towards systolic dysfunction was an even later event.

The association of LV hypertrophy and systolic dysfunction has therefore shown to be age-specific, providing a clue for the diagnosis of the underlying aetiology and strengthening the approach suggested by the ESC based on a 'red-flags' philosophy in order to improve diagnostic accuracy.[13]

Finally, this is the first study assessing prognosis according to the specific aetiology of HCM. This study confirms a general idea that phenocopies, in particular cardiac amyloidosis, are burdened by a more severe prognosis due to all-cause mortality, including cardiovascular death, heart transplantation and non-cardiac death, compared to other aetiologies. Onset of systolic dysfunction confirmed to carry a worst prognosis and therefore strengthen the importance of an early detection of the end-stage phase and the need for more aggressive treatment such as chemotherapy when in relation to AL amyloidosis, heart transplantation and ICD implantation.

Limitations

Both the Heart Hospital, London and Bologna University Hospital represent tertiary referral centres for specific cardiomyopathies, respectively AFD and mitochondrial disease for the Heart Hospital and cardiac amyloidosis for Bologna University Hospital. This could represent a bias in our population but the combination of both represents nonetheless a significant denominator for studying the different aetiologies underlying the hypertrophic phenotype cardiomyopathy and especially the prevalence of LV systolic dysfunction.

CONCLUSION

In a large cohort of patients with HCM, phenocopies represent a frequent aetiology responsible for this phenotype and prognosis varies according to the underlying aetiology therefore the need for a correct diagnosis for specific treatment.

The presence of the combined phenotype characterised by HCM and systolic dysfunction could act as an age-specific “red flag” helping clinicians in achieving the correct diagnosis.

TABLES

Table 1. Overall population

	Overall 1697	The Heart Hospital 987 (58%)	Bologna University Hospital 710 (42%)
HCM, n (%)	1288 (76)	826 (64)	462 (36)
Phenocopies, n (%)	409 (24)	161 (39)	248 (61)
AL amyloidosis	115 (7)	6	109
Hereditary TTR amyloidosis	86 (5)	6	80
Anderson-Fabry disease (AFD)	85 (5)	77	8
Wild-type or SSA	48 (3)	8	40
Noonan syndrome	15 (1)	11	4
Mitochondrial diseases	23 (1)	21	2
Friedreich's ataxia	11 (1)	9	2
Glycogen storage disease (GSD)	16 (1)	14	2
LEOPARD syndrome	7 (0.4)	6	1
FHL1	2 (0.1)	2	0
CPT II deficiency	1 (0.1)	1	0

Table 2. Demographic and clinical features of patients with HCM and phenocopies at first evaluation at the referral centres.

	Overall (1697)	HCM (1288)	Phenocopies (409)	p
Male, n (%)	1160 (68)	860 (67)	300 (73)	0.012
Modality of diagnosis				
Incidental, n (%)	475 (28)	437 (34)	38 (9)	<0.001
Cardiac symptoms, n (%)	822 (48)	660 (51)	162 (40)	
Family screening, n (%)	180 (11)	128 (10)	52 (13)	
Non cardiac symptoms, n (%)	140 (8)	0 (0)	140 (34)	
Age at diagnosis of HCM, median (IQR)	50 (38-62)	49 (37-60)	58 (44-69)	<0.001
Age at first evaluation, median (IQR)	52 (40-63)	51 (39-61)	60 (47-69)	<0.001
NYHA III-IV at first evaluation, n (%)	241 (14)	144 (11)	97 (24)	0.013
Rhythm at first evaluation, n (%)				
Sinus rhythm	1461 (86)	1124 (87)	337 (82)	<0.001
Atrial fibrillation/Atrial flutter	124 (7)	74 (6)	50 (12)	
Paced	53 (3)	33 (3)	20 (5)	
Max LVWT at first evaluation, (mm), median (IQR)	18 (16-21)	18 (16-22)	16 (14-19)	<0.001
LVED diameter at first evaluation, (mm), median (IQR)	45 (41-49)	45 (41-49)	45 (40-49)	0.145
EF at first evaluation, (%), median (IQR)	65 (57-71)	66 (60-72)	60 (48-68)	<0.001
EF <50% at first evaluation, n (%)	145 (9)	40 (3)	105 (26)	<0.001
LA diameter at first evaluation, (mm), median (IQR)	44 (39-49)	44 (40-49)	44 (38-48)	0.072

HCM= hypertrophic cardiomyopathy, NYHA= New York Heart Association functional class, LVWT= left ventricular wall thickness, ED= end-diastolic, EF= ejection fraction, LA= left atrial.

Table 3. Frequencies of all-cause mortality/HTx, CV death/HTx and HTx alone in the overall population, in patients with HCM and with phenocopies.

	Overall population (1697 pts)	HCM (1288 pts)	Phenocopies (409 pts)	p
All-cause mortality/HTx, n (%)	250 (15)	121 (9)	129 (32)	<0.001
CV death/HTx, n (%)	160 (9)	89 (7)	71 (17)	<0.001
HF death, n (%)	55 (3)	21 (2)	34 (8)	<0.001
HTx, n (%)	33 (2)	18 (1)	15 (4)	0.004

HTx= heart transplantation, CV= cardiovascular, HF= heart failure.

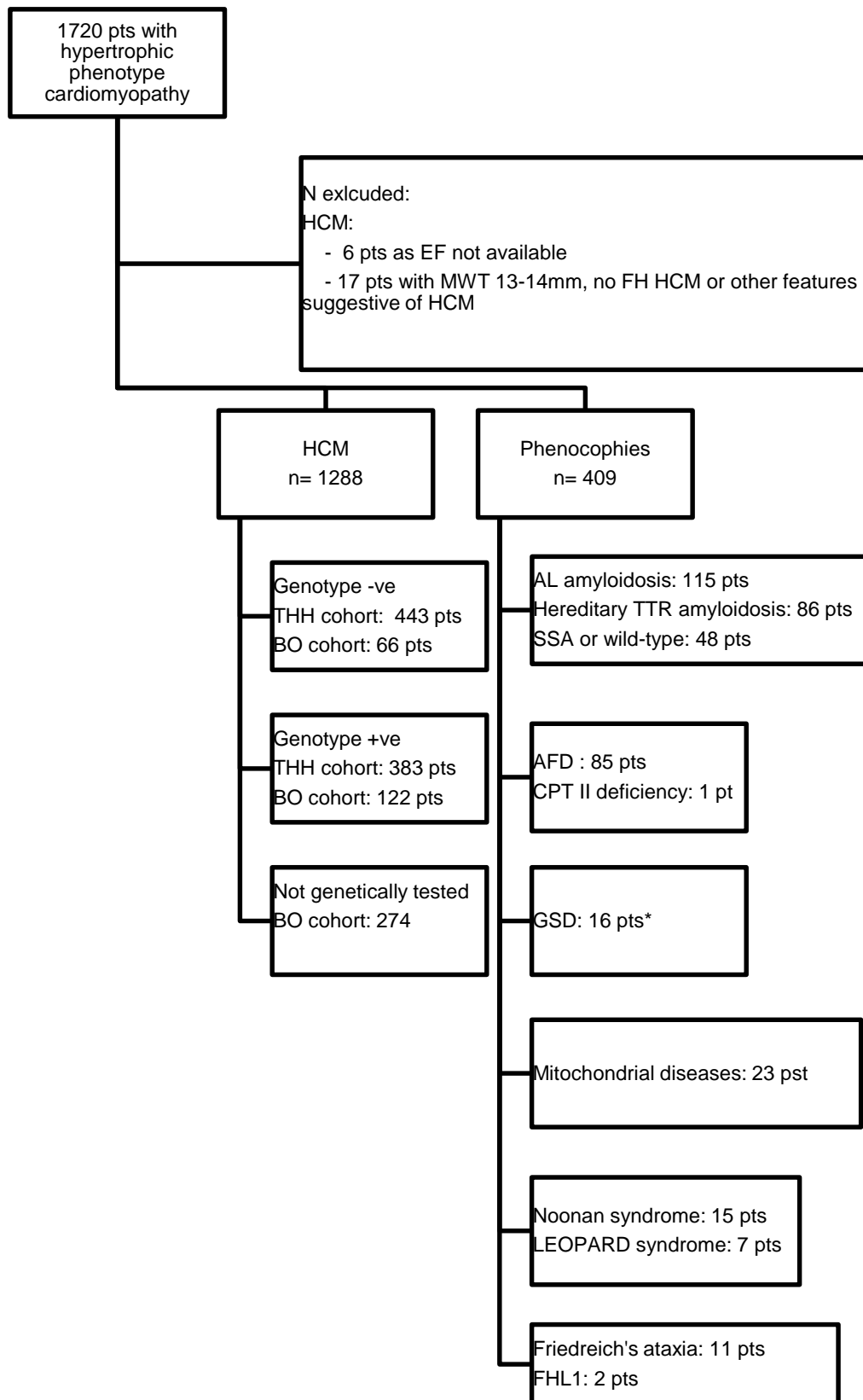
Table 4. Cause of death in the overall population, in HCM and in phenocopies.

	Overall population (1697 pts)	HCM (1288 pts)	Phenocopies (409 pts)
All-cause mortality, n (%)	222 (13)	103 (8)	119 (29)
Sudden death, n (%)	60 (4)	41 (3)	19 (5)
HF-related death, n (%)	55 (3)	21 (2)	34 (8)
Stroke-related death, n (%)	11 (1)	9 (1)	2 (0.5)
Non CV death, n (%)	46 (3)	26 (2)	20 (5)
Unknown, n (%)	50 (3)	6 (0.5)	44 (11)

HF= heart failure, CV= cardiovascular

FIGURES

Figure 1. Patient population selection process.



* 3 pts with Danon syndrome and 5 pts with AMP-protein kinase deficiency or PRKAG2.

Figure 2. Prevalence of the different aetiologies in the population with systolic dysfunction (145 pts).

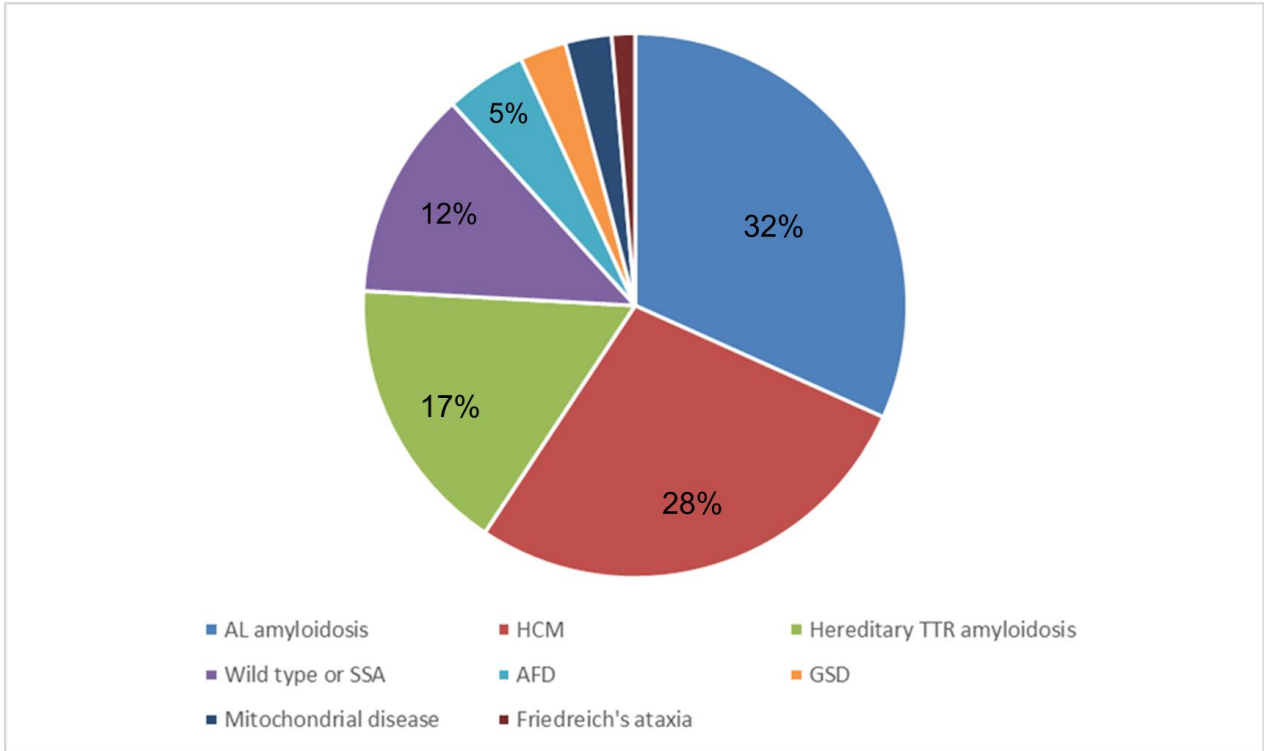


Figure 3. Distribution of the different aetiologies according to age at first evaluation.

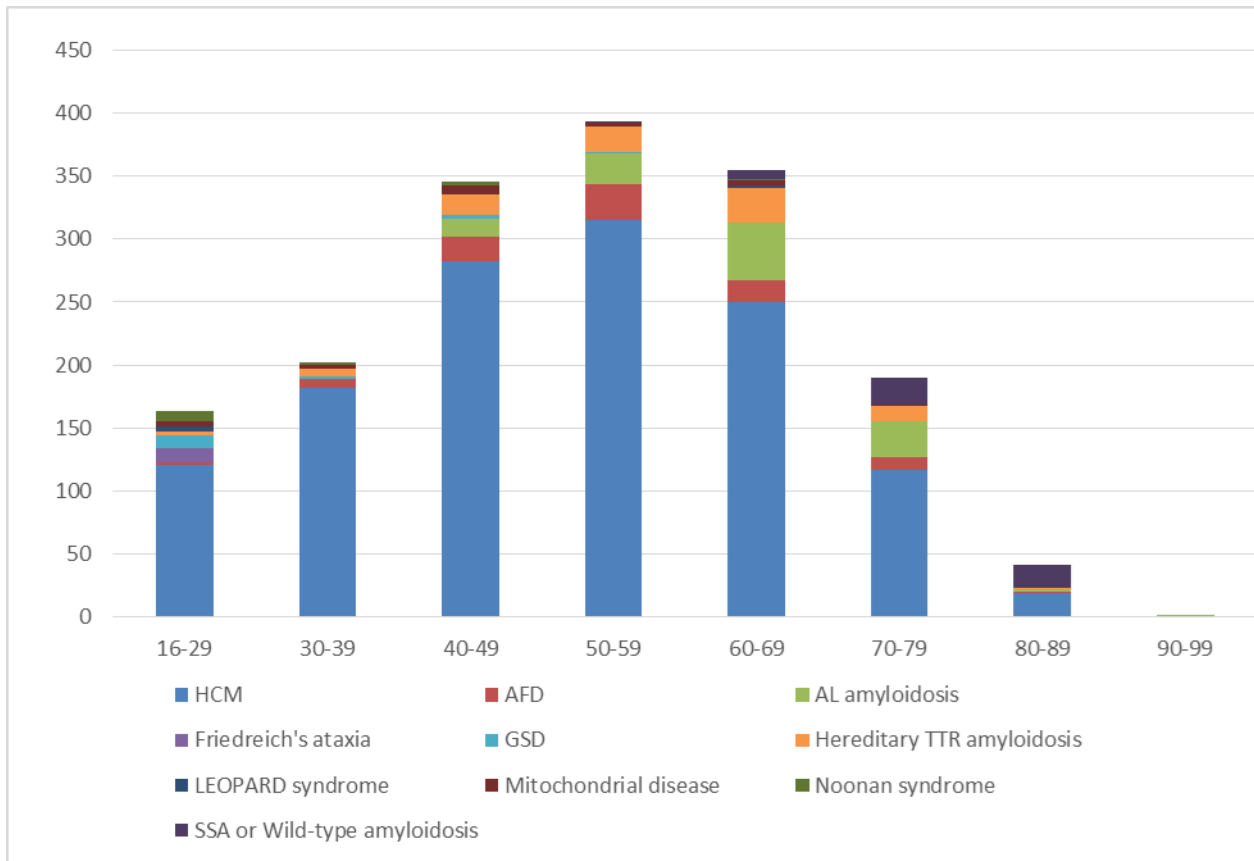


Figure 4. Age at first evaluation according to aetiology.

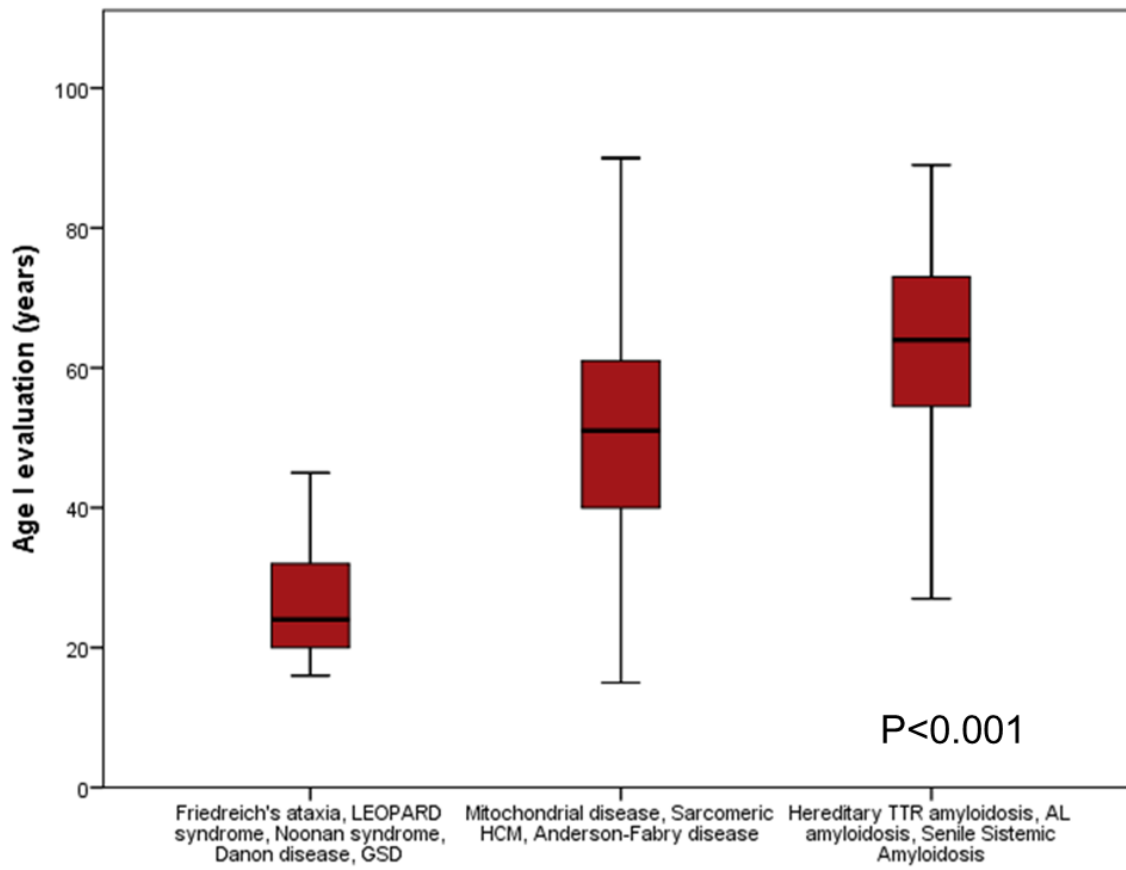


Figure 5. Age at first evaluation according to main aetiologies in the overall population.

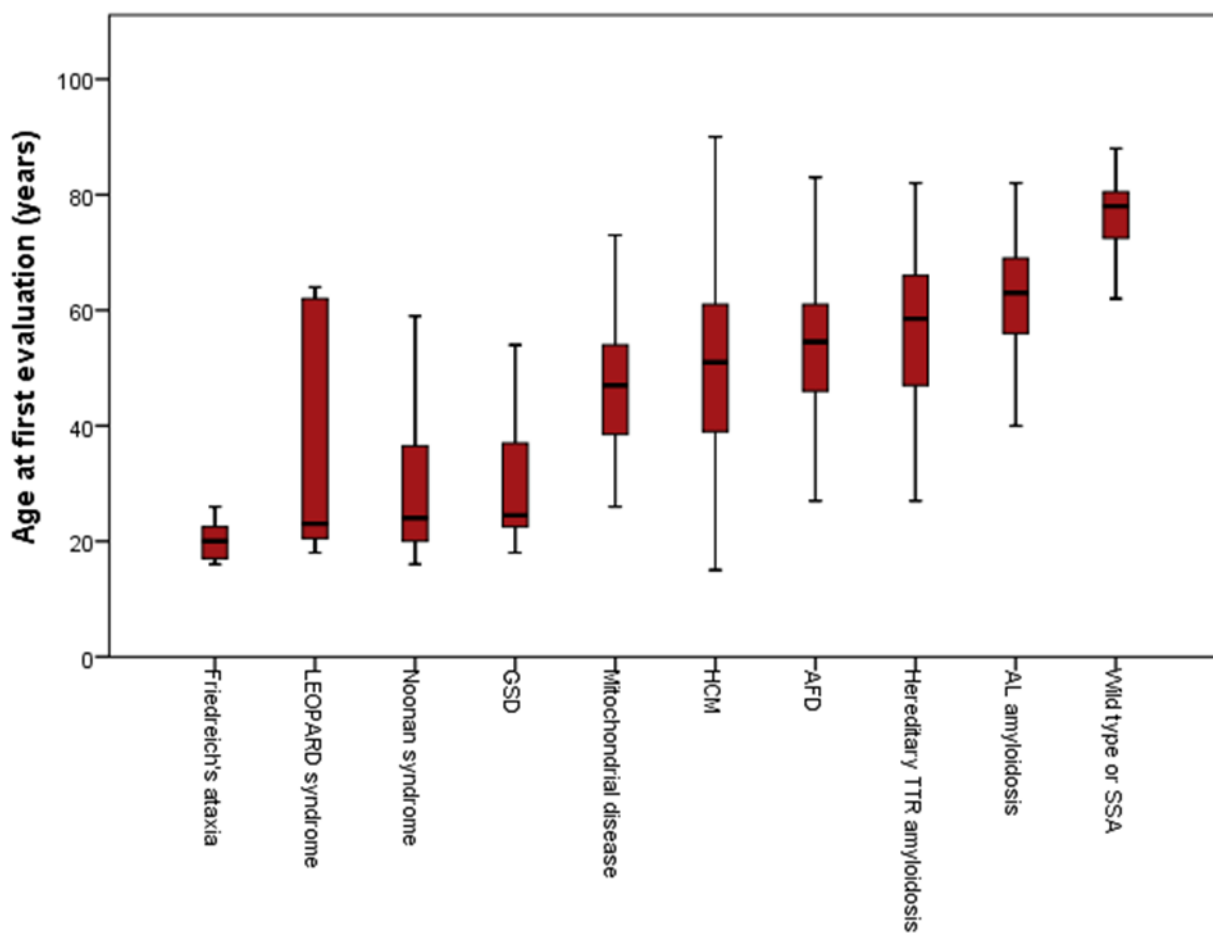


Figure 6. Age at first evaluation according to aetiology in patients with systolic dysfunction (145 pts).

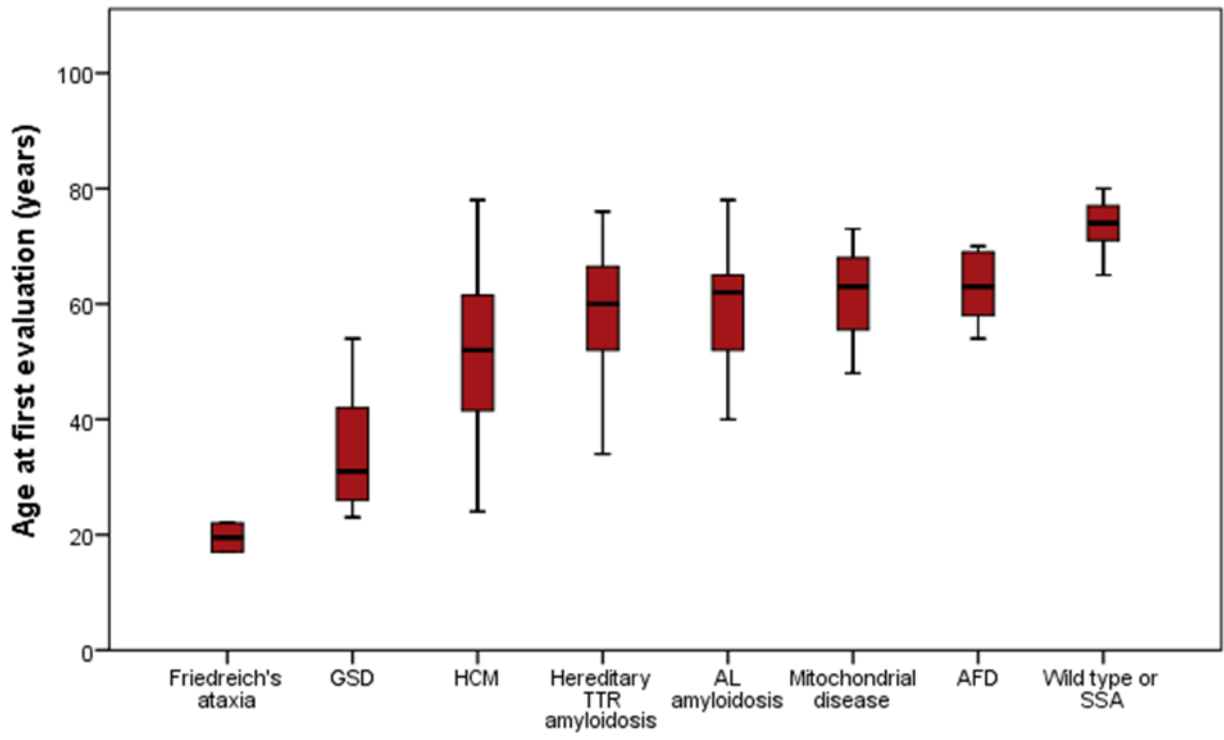


Figure 7. All-cause mortality/HTx in HCM and phenocopies.

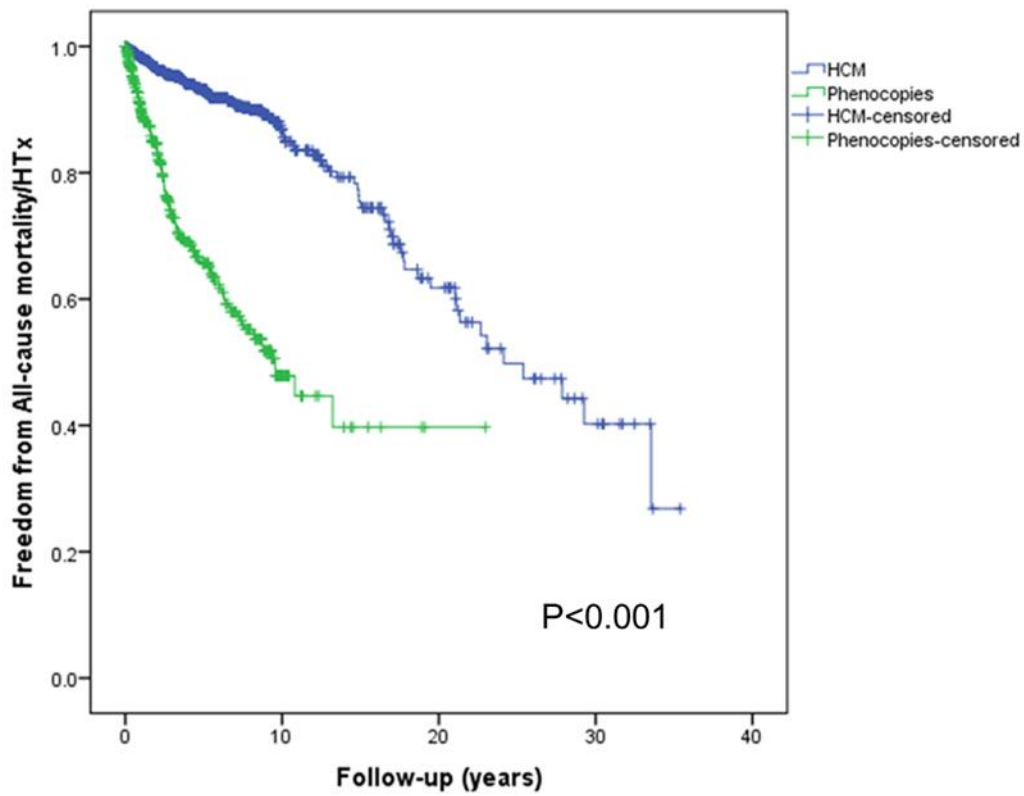


Figure 8. HF-related death in HCM and phenocopies

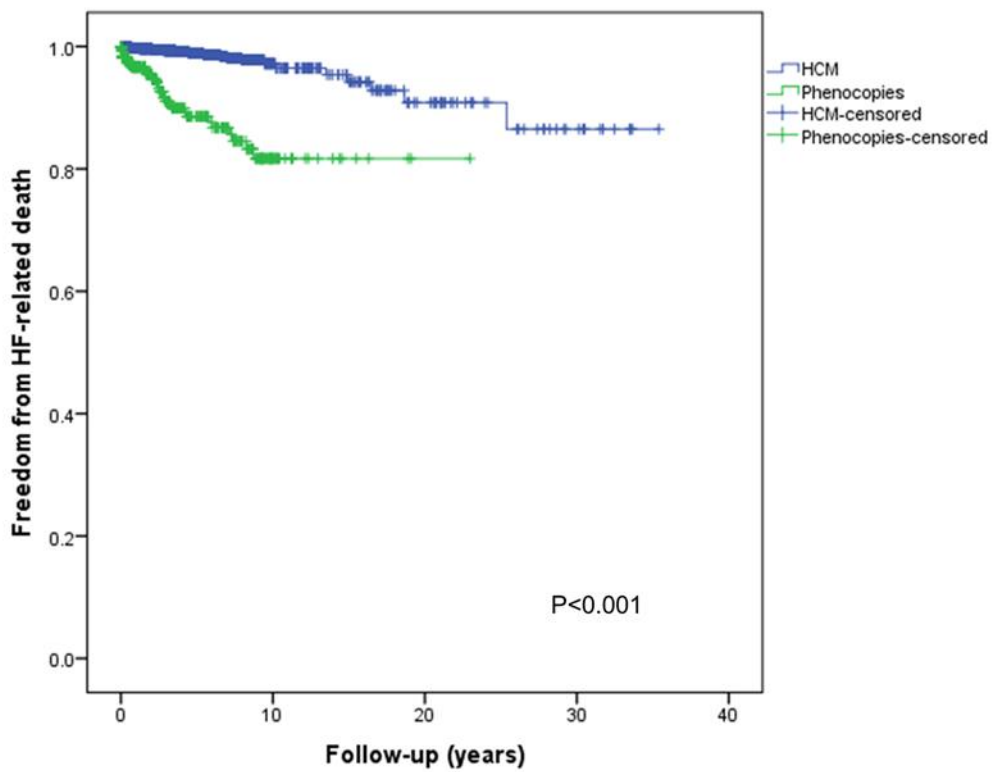


Figure 9. All-cause mortality and HTx according to specific aetiology.

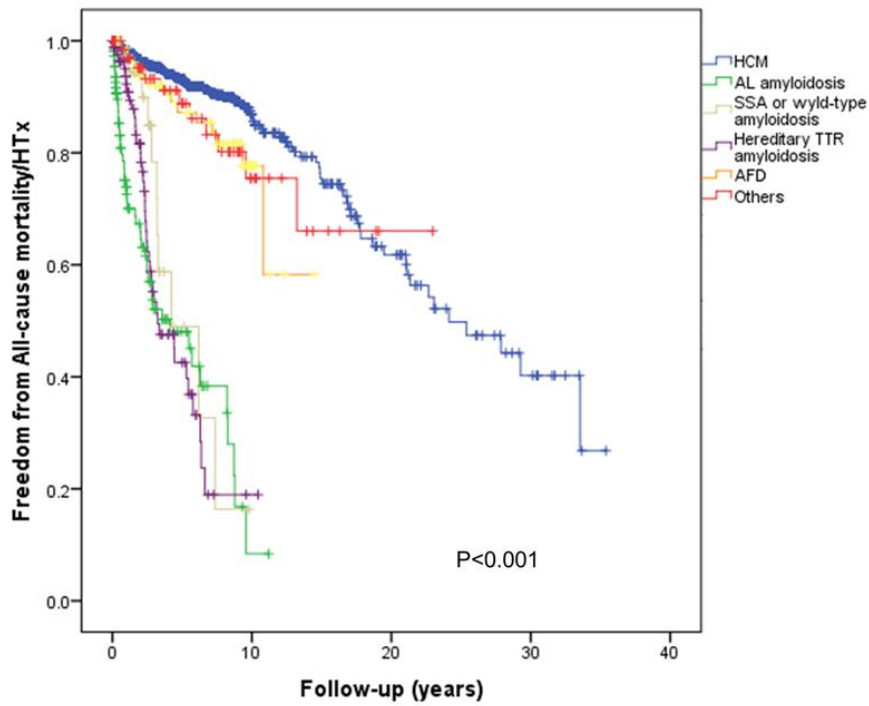


Figure 10. HF-related death according to specific aetiology.

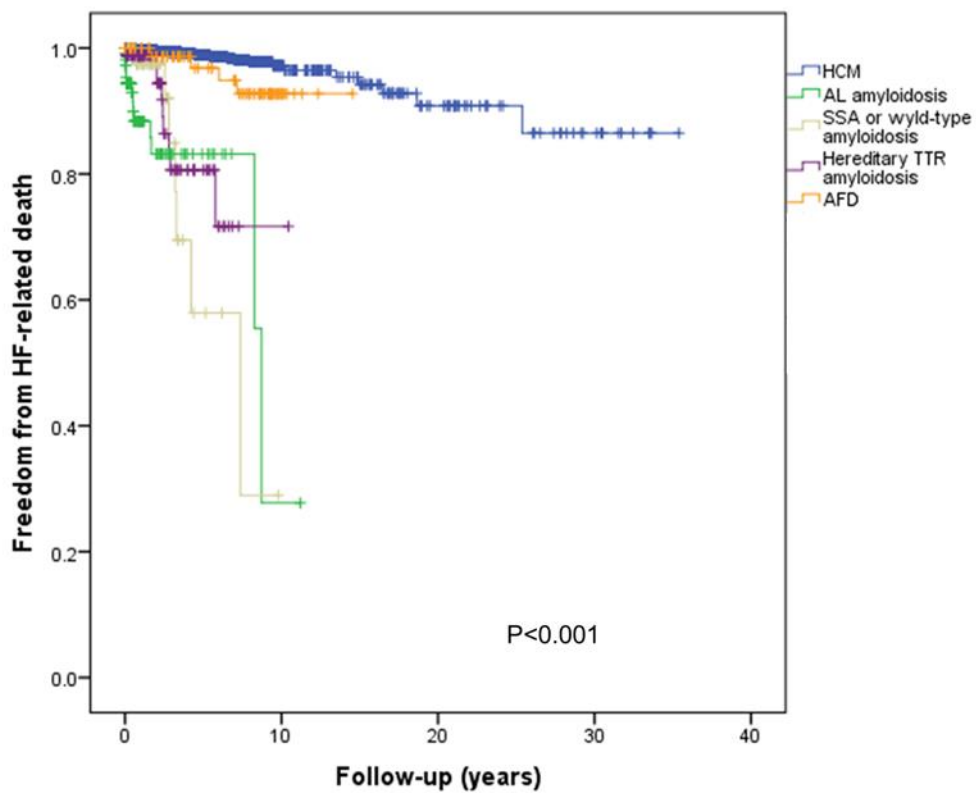


Figure 11. All-cause mortality/HTx in HCM patients with and without LV systolic dysfunction.

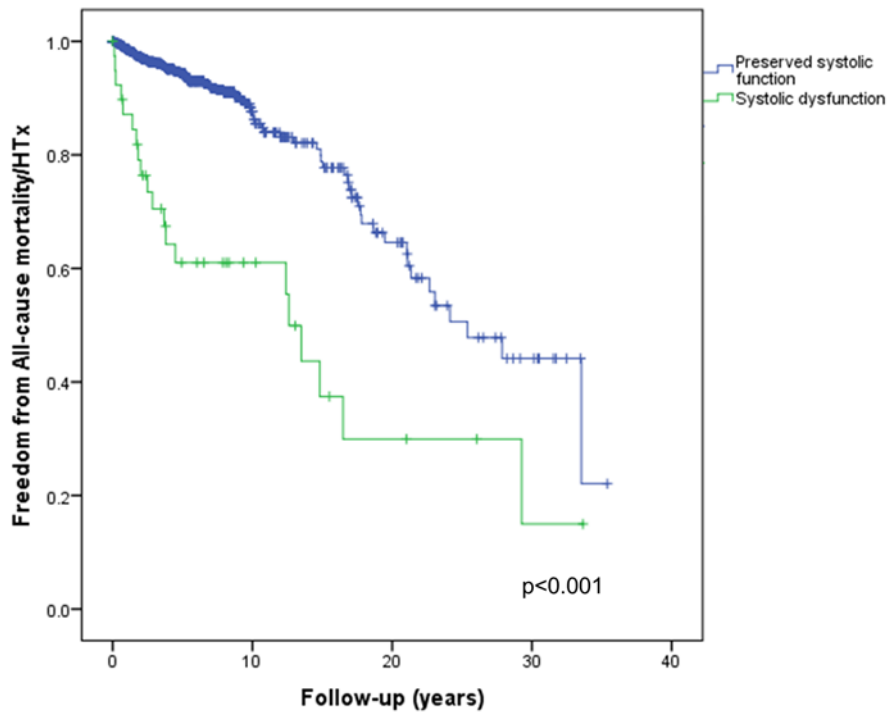
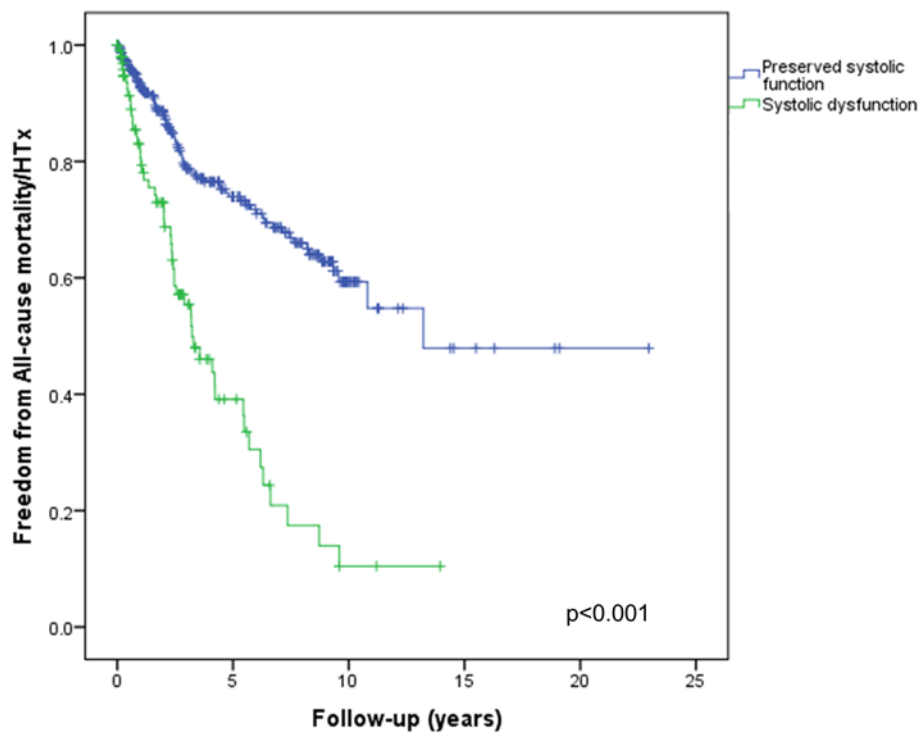


Figure 12. All-cause mortality/HTx in phenocopies with and without LV systolic dysfunction.



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