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Hypertrophic cardiomyopathy due to truncating variants in myosin binding protein C: a Spanish cohort

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ABSTRACT

Background Hypertrophic cardiomyopathy (HCM) is an inherited disorder whose causal variants involve sarcomeric protein genes. One of these is myosin-binding protein C (MYBPC3), being previously associated with a favourable prognosis. Our objective is to describe the clinical characteristics and events of a molecularly homogeneous HCM cohort associated with truncating *MYBPC3* variants.

Methods and results A cohort of patients and relatives with HCM diagnosis and carrying a truncating *MYBPC3* variant were retrospectively recruited. Subjects had an average follow-up of 7.77 years, with an incident HCM phenotype of 10%. They were middle-aged adult patients (47±16.8 years) without significant comorbidities or symptoms. Hypertrophy was discrete with a significative difference between probands and relatives (17.5±4 mm vs 14.6±5 mm; p<0.0001). Ejection fraction was predominantly preserved (65%±10%). Despite it being the most common clinical event, relevant heart failure (observed in 8.1% of patients) was infrequent and commonly found in the presence of a second environmental precipitating agent. ESC-HCM risk calculator and modifier factors did not correlate with the risk of major events predicting events, which were low (1.51 per 100 patients/year) and associated with the severity of HCM, abnormal QRS in the ECG and age. Genetic factors and sex were not associated with major events.

Conclusions This is the first molecularly homogeneous, contemporary cohort, including HCM patients secondary to *MYBPC3* truncating variants. Patients showed a good prognosis with a low event rate. In our cohort, major arrhythmic events were not related to measured environmental or genetic factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiac myosin-binding protein C (MYBPC3) mutations have usually been associated with milder phenotypes and good prognosis, except for some truncating variants and the presence of genetic overlap. However, there are no robust genotype–phenotype correlations so this study is the first to describe a genetically homogeneous hypertrophic cardiomyopathy (HCM) cohort of MYBPC3 truncating variants.

WHAT THIS STUDY ADDS

⇒ HCM associated with MYBPC3 truncating variants is associated with a low incidence of major events in this contemporary cohort. Most of these events are related to heart failure (HF).

⇒ A delay in diagnosis of HCM in women compared with men is also detected in our cohort as in many other cardiovascular conditions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Environmental factors, traditionally considered illness modifiers, may serve as triggers for HF worsening in the presence of MYBPC3 truncating variants. In the presence of ventricular systolic dysfunction, it may be advisable to engage in an active search for precipitating factors (rapid response atrial fibrillation/AFT, alcohol abuse, advanced hepatic, renal disease, etc) and to consider the known increased risk of major events.

⇒ General scales and indexes for risk assessment might be more useful if molecular information is included. More studies are needed in the field of risk assessment scales, considering QRS interval morphology and small deviations in EF.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited disease,[1 2] with incomplete penetrance and heterogeneous expressivity. The majority of genotype-positive HCM cases are associated with genetic

variants in sarcomeric proteins.[3] Cardiac myosin-binding protein C (MyBPC) genetic variants represent almost half of the HCM-associated mutations.[4 5]

Frameshift and nonsense mutations are common in *MYBPC3* and can potentially cause haploinsufficiency,[5 6] producing disarray and fibrosis, apart from hypertrophy, resulting in diastolic dysfunction.[5 6] In advanced stages, dilatation or systolic ventricular dysfunction may appear.[6]

Despite *MYBPC3* mutations are common, we still lack robust genotype–phenotype correlations. Previous works have not encountered differences between missense and truncating mutations.[6 7] Studies in small cohorts suggest that truncating variants present more arrhythmic events during follow-up.[8] A possible explanation for this difference might be related to the presence of additional precipitating factors, either genetic or environmental.

The aim of our study is to describe a cohort of HCM patients with truncating variants in *MYBPC3*, with a particular focus on clinical events. The secondary objectives were to describe structural characteristics, through imaging techniques, and determine whether adverse events were associated with structural, clinical or genetic variables.

Material and methods

Patient population

Consecutive patients aged ≥18 years (N=276) with truncating mutations (positive genetic test or being an obliged carrier) in *MYBPC3* from 14 heritable cardiomyopathies units were recruited in the framework of cardiovascular biomedical investigation centre network (CIBER-CV) in Spain. Patients with splice-site or in-frame deletion variants were excluded (N=88) due to the mostly unpredictable consequences in terms of the protein of these variants. The final cohort was composed of 188 carriers of non-sense and frameshift mutations (online supplemental figure 1). For probands (N=80), a maximum ventricular wall thickness of at least 15 mm, in the absence of confounding diseases, was used as the cut-off point for considering HCM. For first-degree relatives (N=68), the threshold was set at 13 mm.

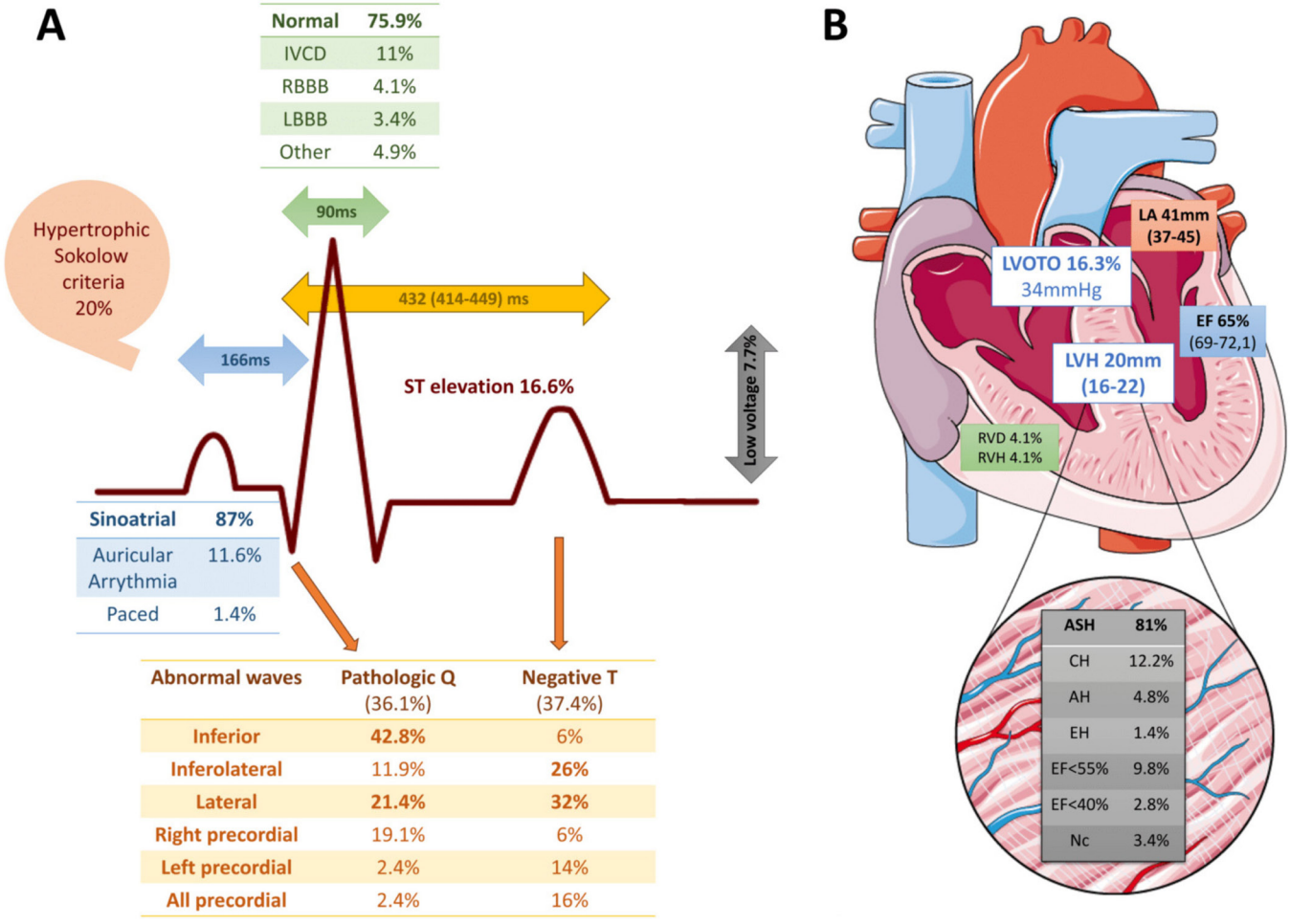

Figure 1 ECG (A) and echocardiographic (B) findings in patients with hypertrophic cardiomyopathy due to truncating variants. ASH, asymmetric hypertrophy; CH, concentric hypertrophy; EH, eccentric hypertrophy; EF, ejection fraction; IVCD, interventricular conduction delay; LA, left atrial anteroposterior diameter; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; Nc: non-compacted myocardium; RBBB, right bundle branch block; RVD, right ventricular dysfunction; RVH, right ventricular hypertrophy.

Phenotype, defined by HCM diagnostic criteria,[9] was identified in 148 patients. Exclusion criteria were the presence of severe respiratory, pericardial illness or having a haemodynamic situation that justified the presence of ventricular hypertrophy.

Follow-up and study outcomes

All the pertinent clinical and imaging information was received, reviewed and incorporated into a database in 2022. Family trees were drawn up with at least three consecutive generations. Follow-up and clinical management were performed by each institution, following standard guidelines and local protocols.

The cause of death was ascertained by a specialist cardiologist at each hospital based on healthcare records, differentiating between CV or non-CV origin. Sudden cardiac death (SCD) was defined as the 'sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation'[10] with or without a documented ventricular arrhythmia (VA). Apart from death of any cause, other major events were investigated and collected from local medical records at each centre: aborted SCD, the presence of sustained ventricular tachycardia (VT), the requirement for cardiac transplant, the indication of an implantable cardioverter defibrillator (ICD) in secondary prevention, ICD appropriate shock and antitachycardia pacing (ATP) therapy (considered if the treated tachycardia was considered of ventricular origin after reviewing the stored ICD's electrograms by attending physicians).

Secondary outcomes were heart failure (HF), considered as signs and symptoms, compatible with HF, which required hospitalisations or emergency visits, and other clinically relevant arrhythmic events.

Genetic study

Genetic test was carried out according to each participating centre protocol. Sequencing included at least all the five main sarcomeric genes. For probands, a genetic test using NGS sequencing of a panel including 18 genes was commonly performed (online supplemental table 1). Sequencing was obtained according to local protocols Familiar genetic and clinical cascade screening was performed using Sanger sequencing. Variant pathogenicity was classified according to the American College of Medical Genetics and Genomics guidelines.[11]

Other studies

12-lead surface ECG, transthoracic echocardiography, cardiac MR (CMR) and additional studies were performed following local protocols.

Late gadolinium enhancement (LGE) was quantified using a 6SD approach, with one unaffected segment designated as the standard ROI.[12] The LGE analysis was performed qualitatively.

Statistical analysis

Baseline characteristics of study patients were described as mean±SD for continuous variables. Not normally distributed variables were summarised as median and IQR. Absolute and relative frequencies (as percentages) were used to summarise categorical variables. Differences in baseline characteristics between groups were compared using Student's t-test or Wilcoxon-Mann-Whitney test for quantitative variables, and Pearson's χ^2 or Fisher's exact test for categorical variables. The incidence rates of death and major events were calculated and represented by Kaplan-Meier curves. Univariable and multivariable Cox proportional hazards risk regressions were used to calculate the HRs. Variables with a statistically significant association with the outcome in the univariable analysis and those with a documented biological or clinical association were included in the multivariable model. Then, they were sequentially removed using a backward-step method. Statistical analyses were conducted using R and RStudio. A two-sided $p<0.05$ was considered statistically significant and Bonferroni correction was used in case of several hypothesis contrasting.

RESULTS

Baseline characteristics

188 patients were included. 78.72% of them showed the phenotype at baseline evaluation (N=148: 80 probands and 68 relatives). Of those who did not show HCM, 10% developed it in a mean follow-up of 7.77±6.8 years (median 6.62 years). All patients were Caucasians, and middle-aged adult patients (47±16.8 years old) with a low prevalence of major comorbidities. Women were diagnosed at an older age when compared with men (52.2 vs 44.0 years, $p<0.001$). There were no substantial basal differences between probands and relatives (see table 1).

At first evaluation, most patients had symptoms (55.1%), being mild dyspnoea (New York Heart Association-II) the principal reason for consultation (see table 1). Two cases (1.35%) experienced SCD at the time of diagnosis of which only one was resuscitated. That is the reason why follow-up is reported in 147 individuals. After treatment instalment, 19.8% (N=16) of symptomatic patients became asymptomatic. The use of beta-blockers/calcium antagonists increased from 40% to 64.6% of patients, as well as diuretics (from 6.8% to 19.7%) and antiarrhythmic drugs (from 2% to 12.9%).

In the ECG, 87% of patients exhibited sinus rhythm, but only 22.8% had a completely normal ECG. The QRS, predominantly narrow, was wider in probands compared with relatives (96.3±20.4 vs 89.2±14.9, p=0.04, respectively). There were no striking repolarisation abnormalities (figure 1A): only 35.1% of cases with hypertrophy documented in the TTE showed an ECG pattern indicative of left ventricular (LV) hypertrophy. The ECG signs of hypertrophy were strongly correlated with its severity (p=0.0018). The median of maximum wall thickness was 20 mm (IQR 16–22). Hypertrophy was asymmetrical in 81% of cases. There were no differences between sexes (figure 1B). There was no significant valvular disease. The prevalence of systolic ventricular dysfunction was

Table 1 Baseline characteristics

Variable	Total (147)	Non-probands (68)	Probands (79)	P value
Sex (male)	91 (61.9%)	38 (55.9%)	53 (67.1%)	0.221
Age	47.0±16.8	47.2±15.0	47.0±13.6	0.957
Hypertension	33 (22.4%)	17 (25.0%)	16 (20.3%)	0.624
Diabetes	12 (8.2%)	7 (10.3%)	5 (6.3%)	0.566
CKD IV	4 (2.7%)	2 (2.9%)	2 (2.5%)	1.000
Smoker	40 (27.2%)	18 (26.5%)	22 (27.8%)	0.999
Obesity	14 (9.5%)	7 (10.3%)	7 (8.9%)	0.989
Sports practice	16 (10.9%)	9 (13.2%)	7 (8.9%)	0.559
Prior CVA	1 (0.7%)	0 (0%)	1 (1.3)	1.000
Initial symptoms				
Any	81 (55.1%)	36 (52.9%)	45 (57.0%)	0.747
Chest pain	26 (17.1%)	8 (11.8%)	18 (22.8%)	0.126
Dyspnoea	58 (39.5%)	27 (39.7%)	31 (39.2%)	1.000
Palpitations	22 (15%)	13 (19.1%)	9 (11.4%)	0.281
Syncope	8 (5.4%)	2 (2.9%)	6 (7.6%)	0.287
ECG				
Rhythm				
Sinus rhythm	127 (87%)	59 (88.1%)	68 (85.9%)	0.653
AF/AFT	17 (11.6%)	8 (11.9%	9 (11.5%)	
Paced	2 (1.4%)	0 (0%)	2 (2.6%)	
PR interval Me (IQR)	166 (146–183)	165±29.6 160 (145–180)	170.3±41.2 174 (157–184)	0.461 0.170
QRS interval Me (IQR)	90 (80–100)	89.2±14.9 87 (79–96)	96.3±20.4 94 (82–104)	**0.049** 0.053
QTc interval Me (IQR)	432 (412–449)	424.6±27.0 426 (409–441)	432.8±28.4 438 (420–454)	0.158 0.080
QRS morphology				0.244
RBBB	6 (4.1%)	1 (1.5%)	5 (6.5%)	
LBBB	5 (3.4%)	1 (1.5%)	4 (5.2%)	
IVCD	16 (11%)	6 (9.0%)	10 (13.0%)	
Normal	110 (75.9%)	52 (77.6%)	58 (74.0%)	
Pathologic Q wave	52 (36.1%)	25/67 (37.3%)	27/77 (35.1%)	0.915
Negative T waves	55 (37.4%)	24/67 (35.8%)	43/77 (55.8%)	**0.016**
Low voltages	11 (7.7%)	5 (7.5%)	6 (7.8%)	1.000
Sokolow	41 (28.5%)	10 (14.9%)	31 (40.3%)	**0.001**
Basal echocardiogram				
LV thickness Me (IQR)	20 (16–22)	14.6±5.1 mm 14 (10–17)	17.5±4.1 mm 16 (15–20)	**<0.001** **<0.001**
LVH	147 (100%)	68 (100%)	79 (100%)	0.230
LA (mm)	41 (37–45)	38.895±7.343	43.219±7.052	**0.001**
LA area Me (IQR)	23 (20–26)	165.1±29.6 160 (146–180)	170.3±29.6 174 (157–184)	0.461 0.170
LVTDD Me (IQR)	43 (40–47)	43.778±6.425 43 (40–48)	43.279±4.8 43 (40–46)	0.631 0.687
LVTSD Me (IQR)	26 (23–30)	26.469±7.132 26 (23–30)	26.212±5.142 26 (23–28)	0.838 0.873

Continued

Table 1 Continued

Variable	Total (147)	Non-probands (68)	Probands (79)	P value
LVEF Me (IQR)	65% (69–72.12)	64.276±9.805 64 (60–70)	66.685±10.339 66 (60–72)	0.156 0.052
Non compacted	5 (3.4%)	4/66 (6.1%)	1 (1.3%)	**0.042**
RV dilatation	2 (1.4%)	1/66 (1.5%)	1 (1.3%)	1.000
RV dysfunction	6 (4.1%)	3 (4.5%)	3 (3.8%)	0.819
RV hypertrophy	6 (4.1%)	1 (1.3%)	5 (6.5%)	0.267
TAPSE		23.931±4.301	22.806±3.331	0.265
LVOTO	24 (16.3%)	6 (9.0%)	18/77 (23.4%)	**0.036**
Maximum gradient Me (IQR)	34 (7–71)	39.083±41.43 20 (7–58)	49.121±44.864 39 (8–74)	0.490 0.643
Basal cardiac MR				
LV thickness Me (IQR)	20 (17–23)	17.892±4.354 15 (18–21)	22.793±6.251 21 (19–26)	**<0.001** **<0.001**
LVTDV (indexed) Me (IQR)	77.8±13.6	70.475±13.934 68 (61–78)	81.674±11.616 78 (73–88)	**0.012** **0.008**
LVTSV (indexed) Me (IQR)	41±27.7	24.687±7.415 21 (19–31)	29.476±12.46 26 (23–30)	0.136 0.146
Systolic volume (indexed) Me (IQR)	54±11.7	48.083±5.103 48 (44–52)	55.545±12.437 54 (50–60)	**0.008** **0.006**
LVEF Me (IQR)	68 (62–72)	67.447±7.009 68 (63–73)	65.44±10.216 68 (61–72)	0.283 0.614
Mass (indexed)	82 (65–96)	62.05±23.293	89.056±24.894	0.097
Non compacted	13 (14.2%)	5/37 (13.5%)	8/54 (14.0%)	0.706
Presence of LGE	60 (67.4%)	16 (32.6%)	44 (80%)	**0.000**

AF, atrial fibrillation; CKD, chronic kidney disease; CVA, cerebrovascular accident; IVCD, interventricular conduction delay; LA, left atrial; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, LV ejection fraction; LVH, LV hypertrophy; LVOTO, left ventricular outflow tract obstruction; LVTDD, LV tele-diastolic diameter; LVTDV, LV tele-diastolic volume; LVTSD, tele- systolic diameter; LVTSV, LV tele-systolic volume; RBBB, right bundle branch block; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

low (median TTE LV ejection fraction (LVEF)=65% (IQR 69%–72.2%) and 68% by CMR (IQR 62%–72%)). LV outflow tract obstruction was documented in 16.3% of carriers (median gradient 34 mm Hg; IQR 7–71) (see table 1).

In patients with available CMR (N=89), LGE was present in 67.4% of patients. The pattern was predominantly patchy, and it was predominantly distributed at the septum (78.3%), followed by anterior (48.3%), apical (30%), inferior (21.7%) and lateral (10%) LV walls.

Genetically, frameshift mutations represented the majority of the variants (62.6%) (table 2). We documented 58 different variants, most of which were predominantly located within the first immunoglobulin domain, especially around position 850 (online supplemental figure 2). There were no differences in prognosis related to variant position.

In 18.4% of patients, a second variant was documented. Only one (3.7%) of these second variants was considered pathogenic or likely pathogenic, and it was not related to any major event in our follow-up.

Clinical events and outcomes

Relevant VA was scarce. Although only 22.5% of patients were free of any rhythm abnormality, most of them were monomorphic premature ectopic ventricular beats. In 30.3% of cases, non-sustained VT was documented. Only four cases (2.7%) presented sustained VT, one of them treated by catheter ablation. Atrial arrhythmias were documented in 30% of cases during follow-up: atrial fibrillation (AF) was managed with an anticoagulation and rate-control strategy in 98% of cases. There was a low incidence of stroke, with only six patients (4.1%) suffering it during follow-up, all of them without sequelae.

ICD was implanted in 41 (27.7%) and 2 (1%) patients as primary and secondary prevention, respectively. The incidence of appropriate therapies was 20%; among these, six received an appropriate shock and three additional patients required appropriate ATP. SCD constituted the first manifestation in one case. Clinically relevant VA was present in nine patients (6.08%), coexisting in half of the cases with HF (see table 3 and online supplemental table 2).

Table 2 Familiar and genetic features

Family characteristics		N=147
Ethnicity		
Caucasian		146 (99.3%)
Other/mixed		1 (0.7%)
Probands		79 (53.7%)
Family history of cardiovascular disease		114 (78.1%)
Family history of sudden cardiac death		58 (40.0%)
Family history of HCM		89 (ta60.5%)
Genetic characteristics		N=147
Sequencing method		
NGS		61 (41.5%)
Sanger		75 (51.0%)
Other		11 (7.5%)
Protein position (median, years, IQR)		
Variant type		
Nonsense		55 (37.4%)
Frameshift		92 (62.6%)
Main MYBPC3 mutations (≥3 patients)		
p.Lys600Asnfs*2	17	11.6%
p.Arg891Alafs*160	14	9.5%
p.Tyr373*	9	6.1%
p.Gln1070Argfs*5	7	4.8%
p.Gln791*	7	4.8%
p.Gly263*	5	3.4%
p.Tyr908*	5	3.4%
p.Arg943*	4	2.7%
p.Pro955Argfs*95	4	2.7%
p.Trp486*	4	2.7%
p.Ala328Hisfs*22	3	2.0%
p.Arg1271*	3	2.0%
p.Gln921*	3	2.0%
p.Pro106Hisfs*10	3	2.0%
Other mutations		27 (18.4%)
Pathogenic/Likely pathogenic HCM		1 (3.7%)

HCM, hypertrophic cardiomyopathy; NGS, new generation sequencing.

Table 3 Arrhythmic and major events

All arrhythmic and major events	N=147 N (% or IQR)
Atrial arrhythmia (mainly AF)	
► ECG	17 (11.6%)
► 'De novo' AF	16 (18.6%)
► Paroxysmal	17 (13.6%)
► Persistent	5 (3.4%)
► Permanent	22 (15%)
► Never	103 (70%)
Ventricular arrhythmias ergometry	5 (6.3%)
Holter monitoring with information	132 (89.8%)
Ventricular extrasystoles	70 (53%)
► Density (mean absolute count)	22 (0–180)
► Monomorphic	62 (53.9%)
► Bimorphic	1 (0.009%)
► Polymorphic	7 (6.9%)
► Not information about VE	16 (12.12%)
► None VE	46 (40%)
Non-sustained VT	
► Debut	30 (22.9%)
► Follow-up	44 (30.3%)
Sustained VT	4 (2.7%)
VT ablation	1 (0.7%)
1° prevention ICD	41 (27.7%)
2° prevention ICD	2 (1%)
ICD therapy	
► Antitachycardia pacing	3 (2.03%)
► Shock	6 (4.05%)
Severe HF	
► HFrEF	7 (4.7%)
► Cardiac transplant	5 (2.6%)
Deaths	14 (9.46%)
► SD	1 (0.67%)
► Terminal HF	5 (3.38%)
► CV death	3 (2.03%)
► Non-CV death	5 (3.38%)

AF, atrial fibrillation; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFrEF, heart failure with reduced EF; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia.

Despite the development of HF was apparently low (30 patients, 16%), it represented the main complication registered in our cohort. According to the type, 58.3% of subjects developed HF with reduced EF (HFrEF), 25% with preserved EF and 16.7% with mildly reduced EF. Five patients (2.6% of total and 41.7% of HF events) underwent heart transplantation. Progression of HF, to both reduced EF and advanced HF (8.1% of patients and 52.5% of all the major events in the follow-up), was commonly seen with a second environmental trigger in our cohort (the presence of tachycardia, hepatic or renal significant dysfunction, etc). None of the second variants found in patients who developed HF were classified as pathogenic or likely pathogenic (online supplemental table 3).

There was a significant association between HFrEF and major events, with all patients showing HFrEF suffering at least one, although most of these events were predominantly related to HF itself (p<0.001).

Major events were documented in 23 patients (15.5%), mostly in patients older than 65 years (see online supplemental table 3). There were 13 deaths during 7.77±6.8 years of follow-up, mostly secondary to end-stage HF. Mortality rate was 1.058 per 100 patients/year, while composed major event rate was 1.511 per 100 patients/year (see figure 2 and online supplemental figure 3 for more details).

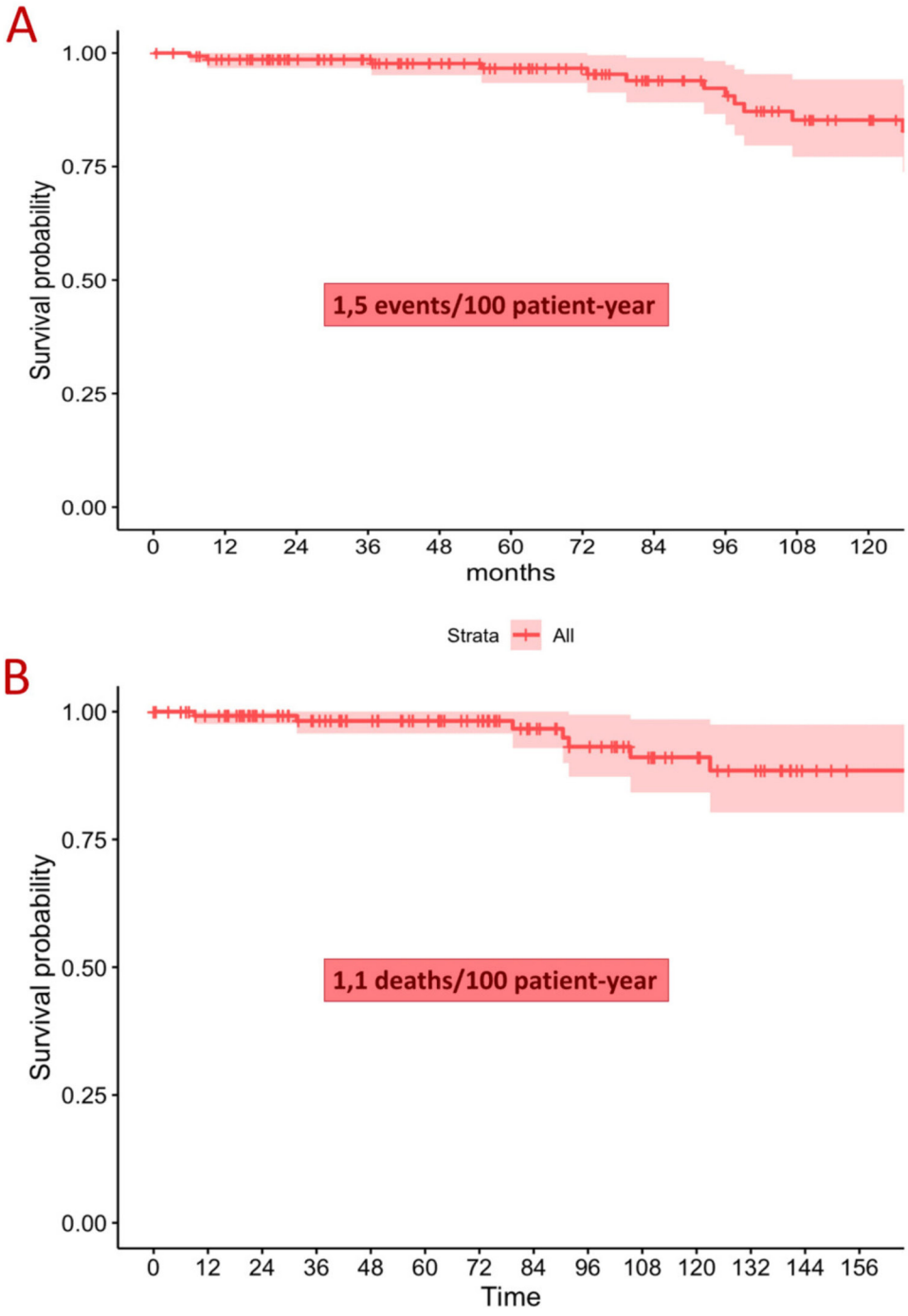

Figure 2 Free major events (A) and death (B) survival curves.

Risk prediction

In the univariate analysis, some clinical, ECG or structural variables were associated with major events. This correlation was mostly not reproduced in the multivariable analysis (see online supplemental table 4).

Only three variables were correlated in the multivariable analysis with major clinical events: any systolic ventricular dysfunction (LVEF<58%; HR 12.28; 95% CI 3.14 to 48.10; p<0.0001), older age (age >66 years; HR 9.88; 95% CI 2.57 to 37.92; p<0.0001) and abnormal QRS (both morphology and duration) in the ECG (HR 3.53, 95% CI 1.01 to 12.31; p=0.047). Neither isolated environmental nor genetic factors were found to be related to clinical events. A trend towards higher, but not significative, rates of major events and death was observed in females. Only polymorphic ventricular extrasystoles were related to CV death, and only older age was correlated with death of any cause.

We calculated the SCD risk based on the model proposed in the European Society of Cardiology guidelines.[13] The mean calculated 5-year risk of SCD for the cohort was low (2.44%±1.54%). We did not find a correlation between the calculated risk with either major events or death from any cause (including sudden or arrhythmic death).

DISCUSSION

The present study is the first to analyse phenotypic characteristics and clinical events in the follow-up of a large contemporary genetically homogeneous cohort of HCM associated with truncating variants in *MYBPC3*.

HCM-affected patients were predominantly middle-aged adult patients (47 years), as previously described in the literature (from 55%[14] to 63%[15] and 44[15] to 54[14] years). A family history of the disease was rather more frequent than in other cohorts (78.1% of cases vs 21%[13]–35%: SCD 40%, HCM 60.5%), which might be related to the detailed clinical evaluation and family screening performed at dedicated cardiomyopathies units.

Most of the variants in our cohort are clustered around position number 850. We did not find a correlation between clinical variables and variant position. The high frequency of variants in these regions allows us to hypothesise about a potential mutational hotspot located in this immunoglobulin domain. Despite Sanger being the predominant genotyping method (51% of all cases), the finding of second variants was more frequent than in other cohorts (18.4% vs 6%[7]–13%[16]), probably due to the refinement of NGS tools. However, only 0.68% were considered pathogenic/likely pathogenic.

LV hypertrophy showed an age-dependent penetrance among carriers in our cohort (47.1% at 30, and 71.1% at 60 vs 31% in ≤20[17] and 83% at ≥50[17]). On the other hand, only 10% of relatives developed the phenotype at 7.8 years of follow-up. Incomplete age-dependent penetrance is a known characteristic of most mutations associated with HCM, particularly in *MYBPC3*.[17] The low penetrance of relatives carrying the mutation might be related to a strong influence of genetic or environmental modulators in phenotype development.

In terms of the severity of the phenotype, our cohort shows a similar maximum wall thickness to previous HCM and *MYBPC3*-associated HCM cohorts.[2 14 17 18] However, there[19] was a lower prevalence and severity of LV outflow tract obstruction at diagnosis. Although it might be explained by a smaller proportion of patients in our cohort evaluated by stress echocardiography, it is still low (16.3% vs 39%[14]) when compared with previous (*MYBPC3*-related and general) HCM cohorts.[17 19]

In line with previous literature,[14] most patients were symptomatic at the initial evaluation (55.1%). During follow-up, 55.7% became asymptomatic, highlighting the importance of treatment optimisation.

Clinical events and risk

In contrast to as noted about sarcomeric[2] and *MYBPC3*[18] variants, our cohort showed a low prevalence of arrhythmic events and more HF than probably expected. Non-major arrhythmias, such as non-sustained VT and AF, were more common in the follow-up than previously described (30.3% vs 12%,[2 15] and 30% vs 20%,[14 15] respectively).

Strikingly, more primary prevention ICDs were implanted than in other cohorts (27.7% vs 16%[14]–21%[15]) with a similar percentage of appropriate therapies. The number of ICD implants exceeded expectations, particularly in a context where the majority were considered low risk (average HCM risk-score average: 2.44±1.54, median 2.08). This outcome may be associated with the care provided at tertiary centres. It is important to consider that other factors in risk stratification (such as LGE, LV dysfunction, aneurysms) and other clinical situations (including bradycardias, SRT, etc) may have influenced medical decisions. The HCM-risk score should be interpreted as a guideline, rather than an infallible measure.[20]

Death rate during follow-up was 9.45%, similar to the 8% described in other HCM cohorts.[15] HF represented the main complication, with a similar prevalence to other sarcomeric cohorts (16% vs 22%[15]), but with poorer outcomes (8% of patients developed EF<40% or HF hospitalisations, 3.4% end-stage HF[14] and 2.6% were transplanted[14]). HF usually coexisted with a second clinical hit. HF development, particularly HFrEF, and its correlation with major events in HCM are explained by disease progression.

LVEF is not a reliable tool to measure ventricular function in HCM patients. All three dimensions of contraction can be abnormal long before a decreased EF.[21] LVEF 60% is considered the current threshold for ventricular dysfunction in HCM.[22 23] Moreover, our threshold after statistical analysis (maximally selected rank statistics) was 58%, which could be considered equivalent to the standard when considering intercycle and interoperator variability. Near normal or lower limit EF (<50%) is commonly considered an 'end-stage' of disease[24], possibly explaining its association with major events in our cohort.

We did not find an association between the ESC SD-risk score and major events. Most traditional risk markers as maximum wall thickness were not significantly associated with major events.[17] These could be explained by the lack of power derived from the good prognosis and the low rate of events.

Nevertheless, the presence of subtle left dysfunction, older age and abnormal QRS, which might only indicate disease progression, were found to be associated with events.[20] Only polymorphic ventricular extrasystoles were related to CV death.

In terms of the wider QRS and abnormal ECG, fragmented QRS is a representation of a non-homogeneous ventricular activation, and it may indicate the presence of fibrosis.[24 25] Moreover, it had been previously linked to more clinical events, an increased risk of CV death[26] and SD.[27 28]

Both genders had similar prognoses associated with *MYBPC3* truncating variants HCM, with slightly higher—but not statistically significant—rates of major events in females during follow-up. Women have also demonstrated a worse clinical course in general HCM cohorts,[29] probably due to a bias resulting in delayed diagnosis, as observed in our cohort.

Limitations and strengths

These results emanate from retrospective data from 14 different tertiary hospitals, with the limitations inherent to this type of design. That includes the lack of data in certain areas as the result of stress TTE in our case. The possibility of ascertainment bias must be considered. Patients were recruited in highly specialised units, with a possible enrichment of complicated cases, closer monitoring of patients and higher guidelines-directed therapy prescription. Additionally, the small number of events in our cohort makes it difficult to draw conclusions about the associated risk factors.

CONCLUSION

We submit a cohort of 148 patients with truncating variants in *MYBPC3*. This is the first molecular homogeneous cohort in HCM. Patients were followed for 7.7 years, proving a predominantly benign behaviour, with low mortality and major events rate. Neither accepted risk models nor genetic factors were able to predict arrhythmic/death events in our cohort. HF was the main clinical event, and it was often accompanied by the presence of a clinical second hit. Further studies of homogeneous cohorts are necessary to correctly assess the genotype–phenotype correlations in HCM.

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