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REVIEW

Natural history and clinical outcomes of patients with hypertrophic cardiomyopathy from thin filament mutations

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Abstract

Hypertrophic cardiomyopathy (HCM) due to thick filament variants is more common; however, HCM due to thin filament variants (HCM-Thin) may be associated with a more malignant phenotype with an increased risk of sudden cardiac death. The aim of this study was to review all the published cases of HCM-Thin to better understand the natural history and clinical outcomes of this disease. A literature review of HCM-Thin identified 21 studies with a total of 177 patients that were suitable for analysis. There were three outcomes of interest, which included a heart failure composite, a ventricular arrhythmia composite and a heart failure and arrhythmia composite outcome. Kaplan–Meier (KM) survival analyses for freedom from each of the above-mentioned composite outcomes were completed for the entire cohort and stratified by age of onset and sarcomeric variant. The heart failure composite occurred in 24 (13.6%) patients, the ventricular arrhythmia composite occurred in 30 patients (16.9%) and the combined heart failure and arrhythmia composite occurred in 50 patients (28.2%). In regard to left ventricular ejection fraction (LVEF), the majority of patients were preserved (LVEF $>$ 50%) compared with mildly reduced (LVEF 41%–50%) and reduced (LVEF $\leq$ 40%) (respectively 26.6% vs. 0.6% vs. 3.4%). The median maximal left ventricular wall thickness (LVWT) was 19.0 mm [interquartile range (IQR) 5.3]. Only 10.7% of the cohort had evidence of left ventricular outflow tract (LVOT) obstruction. Those with paediatric-onset HCM had earlier onset and were at higher risk for each endpoint than their adult counterparts. When stratified by genetic variant, patients with TNNI3 and TPM1 were at a higher risk of the heart failure composite endpoint and the combined heart failure and arrhythmia composite endpoint in comparison with those with the other genetic variants. HCM-Thin is associated with significant morbidity and mortality, with a high arrhythmia burden despite low rates of cardiac obstruction and mild hypertrophy. The paediatric onset of disease and certain sarcomeric variants appear to be associated with a worse prognosis than their adult-onset and other sarcomeric variant counterparts. HCM-Thin seems to have a distinct phenotype, which may require a different management approach.

Keywords hypertrophic cardiomyopathy; sudden cardiac death; thin filament; ventricular arrhythmia

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy, with an estimated prevalence of 1 in 500 people and over 1400 pathogenic variants identified. The genotype–phenotype associations are highly complex and variable, so the disease manifestations can be diverse.[1–7] In HCM, the majority of pathogenic variants affect the thick filaments (beta myosin heavy chain and myosin binding protein C), while those involving the thin filaments, including cardiac troponin T, I and C (*TNNT2*, *TNNI3*, *TNNC1*), α-tropomyosin (*TPM1*) and cardiac actin (*ACTC*), are only seen

in 10%–30% of cases.[8–14] Early small studies characterized HCM patients with a thin filament variant (HCM-Thin) as having more malignant phenotypes with a higher burden of lethal arrhythmias and sudden cardiac death (SCD) despite only having mild left ventricular hypertrophy (LVH) and lower rates of resting left ventricular outflow tract (LVOT) obstruction compared with those with HCM and a thick filament variant (HCM-Thick). Subsequent, larger studies have challenged these findings, suggesting no difference in SCD and ventricular arrhythmias when comparing sarcomere locations.[14–16] It has also been recognized that paediatric-onset HCM confers a higher risk of ventricular arrythmias and advanced heart failure (HF) compared with their adult-onset counterparts; however, it is unclear if there may be a difference in risk profile within the paediatric-onset HCM population depending on sarcomere location.[17]

The aim of this study was to systematically review all the published cases of HCM-Thin to better understand the natural history and clinical outcomes of this patient population.

Methods

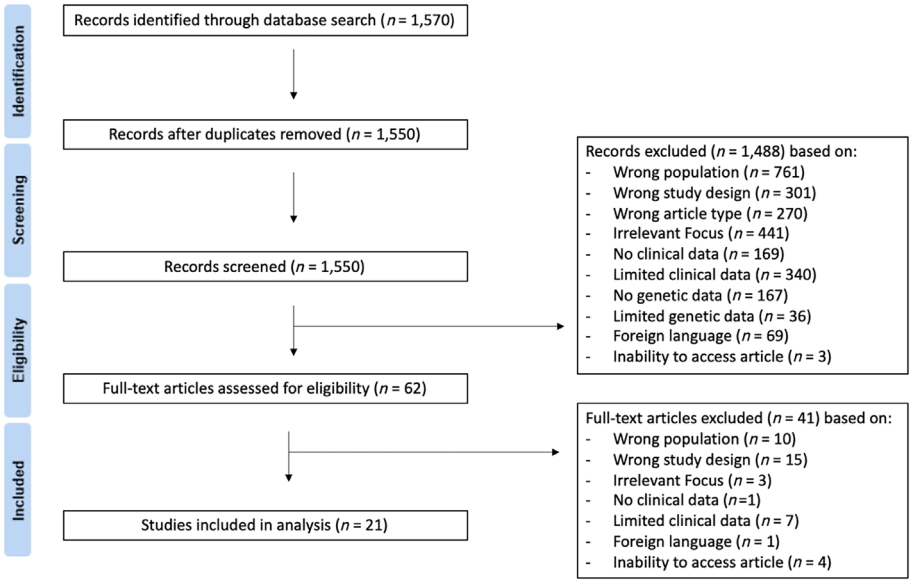
Search strategy

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for a scoping review. A compilation of HCM-Thin articles was created by searching PubMed on 30 January 2024 with the following key terms: (Hypertrophic Cardiomyopathy OR Left Ventricular Hypertrophy) AND (Thin Filament OR Troponin OR Tropomyosin OR Actin OR TNNT2 OR TNNI3 OR TPM1 OR ACTC) AND (Human OR Humans). Both case reports and case series were included, with the caveat that the latter had clinical information for every case (*Figure* 1).

Data extraction and management

References were uploaded into Rayyan, and duplicates were removed. Three independent authors (Q. M. B., T. S. and L. K.) manually filtered eligible studies based on the full texts and abstracts. Studies were excluded for various reasons, including the wrong population (i.e., animal models, other diseases, non-pathogenic variants or different types of variants), the wrong article type (i.e., editorial or review), an unavailable full text, incomplete genetic data, incomplete clinical data and a foreign language. Sixty-two articles remained eligible after the exclusion criteria were applied, as described above. Additional texts were excluded from this study subsequently for inaccessibility (n = 4), foreign language (n = 1), wrong study design (n = 15), limited clinical data (n = 7), no clinical data (n = 1), wrong population (n = 10) and irrelevant focus (n = 3), leaving 21 manuscripts for final analysis (Table S2). The reviewers could eliminate a study for different reasons, and thus, a single manuscript may have met more than one elimination criterion. All data were extracted from article texts, tables and figures and managed using Microsoft Excel. HCM was defined as a maximal left ventricular wall thickness (LVWT) >15 or 13 mm associated with a family history of HCM. HCM-Thin was defined by a confirmed pathogenic or likely pathogenic thin filament variant on genetic testing with

Figure 1 Study flow diagram.



a diagnosis of HCM. Patients with non-pathogenic variants defined as 'variant of uncertain significance', 'likely benign' or 'benign' were excluded. Reported symptoms, electrocardiogram (ECG) and echocardiogram data were collected for the entire cohort. An abnormal ECG was defined as an ECG that had evidence of atrial arrhythmias (atrial fibrillation, atrial flutter and supraventricular tachycardia), ventricular arrhythmias [premature ventricular contractions, ventricular tachycardia (VT) and ventricular fibrillation (VF)], conduction abnormalities [bundle branch block and varying degrees of atrioventricular (AV) block], LVH or ST/T wave abnormalities. For categorical variables, missing data were included in the analysis. Available data from each manuscript can be reviewed in Table S3.

Outcomes

There were three composite outcomes of interest. The first was an HF composite outcome that included all-cause death, heart transplant (HTx) or left ventricular assist device (LVAD) implantation. The second was a ventricular arrhythmia composite, which included SCD, VT, VF and an implantable cardio-defibrillator (ICD) placed for secondary prevention. The third was an HF and arrhythmia composite, which included the components of the HF composite outcome, the ventricular arrhythmia composite outcome and atrial fibrillation/flutter. Additional outcomes included left ventricular ejection fraction (LVEF) $<$ 50%, HF hospitalizations, New York Heart Association (NYHA) functional class III/IV, ICD implantation for any indication and atrial fibrillation. Kaplan–Meier (KM) survival analyses for freedom from each of the abovementioned composite outcomes were completed for the entire cohort and stratified by age of onset (paediatric vs. adult) as well as genetic variants, including TNNT2, TNNI3 and TPM1 (ACTC and TNNC1 were excluded given low *n*, respectively, *n* = 2 and *n* = 4). Paediatric was defined as $<$18 years old, while adult was defined as $\geq$18 years old.

Statistical methods

Continuous variables were reported either as a mean with standard deviation or as a median with an interquartile range (IQR) based on the normality of the distribution. Differences in continuous variables were tested using the Student *t*-test or the Mann–Whitney *U* test. Categorical variables were expressed as counts with percentages and compared using the χ^2 test. A KM estimate of mortality was performed and was compared for all groups using the log-rank test. For all analyses, a *P*-value $<$ 0.05 was considered statistically significant. Statistical analyses and figures were completed using SPSS Version 28.0 (IBM Corp., Armonk, NY, USA).

Results

Selection of patients

The selection of HCM-Thin patients is summarized in *Figure* 1. The PubMed query yielded 1550 unique studies for evaluation. After the exclusion criteria were applied, 21 manuscripts remained suitable for analysis.

Demographics

A total of 177 patients with HCM-Thin were identified. Patients were predominantly male (57.1%), with a mean

Table 1 Baseline characteristics stratified by age of disease onset.

	Cohort total (*n* = 177)	Cohort total (*n* = 176)		
		Paediatric onset (*n* = 29)	Adult onset (*n* = 147)	
Baseline characteristics	Number of patients, *n* (%), or age of diagnosis (SD) or maximal LVWT (IQR) or LVEF (IQR)			*P*-value
Male	101 (57.1)	22 (75.9)	78 (53.1)	0.023
Age at diagnosis, mean (SD), years	34.0 (17.0)	13.1 (3.5)	39.4 (14.7)	$<$0.001
Proband	66 (37.3)	17 (58.6)	49 (33.3)	0.008
Race				
White	23 (13.0)	2 (6.9)	21 (14.3)	0.281
Black	2 (1.1)	0 (0)	2 (1.4)	0.528
Asian	20 (11.3)	0 (0)	20 (13.6)	0.035
Maximal LVWT, median (IQR), mm	19.0 (5.3)	18.5 (5.8)	19.0 (5.8)	0.726
LVOT obstruction	19 (10.7)	3 (10.3)	16 (10.9)	0.728
LVEF, median (IQR), %	62.0 (8.7)	62.0 (10.0)	63 (12.3)	0.581
Abnormal ECG	104 (58.8)	12 (41.4)	92 (62.6)	0.034
LVH ECG	25 (14.1)	3 (10.3)	22 (15.0)	0.307
ST/T changes ECG	55 (31.1)	3 (10.3)	52 (35.4)	$<$0.001

Abbreviations: ECG, electrocardiogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness.

Table 2 Baseline characteristics stratified by heart failure composite outcome.

		Cohort total (n = 177)	
	Cohort total (n = 177)	No HF composite outcome (n = 153)	HF composite outcome (n = 24)	
Baseline characteristics	Number of patients, n (%), or age of diagnosis (SD) or maximal LVWT (IQR) or LVEF (IQR)			P-value
Male	101 (57.1)	83 (54.2)	18 (75.0)	0.056
Age at diagnosis, mean (SD), years	34.0 (17.0)	36.2 (16.0)	20.5 (17.2)	<0.001
Proband	66 (37.3)	58 (37.9)	8 (33.3)	0.884
Race				
White	23 (13.0)	23 (15.0)	0 (0)	0.042
Black	2 (1.1)	0	2 (8.3)	<0.001
Asian	20 (11.3)	17 (11.1)	3 (12.5)	0.842
Maximal LVWT, median (IQR), mm	19.0 (5.3)	19.0 (6.0)	17.0 (4.0)	0.163
LVOT obstruction	19 (10.7)	19 (12.4)	0 (0)	0.093
LVEF, median (IQR), %	62.0 (8.7)	62.0 (9.1)	48.0 (42.3)	0.236
Abnormal ECG	104 (58.8)	93 (60.8)	11 (45.8)	0.167
LVH ECG	25 (14.1)	21 (13.7)	4 (16.7)	0.901
ST/T changes ECG	55 (31.1)	54 (35.3)	1 (4.2)	<0.001

Abbreviations: ECG, electrocardiogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness.

age at diagnosis of 34 ± 17 years old, and represented a multinational population; however, only a quarter of the cohort had a reported race. Approximately one third of the cohort were probands (*Tables* 1–4).

Genetics

A genetic variant for HCM-Thin was confirmed in 100% of the patients. The most frequent variants were reported in the TNNT2 (41.2%), TPM1 (28.2%) and TNNI3 (27.1%) genes (Figure S1A). The type of genetic variant was available for approximately half of the cohort, with the most common being missense (33.3%) and frameshift (6.8%) (Figure S1B).

Baseline characteristics and phenotypes

In regard to ejection fraction, the majority were preserved (LVEF $>$ 50%) compared with mildly reduced (LVEF 41%–50%) and reduced (LVEF $\leq$ 40%) (respectively 26.6% vs. 0.6% vs. 3.4%). Nearly two thirds of the cohort had reported HF symptoms, with 10.2% of the cohort reporting NYHA classes III–IV (Table S1). The median maximal LVWT was 19.0 mm (IQR 5.3). Only 10.7% of the cohort had evidence of LVOT obstruction. When comparing paediatric- to adult-onset disease, there were no significant differences in maximal LVWT, LVOT obstruction or LVEF; however, abnormal ECGs (62.6% vs. 41.4%, P = 0.034) and ST/T changes (35.4% vs. 10.3%, P < 0.001) were seen more frequently in adult-onset compared with paediatric-onset HCM-Thin (*Table* 1).

Table 3 Baseline characteristics stratified by ventricular arrhythmia composite outcome.

		Cohort total (n = 177)	
	Cohort total (n = 177)	No ventricular arrhythmia composite (n = 147)	Ventricular arrhythmia composite (n = 30)	
Baseline characteristics	Number of patients, n (%), or age of diagnosis (SD) or maximal LVWT (IQR) or LVEF (IQR)			P-value
Male	101 (57.1)	80 (54.4)	21 (70.0)	0.116
Age at diagnosis, mean (SD), years	34.0 (17.0)	35.2 (16.9)	27.0 (15.9)	0.053
Proband	66 (37.3)	57 (38.8)	9 (30.0)	0.665
Race				
White	23 (13.0)	22 (15.0)	1 (3.3)	0.084
Black	2 (1.1)	0 (0)	2 (6.7)	0.002
Asian	20 (11.3)	14 (9.5)	6 (20.0)	0.099
Maximal LVWT, median (IQR), mm	19.0 (5.3)	19.0 (5.0)	18.5 (6.3)	0.740
LVOT obstruction	19 (10.7)	19 (12.9)	0 (0)	0.047
LVEF, median (IQR), %	62.0 (8.7)	64.0 (10.0)	60.0 (37.3)	0.053
Abnormal ECG	104 (58.8)	79 (53.7)	25 (83.3)	0.003
LVH ECG	25 (14.1)	15 (10.2)	10 (33.3)	0.018
ST/T changes ECG	55 (31.1)	53 (36.1)	2 (6.7)	<0.001

Abbreviations: ECG, electrocardiogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness.

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Table 4 Baseline characteristics stratified by heart failure and arrhythmia composite outcome.

		Cohort total (n = 177)		
	Cohort total (n = 177)	No HF or arrhythmia composite (n = 127)	HF and/or arrhythmia composite (n = 50)	
Baseline characteristics	Number of patients, n (%), or age of diagnosis (SD) or maximal LVWT (IQR) or LVEF (IQR)			P-value
Male	101 (57.1)	67 (52.8)	34 (68.0)	0.065
Age at diagnosis, mean (SD), years	34.0 (17.0)	35.7 (16.3)	29.4 (18.2)	0.057
Proband	66 (37.3)	46 (36.2)	20 (40.0)	0.436
Race				
White	23 (13.0)	18 (14.2)	5 (10.0)	0.457
Black	2 (1.1)	0 (0)	2 (4.0)	0.023
Asian	20 (11.3)	13 (10.2)	7 (14.0)	0.476
Maximal LVWT, median (IQR), mm	19.0 (5.3)	19.0 (5.0)	18.0 (6.2)	0.667
LVOT obstruction	19 (10.7)	17 (13.4)	2 (4.0)	0.086
LVEF, median (IQR), %	62.0 (8.7)	64.0 (10.0)	60.0 (22.0)	0.100
Abnormal ECG	104 (58.8)	68 (53.5)	36 (72.0)	0.025
LVH ECG	25 (14.1)	14 (11.0)	11 (22.0)	0.351
ST/T changes ECG	55 (31.1)	49 (38.6)	6 (12.0)	<0.001

Abbreviations: ECG, electrocardiogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness.

Clinical outcomes

The HF composite of all-cause death, HTx or LVAD implantation occurred in 24 patients (13.6%). The ventricular arrhythmia composite, which included SCD, VT/VF and ICD for secondary prevention, occurred in 30 patients (16.9%). The HF and arrhythmia composite, which included the components of the HF composite, ventricular arrhythmia composite and atrial fibrillation/flutter, was present in 50 patients (28.2%). All three composite outcomes were more common in the paediatric-onset group compared with the adult-onset group (HF composite: 37.9% vs. 8.8%, $P < 0.001$; ventricular arrhythmia composite: 34.5% vs. 13.6%, $P = 0.006$; and HF and arrhythmia composite: 44.8% vs. 23.1%, $P < 0.001$) (Table S1). ICD implantation for any indication was higher in paediatric-onset compared with adult-onset HCM (41.4% vs. 12.2%, $P = 0.001$); however, there was no statistically significant difference in regard to ICD placement for secondary prevention between paediatric- and adult-onset HCM. Between paediatric- and adult-onset HCM, there was also no statistically significant difference in their echocardiographic parameters, including LVEF, maximal LVWT or LVOT obstruction. However, those with adult-onset HCM reported more HF symptoms than their paediatric-onset counterparts (NYHA functional class III/IV: 11.6% vs. 3.4%, $P = 0.030$).

Patients who experienced the HF composite outcome were younger compared with those who did not (age at diagnosis: 20.5 ± 17 vs. 36 ± 16, $P < 0.001$). Also, those with ST/T changes on the ECG were less likely to experience all three composite outcomes ($P < 0.001$ for all three); however, those with an abnormal ECG in general were more likely to experience the ventricular and HF/arrhythmia composite outcomes. There was no difference in LVEF, maximal LVWT or prevalence of LVOT obstruction between patients with and without the composite outcomes, except that those with LVOT obstruction were less likely to experience the ventricular arrhythmia composite (12.9% vs. 0%, $P = 0.047$) (*Table*s 2–4).

Survival without the HF composite outcome was 90% at 20 years of age and 80% at 60 years of age in the whole population (*Figure* 2A). Survival without the ventricular arrhythmia composite outcome was 90% at 20 years of age and 70% at 60 years of age (*Figure* 3A). Survival without the combined HF/arrhythmia composite endpoint was 90% at 20 years of age and 60% at 60 years of age (*Figure* 4A). Survival curves for the HF composite endpoint, ventricular arrhythmia composite endpoint and combined HF/arrhythmia composite endpoint were significantly different between patients with paediatric- and adult-onset HCM (*Figure*s 2B, 3B and 4B) in that those with paediatric-onset HCM had earlier onset and were at higher risk for the endpoint than their adult counterparts.

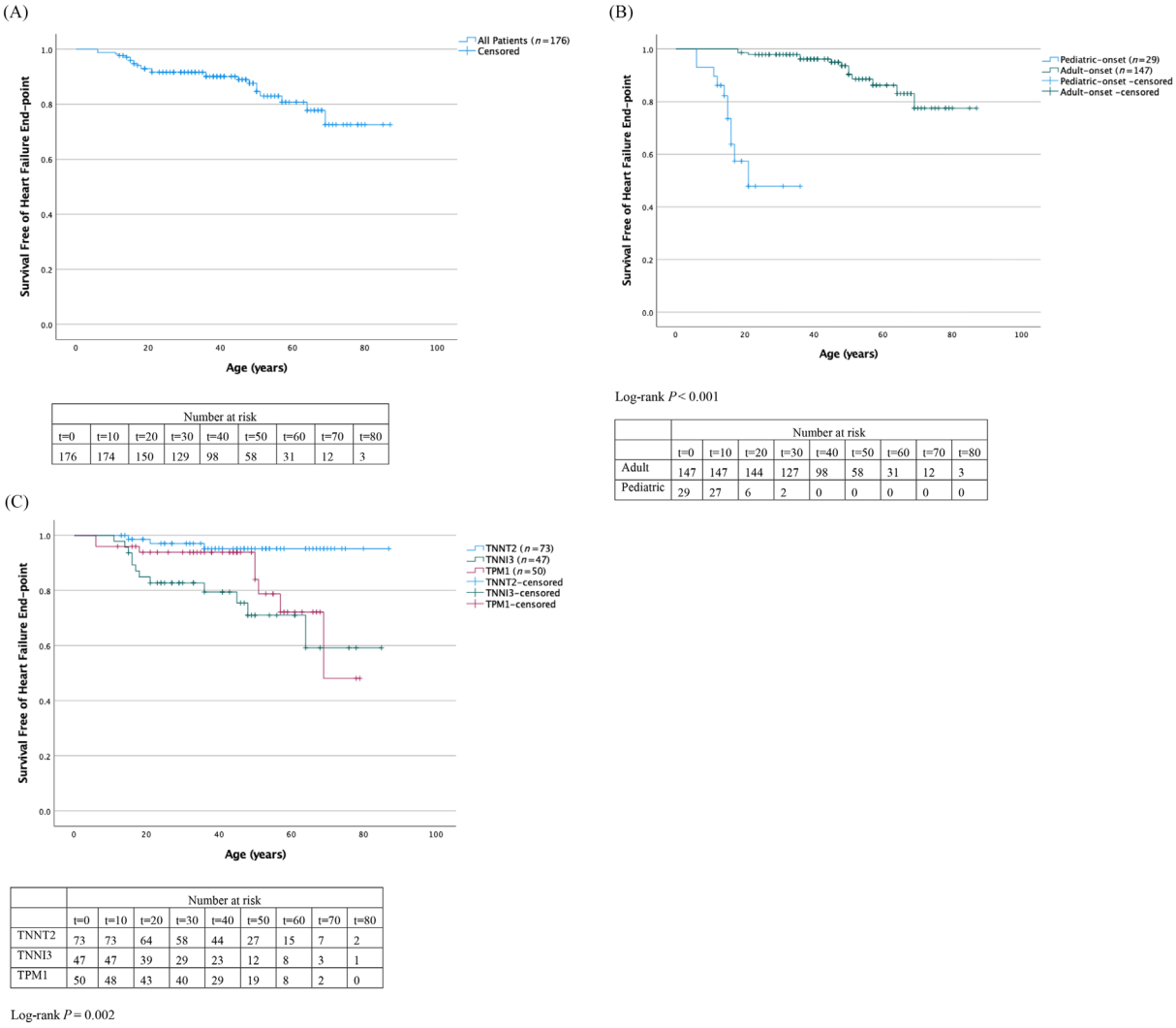
When stratified by genetic variant, patients with TNNI3 and TPM1 had a higher risk of the HF endpoint and the HF and arrhythmia composite endpoint compared with those with TNNT2 (*Figure*s 2C and 4C). HCM due to TPM1 variants had a higher risk of ventricular arrhythmias, although not statistically significant (*Figure* 3C).

Discussion

In this analysis, we demonstrate that patients with HCM-Thin have high morbidity and mortality despite mild LVH, low rates of outflow tract obstruction and preserved LVEF.

Patients with HCM-Thin in the study by Coppini *et al*. showed a higher rate of progression to NYHA class III/IV, worse diastolic dysfunction and a higher prevalence of systolic dysfunction in comparison with their HCM-Thick counterparts. Cardiac magnetic resonance imaging of patients

Figure 2 Kaplan–Meier curves for thin filament cardiomyopathy, assessing survival free of heart failure endpoints: (A) all patients, (B) stratified by paediatric versus adult onset of disease and (C) stratified by genetic mutation.



Number at risk									
t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
176	174	150	129	98	58	31	12	3

Log-rank $P < 0.001$

	Number at risk								
	t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
Adult	147	147	144	127	98	58	31	12	3
Pediatric	29	27	6	2	0	0	0	0	0

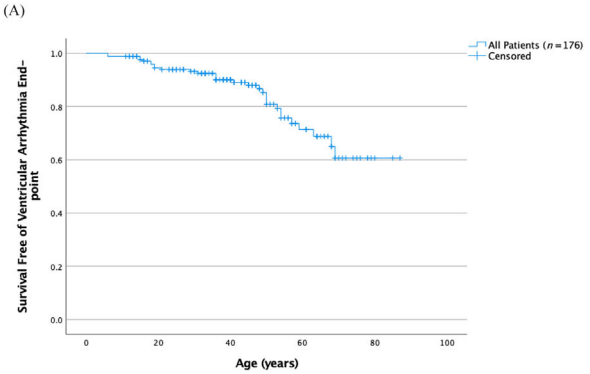
	Number at risk								
	t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
TNNT2	73	73	64	58	44	27	15	7	2
TNNI3	47	47	39	29	23	12	8	3	1
TPM1	50	48	43	40	29	19	8	2	0

Log-rank $P = 0.002$

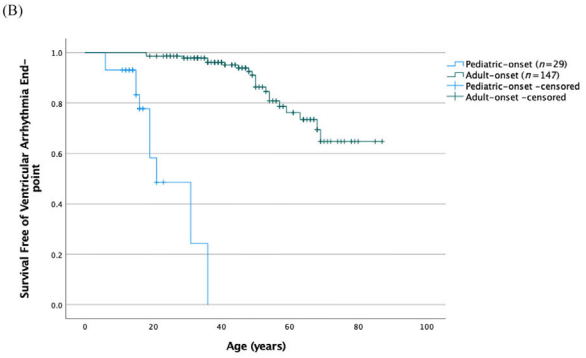
with HCM-Thin showed a greater amount of fibrosis in comparison with those with HCM-Thick.[14] This is further supported by the SHaRe (Sarcomeric Human Cardiomyopathy Registry) HCM registry, which showed that patients with sarcomeric positive variants, and particularly thin filament variants, had the highest risk of developing left ventricular systolic dysfunction, which was associated with higher mortality and the need for advanced therapies.[18] Our study also demonstrates high HF morbidity and mortality; however, the HCM-Thin cohort in our study also showed a trend towards a higher risk of SCD and ventricular arrhythmias.

The SHaRe offers a contemporary dataset of sarcomeric-positive HCM patients. As the SHaRe cohort includes patients with both thick and thin filament variants and our cohort includes only patients with thin filament variants, we understood that comparing the two cohorts would have its limitations, but the differences would be hypothesis generating. The HCM-Thin population from our cohort had a higher ventricular arrhythmia endpoint in comparison with the SHaRe cohort (16.9% vs. 8.0%).[19] Despite this difference in ventricular arrhythmias, the presence of an ICD (16.9% vs. 30.0%) was higher in the SHaRe cohort. Notably, the presence of LVOT obstruction (10.7% vs. 21.0%) was also higher in the SHaRe cohort, although NYHA symptoms and LVWT were relatively the same between the cohorts. The findings are similar when the data from our cohort are compared with the thick filament cohort of 150 patients from the 2014 Coppini *et al.* manuscript.[14] For example, 16.9% of the HCM-Thin population in our cohort had the ventricular arrhythmia endpoint in comparison with 5% of the Coppini HCM-Thick cohort who had sustained VT. However, the Coppini cohort did not include the other components of our

Figure 3 Kaplan–Meier curves for thin filament cardiomyopathy, assessing survival free of ventricular arrhythmia endpoints: (A) all patients, (B) stratified by paediatric versus adult onset of disease and (C) stratified by genetic mutation.

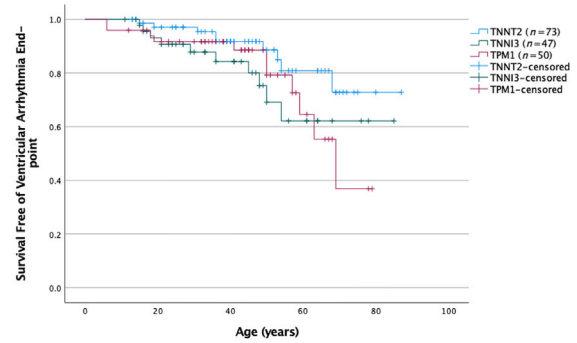


Number at risk								
t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
176	174	150	129	98	58	31	12	3



	Number at risk								
	t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
Adult	147	147	144	127	98	58	31	12	3
Pediatric	29	27	6	2	0	0	0	0	0

Log-rank $P < 0.001$



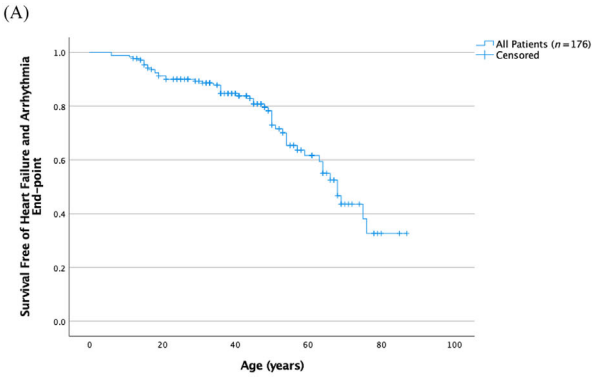
	Number at risk								
	t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
TNNT2	73	73	64	58	44	27	15	7	2
TNNI3	47	47	39	29	23	12	8	3	1
TPM1	50	48	43	40	29	19	8	2	0

Log-rank $P = 0.181$

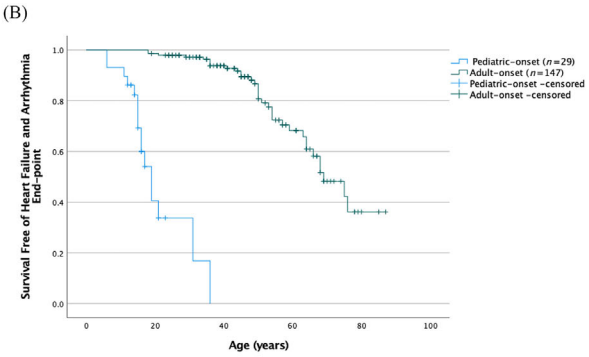
composite endpoint, which may also account for this difference. Nevertheless, despite this difference in ventricular arrhythmias, the placement of an ICD (16.9% vs. 24.0%) was higher in the Coppini HCM-Thick cohort. Similar to the SHaRe cohort, the HCM-Thick cohort had more LVOT obstruction (10.7% vs. 34.0%) and the same amount of reported NYHA III/IV symptoms in comparison with our cohort. Furthermore, those with HCM-Thick had thicker myocardiums than those with HCM-Thin (LVWT: 24 vs. 19 mm). These comparisons suggest that patients with HCM-Thin have a more malignant phenotype in regard to ventricular arrhythmias, and, despite this increased risk, they are not receiving appropriate ICD implantation as they may not meet traditional guideline criteria.[20] Given the under-utilization of the ICD and risk of fatal arrhythmia in the HCM-Thin population found in our study, further prospective studies are needed to confirm the increased risk of SCD and assist in the development of better SCD prediction tools in patients with HCM-Thin.

In our study, patients with paediatric-onset disease showed a worse prognosis compared with those with adult-onset disease, given that they had an earlier onset and increased risk of all three composite endpoints, which included atrial and ventricular arrythmias, SCD, all-cause death and ventricular assist device (VAD)/transplant. Marston *et al*. showed that the natural history of sarcomeric HCM differs in paediatric- versus adult-onset disease, with a 36% increased risk of life-threatening ventricular arrythmias and a two-fold increase in HTx or LVAD implantation in the former.[17] Furthermore, patients with paediatric-onset HCM had an increased risk of lethal arrhythmic events, which followed them

Figure 4 Kaplan–Meier curves for thin filament cardiomyopathy, assessing survival free of heart failure and arrhythmia endpoints: (A) all patients, (B) stratified by paediatric versus adult onset of disease and (C) stratified by genetic mutation.

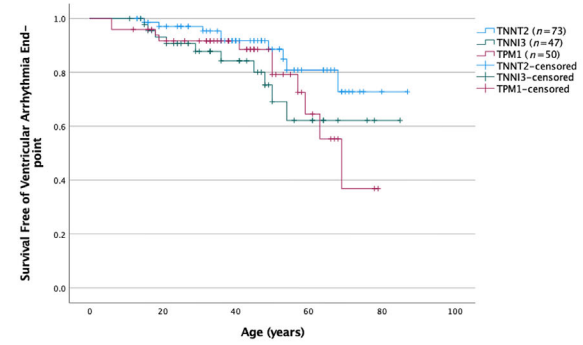


Number at risk								
t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
176	174	150	129	98	58	31	12	3



	Number at risk								
	t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
Adult	147	147	144	127	98	58	31	12	3
Pediatric	29	27	6	2	0	0	0	0	0

Log-rank $P < 0.001$



	Number at risk								
	t=0	t=10	t=20	t=30	t=40	t=50	t=60	t=70	t=80
TNNT2	73	73	64	58	44	27	15	7	2
TNNI3	47	47	39	29	23	12	8	3	1
TPM1	50	48	43	40	29	19	8	2	0

Log-rank $P = 0.017$

into adulthood.[21] It is clear that those with paediatric-onset HCM have a higher risk of morbidity and mortality, and this finding is demonstrated in our study in those who only have HCM-Thin. Paediatric-onset HCM-Thin may then be a very high-risk group for SCD; however, further prospective studies are needed to confirm this risk profile in comparison with those with paediatric-onset HCM-Thick disease.

Specific thin filament variants may further risk stratify patients with HCM-Thin, as those with TNNI3 and TPM1 trended towards a higher risk of death and the need for advanced therapies, as well as the combined HF/arrhythmia composite endpoint. Based on these findings, simple genetic testing may provide important prognostic information for patients with HCM-Thin. Particularly, paediatric-onset patients are more likely to have sarcomeric disease, and thus, the yield and predictive value of genetic testing may be higher in that population.[17] However, further study will be required to determine whether specific pathogenic variants or types of mutations are associated with malignant phenotypes.

The optimal functioning of the sarcomere depends on the interaction between thick (beta myosin heavy chain and myosin binding protein C) and thin filaments (cardiac troponin T, I and C, α-tropomyosin and cardiac actin). The sliding of actin filaments past the myosin fibrils, driven by the power stroke of the myosin motor heads, leads to sarcomere shortening and thus muscular contraction. The process is highly regulated by the troponin complex (cTnI, cTnT and cTnC) and tropomyosin. The troponin–tropomyosin complex plays a regulatory function, impeding inappropriate sarcomere shortening at low calcium concentrations and allowing adequate

sarcomere relaxation. Mutations in the gene encoding for these proteins may lead to an increase in calcium sensitivity, leading to diastolic dysfunction and increased energy consumption that could lead to fibrotic replacement and adverse remodelling.[22,23] The described pathophysiological characteristics may explain the high rate of adverse events in this population, including both HF and arrhythmias.

Over the years, significant progress in understanding the clinical presentation and genetic underpinnings of HCM has been achieved, but translating genotype–phenotype relationships to outcomes and treatments has proven to be more difficult.[11] Mavacamten, the first-in-class cardiac myosin inhibitor, has demonstrated reversal of increased calcium sensitivity and dysregulation of calcium flux, which are fundamental to the thin filament variant disease process at the molecular level.[11,24] Thus far, mavacamten has shown improvement in symptoms related to LVOT obstruction; however, its efficacy in non-obstructive disease has yet to be demonstrated.[25] Gene editing and gene replacement are some of the gene therapy approaches that have been used. However, at the moment, the studies have focused on the treatment of thick filament variants.[26] Before such therapies can be implemented, longitudinal studies further defining the heterogenous genotype–phenotype linkages will be crucial to patient risk stratification and management.

Limitations

This study involved a small sample size, but HCM-Thin is a rare disease. One of the significant limitations of our study is publication bias, which can affect the type and frequency of events and outcomes. Although a review of the grey literature may have been beneficial, it is unclear if it would have provided a different outcome or minimized bias. Furthermore, there was also a risk of selection bias. The studies also did not always provide a time frame or explicitly state whether a patient did not have a certain outcome; thus, the outcomes and/or interventions may have been underestimated or overestimated. We also excluded papers with incomplete clinical data or written in a foreign language, which may have also caused a systematic variation in outcomes. A relatively modest sample size, as our paper had, can affect the latter as well. We attempted to reduce the risk of bias by conducting a dual review, defining inclusion and exclusion criteria clearly and being mindful about excluding studies based on outcomes of interest. Nonetheless, this study may have identified more symptomatic patients with HCM-Thin as opposed to a more malignant phenotype. Thus, these findings are largely hypothesis generating and need to be validated, ideally prospectively. Nonetheless, previous analyses of these genetic cardiomyopathies have demonstrated concordance with subsequent natural history studies.[27,28] While a prospective study would be preferable, given the rarity of these variants, this may be difficult to perform. Lastly, as we used case reports/studies in this analysis, we were unable to perform an assessment of the heterogeneity of the manuscripts.

Conclusions

Our review suggests that thin filament cardiomyopathy is associated with significant morbidity and mortality, with a high prevalence of advanced HF and arrhythmia burden, despite low rates of cardiac obstruction and only mild hypertrophy. The paediatric onset of disease portends a worse prognosis marked by an increase in all-cause death, advanced therapies and atrial and ventricular arrhythmias. These data suggest that thin filament may be a unique endotype that may deserve distinct therapeutic approaches.

Conflict of interest statement

Some of the co-authors have industry relationships to disclose, as below:

Author	Disclosures
Quan M. Bui, MD	Consulting: EcoR1 and Lexeo Therapeutics.
Alessia Argiro, MD	Consulting: Lexeo Therapeutics.
Iacopo Olivotto, MD	Research grants: BMS-MyoKardia, Cytokinetics, Boston Scientific, Sanofi Genzyme, Shire Takeda, Amicus, Menarini International and Bayer. Advisory board/speaker's bureau: BMS-MyoKardia, Cytokinetics, Boston Scientific, Sanofi Genzyme, Shire Takeda, Amicus and Tenaya.
Eric Adler, MD	Chief Science Officer: Lexeo Therapeutics. Consulting: Abiomed, Abbott, Medtronic, Lexeo Cytokinetics and Endotronics. Advisory board: AstraZeneca. Advisory board: Papillion Therapeutics and Corstasis Pharmaceuticals.

The remaining authors have nothing to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. A. Gene mutations and B. Type of Mutation.
Table S1. Clinical Outcomes Stratified by Age of Disease Onset.
Table S2. Studies included in the Meta-Analysis.
Table S3. Data available in each paper.

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