**Genetic and Clinical Determinants of Hypertrophic Cardiomyopathy: A Longitudinal Study of Sarcomeric and Non-Sarcomeric Disease**

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**ABSTRACT:**

***Background***: Rare sarcomere gene variants are a key cause of hypertrophic cardiomyopathy (HCM) but do not account for the majority of patients’ disease. These variants are typically associated with worse clinical outcomes, however the impact of genetic background influences outcomes, the temporal sequence of events, and the association with comorbidities is underexplored.

***Methods***: We conducted a multicenter longitudinal cohort study of genotyped HCM children and adults in the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Patients were classified as sarcomeric HCM (pathogenic/likely pathogenic sarcomere variant) or non-sarcomeric HCM (genetically-elusive). The influence of genetic classification, and comorbidities, on the sequence of cardiovascular events were assessed in time-varying Cox proportional hazards models.

***Results***: Among 6,120 patients (40% female, 87% probands, 50% sarcomeric HCM), with a median follow-up of 5.3 years, sarcomeric HCM (n=3,038) was associated with a younger age at diagnosis (median age 38.1 versus 54.3 years, p<0.001), higher burden and age-standardized incidences (ASI) of atrial fibrillation (ASI ratio 1.28 [CI 1.16-1.40]), LV systolic dysfunction (ASI ratio 1.31 [CI 1.15-1.48]) and ventricular arrhythmias (ASI ratio 1.37 [CI 1.17-1.52]) compared to non-sarcomeric HCM (n=3082). Obesity, hypertension and LV obstruction were more common in non-sarcomeric HCM.

All-cause mortality was similar between groups (10.4% vs. 9.4%), however sarcomeric HCM was associated with younger age at death (mean 7.8 years earlier, p<0.001) and higher HCM-related mortality (HR 1.61 [CI 1.18-2.20]), largely driven by more sudden cardiac death and heart failure.

Temporal analysis identified atrial fibrillation as the strongest modifier of future adverse outcomes, including increased risk of LV systolic dysfunction (HR 2.89 [CI 2.37-3.53]), ventricular arrhythmias (HR 3.17 [CI 2.40-4.20]), and mortality (HR 2.03 [CI 1.72-2.41]) in both groupsInteraction analyses demonstrated that the impact of atrial fibrillation and LV systolic dysfunction on adverse outcomes was higher in sarcomeric HCM, with effect ratios up to 1.97 for severe heart failure and 1.86 for mortality (both p<0.01).

***Conclusions***: Genetic background influences the clinical course of HCM and the impact of cardiovascular comorbidities on adverse outcomes. Sarcomeric HCM was associated with greater risk of severe heart failure, arrhythmias, HCM-related mortality, and worse consequences from atrial fibrillation and LV systolic dysfunction compared to non-sarcomeric HCM. Non-sarcomeric HCM was associated with a higher burden of comorbidities; potentially combining with polygenic risk to cause disease in the absence of a driving monogenic cause.

***Keywords:*** hypertrophic cardiomyopathy, cardiovascular outcomes, heart failure, genetics

**CLINICAL PERSPECTIVE**

**What is new?**

* Sarcomeric HCM has an overall worse clinical trajectory,, with earlier disease onset, more arrhythmias (both atrial and ventricular), and a higher burden of heart failure.
* A higher prevalence of hypertension and obesity was associated with non-sarcomeric HCM, suggesting these comorbidities, in conjunction with polygenic risk, are part of the causal disease pathway in this subgroup.
* Atrial fibrillation was strongly associated with subsequent development of advanced heart failure, ventricular arrhythmias, stroke, and death in all patients, with a larger effect in sarcomeric HCM patients.
* Patients with sarcomeric HCM died earlier than non-sarcomeric HCM patients, and were twice as likely to have HCM-related mortality.

**What are the clinical implications?**

* Patients with sarcomeric HCM are at higher risk for important disease-related adverse outcomes compared with nonsarcomeric, including risk of sudden death and progressive heart failure, thus (?more) vigilant surveillance for cardiac arrhythmias and LV systolic dysfunction is appropriate in these patients.
* Cardiovascular comorbidities, i.e. hypertension and obesity, are more prevalent in patients with non-sarcomeric HCM, suggesting a potential causal link and emphasizing the need for aggressive management of blood pressure and overweight with a possible opportunity for modification of disease severity and trajectory in these patients.

**Abbreviations**

HCM = Hypertrophic cardiomyopathy

ICD = implantable cardioverter defibrillator

LV = Left ventricle

NYHA = New York Heart Association

P/LP = Pathogenic or likely pathogenic

SCD = Sudden cardiac death

SHaRe = Sarcomeric Human Cardiomyopathy Registry

**INTRODUCTION**

Hypertrophic cardiomyopathy (HCM) is a complex cardiovascular disorder characterised by left ventricular hypertrophy, not explained by increased afterload or storage/infiltrative disorders. A considerable proportion of disease is caused by damaging variants in genes encoding sarcomere proteins, most frequently *MYH7*, *MYBPC3*, *TNNT2*, and *TNNI3*.1,2, but a signficant proportion of HCM patients do not have a clear monogenic etiology. Studies comparing the phenotype in patients with HCM carrying sarcomere variants (sarcomeric HCM) to those in whom genetic etiology remains elusive despite genetic testing (non-sarcomeric HCM), have identified a younger age at diagnosis of HCM, higher lifetime burden of adverse events, and less obstruction in patients with sarcomeric HCM3–5. However, how comorbidities influence outcomes in sarcomeric versus non-sarcomeric HCM is less well understood and is necessary to optimize the care of individual patients and their families.

We aim to contrast the experience of patients with sarcomeric and non-sarcomeric HCM, with a particular focus on assessing the impact of comorbidities on the longitudinal sequence of events. By analyzing a large cohort of genotyped HCM children and adults, we seek to uncover patterns influencing disease development, progression, and risk stratification, thus enabling more personalized clinical management of HCM.

**METHODS:**

***Study Design:***

This was a multicenter observational study using data from the Sarcomeric Human Cardiomyopathy Registry (SHaRe).SHaRe is a longitudinal database of patients with HCM who receive care at 12 international expert HCM centers. Collected data include cardiovascular events prior to first visit at a SHaRe site, demographics, clinical characteristics, cardiac imaging results, genetic testing results, cardiovascular comorbidities, and longitudinal, prospective capture of clinical features and outcomes as previously described.3 Institutional review board and ethics approval was obtained in accordance with local policies at each SHaRe site.

***Population:***

This study included SHaRe patients who had undergone genetic testing for sarcomere gene variants. Patients were stratified into two groups based on the presence (sarcomeric HCM) or absence (non-sarcomeric HCM) of pathogenic or likely pathogenic (P/LP) variants in 8 core sarcomere genes (*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL2, MYL3*, and *ACTC*).12 Patients with phenocopies of HCM (e.g., storage disorders), carrying variants of uncertain significance in sarcomere genes, or with no genetic testing were excluded. Genetic variants were classified based on criteria of the American College of Medical Genetics and Genomics and Association for Molecular Pathology.6,7 Variants with conflicting classification were reviewed by the SHaRe variant curation committee and assigned a consensus SHaRe-based classification.

***Clinical Features:***

Features of interest were selected based on their potential clinical relevance and impact on morbidity and mortality. They were categorized into the following groups:

1. Cardiovascular comorbidities: Hypertension and obesity (body mass index > 30).
2. Cardiac remodeling and function: Left ventricular (LV) ejection fraction (EF), LV outflow gradient and maximal LV wall thickness.
3. Heart failure: New York Heart Association (NYHA) functional class III-IV, LV systolic dysfunction (LV EF <50%), cardiac transplantation or LV assist device implantation.
4. Arrhythmias: Unexplained syncope, atrial fibrillation, non-sustained ventricular tachycardia, cardiac arrest, and a composite ventricular arrhythmia outcome which included sudden cardiac death, aborted sudden cardiac death, sustained ventricular tachycardia and appropriate implantable cardioverter-defibrillator [ICD] therapy.
5. Stroke.
6. Mortality: All-cause and HCM-related mortality (defined as death due to sudden cardiac death [SCD], heart failure and stroke). Data on causes of death were evaluated from death certificates, autopsy reports (if available) and by review of available hospital records.

These features were compared between sarcomeric and non-sarcomeric HCM to determine differences in clinical course. Additionally, the occurrence, timing, and sequence of these features were analyzed to better understand the natural history of HCM.

Our next objective was to evaluate whether adverse events occurred in a specific order and if timing differed by genetic status. To do this, we performed Cox proportional hazards modelling, including time-varying effects of key disease-course modifiers (obesity, hypertension, obstruction, atrial fibrillation, LV systolic dysfunction) on seven cardiovascular outcomes (atrial fibrillation, NYHA III/IV symptoms, LV systolic dysfunction, ventricular arrhythmias, stroke, cardiac transplantation, all-cause death). Analyses were adjusted for sex, corrected for multiple testing, and tested for interaction with genetic status.

***Statistical Analyses*:**

SHaRedata through June 2024 were analyzed. Continuous variables are presented as mean ± SD if normally distributed or as median (interquartile range, IQR) if deviating substantially from the normal distribution as evaluated by quantile-quantile plots. Categorical variables are presented as counts and percentages. Between group comparisons were evaluated statistically using Welch’s t-test, Wilcoxon rank sum test, Fisher’s exact test or Chi-square tests as appropriate.

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for comparing the clinical characteristics of patients with sarcomeric and non-sarcomeric HCM.

We computed the relative risk of cardiovascular comorbidities and adverse events in patients with non-sarcomeric and sarcomeric HCM. The incidence of cardiovascular outcomes during follow-up was compared using the Kaplan-Meier method or the cumulative incidence function. In addition, age-specific incidence rates were reported according to age quintiles (<30, 31-45, 46-55, 56-65 and >65 years of age). Age-specific incidence rates were calculated, and Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CI, adjusting for potential confounders. Age-standardized rates were computed, with the reference age set to correspond to the age-distribution of the combined cohort at the time of study inclusion. A standardized incidence ratio was calculated from the age-standardized rates to compare the relative risk of investigated outcomes.

We assessed the clinical course of HCM over time by examining the relative timing of developing LV obstruction, atrial fibrillation, NYHA class III-IV symptoms, LV systolic dysfunction, the composite VA outcome, stroke, cardiac transplantation, LV assist device implantation, and death. We used Cox proportional hazards modeling with age as the timescale with delayed entry (i.e., left-truncated at the time of the first SHaRe visit). Time-varying covariates (modifiers) included obesity, hypertension, LV obstruction, atrial fibrillation, onset of NYHA class III-IV symptoms, LV systolic dysfunction, and the composite ventricular arrhythmia outcome. We adjusted for sex and age at diagnosis with HCM and applied Bonferroni correction for multiple testing.

We also investigated potential interactions between these modifiers and genetic status (non-sarcomeric versus sarcomeric HCM) for all outcomes. If a significant interaction was found, we reported the combined effect of the modifier and genetic status on developing the outcome of interest.

A p-value of <0.05 was considered significant. Statistical analyses were conducted using R version 4.2.2 (R Foundation for statistical computing, Vienna, Austria), and the packages *tidyverse*, *broom*, *ggtext*, *scico*, *survival*, *survMiner*, *epiR*, *epitools*, *gt*, *gtsummary*, *patchwork* and *janitor*. Due to patient privacy concerns, the data that support the findings of this study are not publicly available. The code for statistical analysis and creating figures can be found online8.

**RESULTS:**

Among the 11,335 individuals with HCM in the SHARE registry, we included 6,120 children (N = x) and adults ( overall 40% female, 87% probands) in whom genetic testing had been performed and either identified a P/LP sarcomere variant (sarcomeric HCM, n= 3,082) or no P/LP variant (non-sarcomeric HCM, n= 3,038). Median age of HCM diagnosis was 46.8 years (IQR: 30.7 to 59.0) and age at first visit to a SHaRe site was 51.1 years (IQR: 36.4 to 62.7). In 725 patients (12%), HCM was diagnosed in childhood. At first SHaRe visit, hypertension was present in 32%, atrial fibrillation in 13%, previous stroke in 3.2%; and 2.0% had been resuscitated from cardiac arrest.

**Clinical Characteristics of Sarcomeric versus Non-sarcomeric HCM**

Clinical characteristics at first visit to a SHaRe site stratified by genetic subgroup are presented in **Table 1**. Patients with sarcomeric HCM were ~16 years younger at diagnosis (median age 38.1 versus 54.3 years, p<0.001), more likely to be diagnosed with HCM in childhood (OR 3.57 [CI, 2.98-4.29]), and had slightly higher European Society of Cardiology 5-year SCD risk scores (which was however low for both in absolute terms: median 2.3% versus 1.8%, p <0.001). Patients with non-sarcomeric HCM were less likely to be female (OR 0.74 [CI, 0.67-0.82]) or self-reported as white (OR 0.78 [CI, 0.67-0.92]), but more likely to report advanced symptoms at baseline (NYHA functional class III-IV, OR 1.36 [CI, 1.16-1.65]).

**Figure 1** depicts the relative risk of cardiovascular co-morbidities and adverse events in patients with non-sarcomeric versus sarcomeric HCM. Overall, patients with non-sarcomeric HCM were more likely to have hypertension (RR 1.95 [CI 1.82-2.08]), obesity (RR 1.38 [CI 1.27-1.50]), obstructive physiology (gradient >30 mmHg; RR 1.47 [CI 1.39-1.55]) and to have undergone septal reduction therapy (RR 1.16 [CI 1.04-1.29]). Patients with sarcomeric HCM were more likely to experience ventricular arrhythmias (RR for non-sustained ventricular tachycardias 1.25 [CI 1.15-1.35] and RR for the composite ventricular arrhythmia outcome 1.97 [CI 1.65-2.36]), advanced heart failure (RR for LV systolic dysfunction 1.82 [CI 1.54-2.15] and RR for cardiac transplantation 3.20 [CI 2.11-4.83]) and HCM-related mortality (RR 2.78 [CI 2.02-3.82]).

**Incident events during longitudinal follow-up**

Over a median follow-up of 5.3 years (IQR: 1.7 to 10.4), we evaluated the incidence of LV obstruction, atrial fibrillation, the composite ventricular arrhythmia outcome, and LV systolic dysfunction in patients without these outcomes at baseline. Patients with non-sarcomeric HCM had higher cumulative and age-specific incidences of LV obstruction (**Supplementary Figure 1**), with an adjusted hazard ratio (aHR) of 1.43 (CI: 1.21-1.69) for obstructive physiology (adjusted for age at HCM diagnosis, sex, obesity, presence of hypertension and being the family proband).

Patients with sarcomeric HCM had a higher incidence of ventricular arrhythmias, and higher age-standardized incidence of atrial fibrillation and LV systolic dysfunction (**Figure 2** and **Supplementary Figure 2**). For atrial fibrillation the biggest relative differences in age-specific incidence were observed earlier in life (prior to age 45 years), and sarcomeric HCM was associated with an age-standardized incidence ratio of 1.28 (CI: 1.16 to 1.40, p<0.001) for developing atrial fibrillation. Patients with sarcomeric HCM had a higher age-standardized incidence of the composite ventricular arrhythmia outcome during adolescence and late in life with the biggest relative difference observed in patients 65 years or older with an overall age-standardized incidence ratio of 1.37 (CI: 1.17 to 1.59, p <0.001) (**Figure 2**). Age-standardized incidence of LV systolic dysfunction was higher in sarcomeric HCM in patients over 65 years (age-standardized incidence ratio1.31 [CI: 1.15 to 1.48], p =0.003) (**Supplementary Figure 2**).

**Mortality in sarcomeric and non-sarcomeric HCM**

A total of 605 (9.9%) patients died during follow-up, with similar all-cause mortality in patients with sarcomeric and non-sarcomeric HCM (10.4% and 9.4% respectively). However, the mean age at death was 7.8 years lower (CI: 5.4 to 10.2, p <0.001) in sarcomeric HCM, resulting in a standardized incidence ratio 1.35 [CI: 1.21 to 1.51]) for all-cause mortality. The corresponding hazard ratio was 1.52 (CI: 1.29 to 1.80, p <0.001) using age as the timescale, left-truncated at first SHaRe visit. **Table 2** summarizes causes of death. Patients with sarcomeric HCM were more likely to die from sudden cardiac death (20% versus 9% of deaths) and heart failure (25 versus 8% of deaths). Overall, patients with sarcomeric HCM had an odds ratio of 2.86 (CI: 2.05 to 4.06, p<0.001) of dying of either heart failure or sudden cardiac death. The cumulative incidence of HCM-related death (heart failure, stroke or SCD), from time of first SHaRe visit, and the age-specific incidence of HCM-related death is shown in **Figure 3** Patients with sarcomeric HCM had a higher cumulative incidence of HCM-related death during follow-up (HR 1.61 [CI: 1.18 to 2.20, p <0.001] using follow-up as time-scale), and a significantly higher age-specific incidence after 45 years of age, with an overall standardized incidence ratio of 2.34 (CI: 1.98 to 2.75) for HCM-related death in patients with sarcomeric HCM.

**Temporal patterns of cardiovascular events**

Next, we investigated associations between potential disease modifiers (obesity, hypertension, LV obstruction, atrial fibrillation, and LV systolic dysfunction) on the rate of subsequent outcomes, to identify exposure-outcome pairs (**Figure 4**), combining sarcomeric and non-sarcomeric HCM. Obesity was associated with a higher rate of incident atrial fibrillation (HR 1.66 [CI 1.43-1.92]) and NYHA class III-IV symptoms (HR 2.13 [CI 1.83-2.49]). Obstruction was associated with higher rates of incident atrial fibrillation (HR 1.75 [CI 1.51-2.03]) and NYHA class III-IV symptoms (2.16 [CI 1.85-2.53]). Atrial fibrillation was associated with the most subsequent events with higher downstream rates of developing incident heart failure (HR 2.22 for NYHA III-IV symptoms, HR 2.89 for LV systolic dysfunction, and 7.4 for cardiac transplantation), ventricular arrhythmias (HR 3.17 [CI: 2.40-4.2]), stroke (HR 1.94 [CI: 1.42-2.66]) and all-cause mortality (HR 2.03 [CI: 1.72-2.41]). Finally, LV systolic dysfunction was associated with a higher incidence of NYHA class III-IV symptoms (HR 2.48 [CI 1.94-3.18]), ventricular arrhythmias (HR 4.10 [CI 2.93-5.6]), cardiac transplantation (HR 34 [CI: 23-52]) and all-cause mortality (HR 3.97 [CI 3.26-4.8],).

Interaction analyses were performed to determine how genetic status modified the impact of disease modifiers on outcomes. **Figure 5** shows the time-adjusted hazard ratios for modifier-outcome pairs, stratified by genotype, and using age as the time-scale (left-truncated at the first visit at a SHaRe site). Only pairs in which genetic status had a significant interaction are included. The reported effect ratios represent the relative difference in impact of the exposure for sarcomeric HCM versus non-sarcomeric HCM.

Across all significant interactions, the effect modification was greater in sarcomeric HCM, with the largest interaction effects found for atrial fibrillation. Specifically, atrial fibrillation was associated with larger risk modification for LV systolic dysfunction (effect ratio 1.89 [CI 1.35-2.66]), ventricular arrhythmias (effect ratio 1.88 [CI 1.21-2.92]), and death (effect ratio 1.86 [CI 1.46-2.37]) in sarcomeric HCM. Likewise, LV systolic dysfunction conferred a higher risk in sarcomeric HCM for developing NYHA class III-IV symptoms (effect ratio 1.97 [CI 1.15-3.36]) and death (effect ratio 1.80 [CI 1.23-2.64]).

**DISCUSSION:**

We systematically compared the clinical trajectories of two major subtypes of HCM: sarcomeric and non-sarcomeric. Sarcomeric HCM was characterized by a more severe phenotype with a younger age at diagnosis, a higher burden of cardiac arrhythmias and severe heart failure symptoms, an eight year shorter lifespan and an HCM-related mortality-rate twice that of non-sarcomeric HCM. Furthermore, the consequences of atrial fibrillation and LV systolic dysfunction were greater in sarcomeric HCM, leading to significantly greater risk of developing severe heart failure symptoms and death.

**Patients with Non-sarcomeric HCM Have a Higher Burden of Cardiovascular Comorbidities**

As reported previously, we found that patients with non-sarcomeric HCM were more likely to have common cardiovascular comorbidities (hypertension and obesity) and obstructive physiology.3,9–11 Overall, the age-standardized incidence rate of having obstructive physiology was twice as high in non-sarcomeric HCM. Obesity was associated with an 80% higher rate of obstruction as seen previously,12 but had a larger effect in patients with non-sarcomeric HCM. In previous studies, LV obstruction was linked to a higher risk of ventricular arrhythmias, stroke and death in HCM13. In this study, no significant associations were identified between LV obstruction and these outcomes after adjusting for age and sex.

Hypertension and specifically elevated diastolic blood pressure has been identified as an important comorbidity associated with non-sarcomeric HCM in Mendelian randomization analyses.14,15 Congruent with this, the prevalence of hypertension was almost twice as high in non-sarcomeric HCM. The consistency of these findings supports the hypothesis that hypertension and obesity may bmay contribute to the pathology of non-sarcomeric HCM.

**The Prevalence of and Consequences of Adverse Cardiovascular Outcomes, including HCM-Related Mortality, are Higher in Sarcomeric HCM**

Adding to these prior data, we found that, patients with sarcomeric HCM had a higher prevalence of atrial and ventricular arrhythmias and LV systolic dysfunction, even after performing age-specific analyses to account for the older age of patients with non-sarcomeric HCM. Overall, the age-standardized incidence rates were 28-37% higher in patients with sarcomeric HCM for each of these outcomes. For atrial fibrillation, this finding was primarily due to atrial fibrillation emerging at a younger age in patients with sarcomeric HCM, while the risk of ventricular arrhythmias seemed be equal at younger ages but persist into older age in patients with sarcomeric but not non-sarcomeric HCM. Moreover, the downstream impact of these events also appeared to be more consequential. For example, after atrial fibrillation developed, the rates of developing LV systolic dysfunction, ventricular arrhythmias or death were each ~2-fold higher in patients with sarcomeric than non-sarcomeric HCM.

Finally, patients with sarcomeric HCM had an HCM-related mortality rate double that of non-sarcomeric HCM. Age-specific analysis revealed that HCM-related mortality diverges in the two groups from age 45 years onwards. The largest relative difference in HCM-related mortality was in patients between the age of 46 and 55 years, where mortality was almost 4 times higher in patients with sarcomeric HCM. Previous studies have identified sarcomeric HCM to associate with higher all-cause mortality rates.3,5 However, prior studies did not investigate the difference in age-specific incidence of death or causes of death and may have been influenced by immortal time bias, leading to inflated effect estimates.

**Clinical Implications**

Findings from this study have implications for clinical practice and future research in HCM. Non-sarcomeric HCM was characterized by a higher burden of obesity, hypertension, and LV obstruction but less severe consequences of disease than patients with sarcomeric HCM. We hypothesize that hypertension and obesity, in conjunction with polygenic risk alleles, may be in the causal pathway for developing non-sarcomeric HCM, reinforcing the importance of aggressive management and risk factor modification. On the other hand, patients with sarcomeric HCM appeared to be more susceptible to adverse outcomes intrinsic to their HCM (i.e. advanced heart failure, atrial and ventricular arrhythmias, HCM-related mortality) independent of non-HCM exposures. Atrial fibrillation was more prevalent, earlier in onset, and more consequential in sarcomeric HCM. Whether AF represents a marker of worsening disease, or contributes directly to worse outcome, implying that maintenance of sinus rhythm may be beneficial, is an important avenue of further research. Sudden cardiac death risk was higher and persisted to advanced age. As such, patients with sarcomeric HCM, may benefit from more intensive surveillance and management of ventricular and atrial arrhythmias and LV systolic dysfunction.16–18

Current risk stratification algorithms for sudden cardiac death in HCM do not account for genetic substrate.19–21 However, in this study, carrying a sarcomere variant was associated with a standardized incidence ratio of 1.3 for a composite ventricular arrhythmia outcome, and notably with the highest relative and absolute difference in older patients (>65 years); an age when risk is traditionally thought to be lower. These findings suggest that implementing information regarding genetic substrate into future SCD risk prediction models could improve model performance and better guide management decisions regarding primary prevention ICD. Risk stratification for sudden death could potentially be relaxed in older patients with non-sarcomeric HCM, whereas continuing regular screening may be appropriate for patients with sarcomeric disease.

**Limitations**

Several limitations should be acknowledged. First, our patients are followed at high-volume referral centers and predominantly self-identify as white. As such, findings may not be fully generalizable to those followed in community setting or to a more ancestrally diverse patient population. Second, the study uses a pragmatic, partially retrospective observational design, and therefore, is subject to a potential selection, recall, and information bias. Third, although we attempted to control for potential confounders through statistical adjustments, there may be residual confounding that could impact the results of the study. Finally, we did not have comprehensive data on medical therapy and the potential impact of drugs on cardiovascular co-morbidities or occurrence of outcomes could not be evaluated.

**Conclusions**

Differences in clinical characteristics, trajectory, and susceptibility to adverse events exist between patients with sarcomeric and non-sarcomeric HCM. Patients with sarcomeric HCM had a significantly greater burden of heart failure and cardiac arrhythmias, both of which were associated with more adverse outcomes, including death. Non-sarcomeric HCM was associated with more background obesity and hypertension, suggesting a role in disease etiology, likely in combination with polygenic risk. These findings highlight the importance of genetic characterization in guiding risk stratification, surveillance, and management strategies. Continued research in this field will further refine our understanding of HCM pathophysiology and pave the way for more personalized approaches to the management of patients and families.

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**References**

1. Ho CY, Charron P, Richard P, Girolami F, Van Spaendonck-Zwarts KY, Pinto Y. Genetic advances in sarcomeric cardiomyopathies: state of the art. *Cardiovasc. Res.* 2015;105:397–408.

2. Biddinger KJ, Jurgens SJ, Maamari D, Gaziano L, Choi SH, Morrill VN, Halford JL, Khera AV, Lubitz SA, Ellinor PT, et al. Rare and Common Genetic Variation Underlying the Risk of Hypertrophic Cardiomyopathy in a National Biobank. *JAMA Cardiol.* 2022;7:715–722.

3. Ho Carolyn Y., Day Sharlene M., Ashley Euan A., Michels Michelle, Pereira Alexandre C., Jacoby Daniel, Cirino Allison L., Fox Jonathan C., Lakdawala Neal K., Ware James S., et al. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy. *Circulation*. 2018;138:1387–1398.

4. Li Q, Gruner C, Chan RH, Care M, Siminovitch K, Williams L, Woo A, Rakowski H. Genotype-positive status in patients with hypertrophic cardiomyopathy is associated with higher rates of heart failure events. *Circ. Cardiovasc. Genet.* 2014;7:416–422.

5. Curran L, de Marvao A, Inglese P, McGurk KA, Schiratti P-R, Clement A, Zheng SL, Li S, Pua CJ, Shah M, et al. Genotype-Phenotype Taxonomy of Hypertrophic Cardiomyopathy. *Circ. Genomic Precis. Med.* 0:e004200.

6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* 2015;17:405–423.

7. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 2018;20:899–909.

8. Vissing CR. Comparing Clinical Course of Hypertrophic Cardiomyopathy in Sarcomere Variant Carriers and Non-Carriers [Internet]. 2023;Available from: https://github.com/christoffervi/sarc\_nonsarc

9. Lopes LR, Syrris P, Guttmann OP, O’Mahony C, Tang HC, Dalageorgou C, Jenkins S, Hubank M, Monserrat L, McKenna WJ, et al. Novel genotype-phenotype associations demonstrated by high-throughput sequencing in patients with hypertrophic cardiomyopathy. *Heart Br. Card. Soc.* 2015;101:294–301.

10. Lopes LR, Rahman MS, Elliott PM. A systematic review and meta-analysis of genotype-phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations. *Heart Br. Card. Soc.* 2013;99:1800–1811.

11. Curran L, Marvao A de, Inglese P, McGurk KA, Schiratti P-R, Clement A, Zheng SL, Li S, Pua CJ, Shah M, et al. A genotype-phenotype taxonomy of hypertrophic cardiomyopathy [Internet]. 2023 [cited 2023 Jun 20];2023.03.11.23285908. Available from: https://www.medrxiv.org/content/10.1101/2023.03.11.23285908v2

12. Fumagalli C, Maurizi N, Day SM, Ashley EA, Michels M, Colan SD, Jacoby D, Marchionni N, Vincent-Tompkins J, Ho CY, et al. Association of Obesity With Adverse Long-term Outcomes in Hypertrophic Cardiomyopathy. *JAMA Cardiol.* 2020;5:65–72.

13. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of Left Ventricular Outflow Tract Obstruction on Clinical Outcome in Hypertrophic Cardiomyopathy. *N. Engl. J. Med.* 2003;348:295–303.

14. Harper AR, Goel A, Grace C, Thomson KL, Petersen SE, Xu X, Waring A, Ormondroyd E, Kramer CM, Ho CY, et al. Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity. *Nat. Genet.* 2021;53:135–142.

15. de Marvao A, Dawes TJW, Shi W, Durighel G, Rueckert D, Cook SA, O’Regan DP. Precursors of Hypertensive Heart Phenotype Develop in Healthy Adults: A High-Resolution 3D MRI Study. *JACC Cardiovasc. Imaging*. 2015;8:1260–1269.

16. Marstrand P, Han L, Day SM, Olivotto I, Ashley EA, Michels M, Pereira AC, Wittekind SG, Helms A, Saberi S, et al. Hypertrophic Cardiomyopathy With Left Ventricular Systolic Dysfunction: Insights From the SHaRe Registry. *Circulation*. 2020;141:1371–1383.

17. Alaiwi SA, Roston TM, Marstrand P, Claggett BL, Parikh VN, Helms AS, Ingles J, Lampert R, Lakdawala NK, Michels M, et al. Left Ventricular Systolic Dysfunction in Patients Diagnosed With Hypertrophic Cardiomyopathy During Childhood: Insights From the SHaRe Registry (Sarcomeric Human Cardiomyopathy). *Circulation*. 2023;

18. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J. Am. Heart Assoc.* 2014;3:e001002.

19. O’Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). *Eur. Heart J.* 2014;35:2010–2020.

20. O’Mahony C, Akhtar MM, Anastasiou Z, Guttmann OP, Vriesendorp PA, Michels M, Magrì D, Autore C, Fernández A, Ochoa JP, et al. Effectiveness of the 2014 European Society of Cardiology guideline on sudden cardiac death in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart Br. Card. Soc.* 2019;105:623–631.

21. O’Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, Cecchi F, Olivotto I, Kitaoka H, Gotsman I, et al. An International External Validation Study of the 2014 European Society of Cardiology Guideline on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (Evidence from HCM). *Circulation*. 2017;CIRCULATIONAHA.117.030437.

**Table 1:** Clinical characteristics of the cohort at first SHaRe visit.

| Characteristic | SARCOMERIC HCM N= 3,082 | NON-SARCOMERIC HCM  N = 3,038 | p-value |
| --- | --- | --- | --- |
| **Demographic information** |  |  |  |
| Female | 1,328 (43%) | 1,092 (36%) | <0.001 |
| Age at HCM diagnosis (years) | 38.1 [22.6, 51.0] | 54.3 [42.5, 63.7] | <0.001 |
| Age at first visit to a SHaRe site | 44 [29, 56] | 58 [46, 67] | <0.001 |
| Family proband, n (%) | 2,449 (79%) | 2,886 (95%) | <0.001 |
| HCM diagnosed in childhood (18 years) | 550 (18%) | 175 (6%) | <0.001 |
| **Race** |  |  | <0.001 |
| White | 2,665 (86%) | 2,462 (81%) |  |
| Black | 93 (3.0%) | 161 (5.3%) |  |
| Asian | 101 (3.3%) | 115 (3.8%) |  |
| Native Hawaiian or Other Pacific Islander | 8 (0.3%) | 3 (<0.1%) |  |
| More than One | 4 (0.1%) | 5 (0.2%) |  |
| American Indian or Alaska Native | 3 (<0.1%) | 4 (0.1%) |  |
| Other or Not Reported | 208 (6.7%) | 288 (9.5%) |  |
| **Clinical findings** |  |  |  |
| Systolic blood pressure, mmHg | 120 [110, 131] | 130 [119, 140] | <0.001 |
| Diastolic blood pressure, mmHg | 71 [65, 80] | 76 [70, 82] | <0.001 |
| Body mass index | 26.3 [23.1, 30.1] | 27.8 [24.8, 31.9] | <0.001 |
| Body surface area, m2 | 1.92 [1.73, 2.11] | 1.99 [1.81, 2.17] | <0.001 |
| **Echocardiography findings** |  |  |  |
| Maximal LV wall thickness, mm | 18.0 [14.0, 22.0] | 17.0 [14.0, 20.0] | <0.001 |
| LV ejection fraction, % | 63.6 ± 10.3 | 65.3 ± 9.2 | <0.001 |
| Obstructive physiology (gradient >30 mmHg [resting or provoked]) | 706 (23%) | 1,208 (40%) | <0.001 |
| Left atrial diameter, mm | 40.3 ± 10.5 | 41.0 ± 9.5 | 0.002 |
| **Co-morbidities and medical history** |  |  |  |
| Hypertension | 628 (20%) | 1,345 (44%) | <0.001 |
| Atrial fibrillation | 393 (13%) | 400 (13%) | 0.6 |
| Syncope | 312 (10%) | 273 (9.0%) | 0.13 |
| Stroke | 85 (2.8%) | 116 (3.8%) | 0.020 |
| Family history of sudden cardiac death | 396 (13%) | 156 (5.1%) | <0.001 |
| Resuscitated cardiac arrest | 87 (2.8%) | 48 (1.6%) | <0.001 |
| New York Heart Association class III-IV | 202 (6.6%) | 264 (8.7%) | 0.002 |
| LV systolic dysfunction (LV ejection fraction<50%) | 112 (3.6%) | 51 (1.7%) | <0.001 |
| Severe LV systolic dysfunction (LV ejection fraction<35%) | 5 (0.8%) | 8 (0.3%) | 0.003 |
| **ESC SCD risk** |  |  | <0.001 |
| High (>6% per 5 years) | 179 (9.6%) | 83 (4.3%) |  |
| Moderate (4-6% per 5 years) | 245 (13%) | 151 (7.8%) |  |
| Low (<4% per 5 years) | 1,435 (77%) | 1,701 (88%) |  |
| Unknown | 1,223 | 1,103 |  |
| 5- year risk score | 2.30 (1.50, 3.80) | 1.80 (1.30, 2.70) | <0.001 |
| n (%); Median [Q1, Q3]; Mean ± SD **Abbreviations:** ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; LV = left ventricle; SCD = sudden cardiac death | | | |
|  | | | |

| **Table 2:** All-cause and cause-specific mortality in sarcomeric and non-sarcomeric hypertrophic cardiomyopathy | | | |
| --- | --- | --- | --- |
|  | **Sarcomeric HCM**, N = 3,082 | **Non-sarcomeric HCM**, N = 3,038 | **P-VALUE** |
| All-cause mortality | 320 (10%) | 285 (9.4%) | 0.20 |
| Non-cardiovascular death |  |  | <0.001 |
| *Malignancy* | 8 (2.5%) | 15 (5.3%) |  |
| *Other non-cardiovascular* | 124 (39%) | 185 (65%) |  |
| *Unknown* | 26 (8.1%) | 18 (6.3%) | 0.29 |
| Cardiovascular death |  |  | <0.001 |
| *Heart failure* | 79 (25%) | 24 (8.4%) |  |
| *Sudden cardiac death* | 63 (20%) | 26 (9.1%) |  |
| *Stroke* | 5 (1.6%) | 9 (3.2%) |  |
| *Other cardiovascular death* | 15 (4.7%) | 8 (2.8%) |  |
|  |  |  |  |

**Legend:** Comparison of all‐cause and cause‐specific mortality in patients with sarcomeric and non‐sarcomeric hypertrophic cardiomyopathy (HCM). Values are number of deaths (percentage) within each group. The first row (all‐cause mortality) indicates the percentage of the entire cohort who died. The remaining rows reflect the distribution of causes among those who died in each group..The “Unknown” category encompasses deaths for which no definitive cause was established. P-values were calculated for differences in proportions between the two groups.

**Figure 1:**

Et billede, der indeholder tekst, skærmbillede, nummer/tal

Indhold genereret af kunstig intelligens kan være forkert.

**Legend:** Relative risk of the occurrence of 15 cardiovascular features (y-axis) in patients with sarcomeric versus non-sarcomeric hypertrophic cardiomyopathy (HCM). The relative risk ratio is given on the x-axis and the filled dots denote the point-estimate of the relative risk while the error-bars give the confidence intervals. On the right the overall prevalence of each feature is given separately for each group. **Abbreviations***:* *HCM* = hypertrophic cardiomyopathy, *ICD* = implantable cardioverter defibrillator, *LVSD* = left ventricular systolic dysfunction, *NSVT* = non-sustained ventricular tachycardia, *NYHA* = New York Heart Association functional class, *SRT* = septal reduction therapy, *VA* = ventricular arrhythmia.

**Figure 2** **![Et billede, der indeholder tekst, skærmbillede, diagram, Kurve

Indhold genereret af kunstig intelligens kan være forkert.]()**

**Legend:** Incidence of arrhythmias in sarcomeric versus non-sarcomeric HCM, excluding patients diagnosed with these events prior to or at first SHaRe visit. Panel **A** shows the cumulative incidence of atrial fibrillation during follow-up, including numbers at risk, in sarcomeric (Sarc+, pink) and non-sarcomeric (Sarc-, blue) HCM. Overall, the cumulative incidence is similar between the two groups, with a trend towards a higher rate in non-sarcomeric HCM. Panel **B** shows the age-specific incidence (ASI) rates of atrial fibrillation during follow-up, including accumulated years at risk, in the two groups. Incidence rates are numerically higher for patients with sarcomeric HCM in all investigated groups, reaching statistical significance in the three youngest age-groups, and with a highly significant increased age-standardized incidence (ASI) in sarcomeric HCM (grey shading). Panel **C**, shows the cumulative incidence of the composite ventricular arrhythmia outcome since first SHaRe evaluation, in sarcomeric and non-sarcomeric HCM, showing that there is a higher cumulative incidence in sarcomeric HCM. Panel **D.** Shows the age-specific incidence rate of the composite ventricular arrhythmia outcome, including total person-years at risk in each age-group. The age-standardized incidence rate has been added as the final group. Overall, the largest difference in incidence of this outcome occurs in the group of patients older than 65 years.

**Figure 3**

Et billede, der indeholder tekst, skærmbillede, diagram, linje/række

Indhold genereret af kunstig intelligens kan være forkert.

**Legend:** Incidence of hypertrophic cardiomyopathy (HCM) related mortality (sudden cardiovascular death, heart failure related death, and death due to stroke) in patients with sarcomeric (pink) versus non-sarcomeric (blue) HCM. Panel **A.** Cumulative incidence since first SHaRe evaluation, including numbers at risk by year. Panel **B.** Age-specific incidence (ASI) rates, including total person-years at risk in each age-group. The standardized incidence ratio (SIR) has been added for each age-group at the bottom of the plot.

**Figure 4:**

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**Legend:** Heatmap showing the time-adjusted hazard ratios of being diagnosed with one of 8 cardiovascular outcomes (x-axis) predicated on of the presence of one of the 6 pre-defined disease-modifiers (exposures, y-axis). Hazard ratios larger than 1 are shown with Bonferroni corrected 95% confidence intervals if Bonferroni corrected p <0.05. Colors indicate the level of statistical significance. Hazard ratios are adjusted for sex and if a significant interaction was observed stratified analysis was performed. **Abbreviations***:* *LVSD* = left ventricular systolic dysfunction, *NYHA* = New York Heart Association functional class, *VA* = ventricular arrhythmia.

**Figure 5:**

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**Legend**: Forest plot showing the time-adjusted hazard ratios for the combined effect of each individual modifier (exposure) and genetic status on the hazard of the outcomes (written in cursive). All hazard ratios are adjusted for sex and computed using age as the timescale with left-truncation at the first visit at a SHaRe site. Only exposure-outcome pairs in which the exposure was associated with a higher rate of the outcome and in which a significant interaction was found are included. The effect ratios of the interaction are given in text along with the p for interaction on the right hand side of the plot. **Abbreviations***:* *LVSD* = left ventricular systolic dysfunction, *NYHA* = New York Heart Association functional class, *VA* = ventricular arrhythmia.