**Differences in the Clinical Course of Sarcomeric and Non-Sarcomeric Hypertrophic Cardiomyopathy**

Christoffer R. Vissing, MD, PhD; Neal K. Lakdawala, MD; Anna Axelsson Raja, MD, PhD; Victoria N. Parikh, MD; Adam S. Helms, MD; Jodie Ingles, PhD, MPH; Rachel Lampert, MD, Anjali T. Owens, MD; Joseph W. Rossano, MD, MS; Sara Saberi, MD; Dominic J. Abrams, MD; Euan A. Ashley, MD, PhD; Christopher Semsarian, MBBS, PhD, MPH: John C. Stendahl, MD, PhD; James S. Ware, PhD, MRCP; Michelle Michels, MD, PhD, Erin Miller, MS, CGC; Thomas D. Ryan, MD, PhD; Mark W. Russell, MD, Sharlene M. Day, MD; Iacopo Olivotto, MD; Henning Bundgaard, MD, PhD; Brian Lee Claggett, PhD; and Carolyn Y. Ho, MD.

(AUTHOR LIST INCOMPLETE AND IN SORT OF RANDOM ORDER)

Affiliations

Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, 02115 USA (B.L.C, N.K.L., C.Y.H.).

University of British Columbia, Vancouver, Canada (T.M.R.).

Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA (V.N.P, E.A.A).

Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor (A.S.H., S.S., M.R.).

Centre for Population Genomics, Garvan Institute of Medical Research and University of New South Wales, Sydney, Australia (J.I.)

Center for Cardiovascular Genetics, Department of Cardiology, Boston Children’s Hospital & Harvard Medical School, Boston, MA (D.J.A).

Agnes Ginges Centre for Molecular Cardiology at Centenary Institute, University of Sydney, Australia (C.S.).

Department of Medicine, Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut, USA (R.L, J.C.S).

Department of Cardiology, Thoraxcenter, Erasmus Medical Center Rotterdam, the Netherlands (M.M.)

Division of Cardiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA (A.T.O., S.M.D.).

Division of Cardiology, Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA (J.W.R.).

Royal Brompton & Harefield Hospitals, Guy’s and St. Thomas’ NHS Foundation Trust, London, United Kingdom (J.S.W.).

Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; Division of Cardiology, The Heart Institute, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH (E.M., T.D.R.).

Meyer Children Hospital, Department of Experimental and Clinical Medicine, University of Florence, Italy (I.O,).

Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark (C.R.V., A.A.R., H.B.).

Department of Cardiology, Hvidovre Hospital, Copenhagen University Hospital, Denmark (C.R.V.).

**Running Title:** Sarcomeric and non-sarcomeric HCM

**Corresponding Authors:**

Carolyn Y. Ho, MD

Cardiovascular Division, Brigham and Women’s Hospital

75 Francis Street, Boston, MA 02115

Email : [cho@bwh.harvard.edu](mailto:cho@bwh.harvard.edu)

Tel : 617-732-5685

Fax : 617-264-5265

Christoffer R. Vissing, MD, PhD

Department of Cardiology, Rigshospitalet, Copenhagen University Hospital

Blegdamsvej 9, 2100, Copenhagen, Denmark

Email: [christoffer.rasmus.vissing@regionh](mailto:christoffer.rasmus.vissing@regionh).dk

Tel: +45 20 86 63 96 7 / +1 857-707-2233

**Word count**

Abstract: 356 words (Limit: 350 words)

Manuscript: 3479 words (Limit: 5000 words)

**ABSTRACT:**

***Background***: Rare variants in sarcomere genes cause hypertrophic cardiomyopathy (HCM) in many but not all patients. Clinical differences based on genetic substrate have been identified, but sarcomeric and non-sarcomeric HCM have not been comprehensively compared. Additionally, the relative timing of adverse events and impact of cardiovascular comorbidities have not been assessed.

***Methods***: We conducted a longitudinal cohort study of HCM patients in the Sarcomeric Human Cardiomyopathy Registry (SHaRe). All patients had genetic testing and classified as sarcomeric (pathogenic/likely pathogenic sarcomere gene variant present) or non-sarcomeric (genetically-elusive) HCM. The temporal association and sequence of cardiovascular events were assessed in time-varying Cox proportional hazards models.

***Results***: We analyzed 5,942 patients (39% female, 89% probands, 50% sarcomeric HCM). Patients with sarcomeric HCM were younger at diagnosis (median age 37.8 versus 53.7 years), had a lower burden of obesity, hypertension, and left ventricular (LV) obstruction, but a higher burden and age-standardized incidence of atrial fibrillation, LV systolic dysfunction and ventricular arrhythmias.

We evaluated the timing and impact of cardiovascular co-morbidities on subsequent adverse events. Atrial fibrillation led to higher rates of LV systolic dysfunction (HR 2.71 [CI: 2.22-3.31]), stroke (HR 2.13 [CI: 1.57-2.88]), ventricular arrhythmias (HR 3.21 [CI: 2.42-4.20]) and death (HR 1.99 [CI: 1-68-2.36]). Obesity and hypertension were associated with developing LV obstruction, while LV obstruction and obesity associated with incident atrial fibrillation and NYHA class III-IV symptoms. In interaction analysis, sarcomeric HCM was linked with an amplified risk of subsequent major adverse events in patients with atrial fibrillation, LV systolic dysfunction or ventricular arrhythmias.

Regarding mortality, patients with sarcomeric HCM were more than twice as likely to die from sudden cardiac death, heart failure or stroke. Age-standardized incidence ratio for all-cause mortality was 1.32 (CI 1.18-1.48).

***Conclusions***: Obesity and hypertension were more prevalent in non-sarcomeric HCM, suggesting these comorbidities may be in the causal pathway for disease development. Sarcomeric HCM was associated with greater impact of atrial fibrillation and LV systolic dysfunction, more substantial burden of severe heart failure and arrhythmias throughout life, and an HCM-related mortality-rate twice that of non-sarcomeric HCM.

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

**CLINICAL PERSPECTIVE**

**What is new?**

* Patients with sarcomeric and non-sarcomeric hypertrophic cardiomyopathy (HCM) have different clinical trajectories.
* Hypertension, obesity, and obstructive physiology commonly co-occur and are more prevalent in non-sarcomeric HCM but are not associated with excess risk of advanced heart failure, sudden cardiac death, or mortality.
* Atrial fibrillation is strongly associated with subsequent development of advanced heart failure, ventricular arrhythmias, stroke, and death in all patients, but has a significantly greater impact on patients with sarcomeric HCM.
* The risk of HCM-related mortality is twice as high in patients with sarcomeric HCM compared to non-sarcomeric HCM.
* **What are the clinical implications?**
* Patients with sarcomeric HCM are at higher risk for disease-related adverse outcomes, including death, thus aggressive management of comorbidities and vigilant surveillance for cardiac arrhythmias and LV dysfunction is appropriate.
* Integrating genetic testing results may improve the accuracy of clinical risk stratification and predictive models for adverse outcomes.

**Abbreviations**

BMI = Body-mass index

HCM = Hypertrophic cardiomyopathy

ICD = implantable cardioverter defibrillator

LV = Left ventricle

NYHA = New York Heart Association

P/LP = Pathogenic or likely pathogenic

SHaRe = Sarcomeric Human Cardiomyopathy Registry

VT = ventricular tachycardia

**INTRODUCTION**

Hypertrophic cardiomyopathy (HCM) is a complex cardiovascular disorder defined by unexplained left ventricular hypertrophy (LVH). Although HCM can arise from different etiologies, a considerable proportion of disease is attributable to variants in genes encoding sarcomere proteins, most frequently *MYH7*, *MYBPC3*, *TNNT2*, and *TNNI3*.1,2 Previous studies have investigated the impact of specific genetic mutations and sarcomere variants overall on HCM phenotypes and outcomes.3–5 However, patients with sarcomeric HCM have not previously been comprehensively compared to those with non-sarcomeric HCM where a genetic etiology remains elusive despite genetic testing. Understanding the differences in disease progression, the influence of comorbidities, and drivers of adverse outcomes between these two groups is crucial to optimize the care of individual patients and their families. This study aims to contrast the experience of patients with sarcomeric and non-sarcomeric HCM, with a particular focus on the characterizing clinical trajectories and the temporal sequence of events in these key subgroups. By analyzing a large cohort of genotyped HCM patients, we seek to uncover patterns that may provide valuable insights into 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, high-volume, 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 carrying variants of uncertain significance (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

***Clinical Features:***

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

1. Cardiovascular comorbidities: Hypertension and obesity (BMI > 30).
2. Cardiac remodeling and function: left ventricular (LV) ejection fraction, LV outflow gradient and maximal LV wall thickness.
3. Heart failure: New York Heart Association (NYHA) functional class III-IV, LV systolic dysfunction (LV ejection fraction (EF) <50%), cardiac transplantation or LV assist device (LVAD) implantation.
4. Arrhythmias: Unexplained syncope, atrial fibrillation, non-sustained ventricular tachycardia (VT), cardiac arrest, and a composite ventricular arrhythmia (VA) 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 (sudden cardiac death [SCD], heart failure and stroke).

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

***Statistical Analyses*:**

SHaRedata through June 2023 were analyzed. Continuous variables were 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 using log-rank tests to determine statistical significance. 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-standardized incidence rates were calculated, and Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CI, adjusting for potential confounders. Age-specific and age-standardized rates were compared by computing a standardized incidence ratio and the reference age was set to be the age-distribution of the combined cohort at the time of study inclusion.

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, LVAD 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 4.1.1 (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:**

This study focused on 5,942 patients (39% female, 89% probands) with HCM in whom genetic testing had been performed and either identified a LP/P genetic sarcomere variant (sarcomeric HCM, n= 2,999) or was negative (non-sarcomeric HCM, n= 2,943). Median age at time of HCM diagnosis was 46.3 years (IQR: 30.4 to 58.5) and age at first visit to a SHaRe site was 50.7 years (IQR: 36.0 to 61.9). At first SHaRe visit, hypertension was prevalent or had been diagnosed in 30%, atrial fibrillation in 13%, stroke in 2.9%; 10% had a history of syncope and 2.1% had resuscitated cardiac arrest.

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

Clinical characteristics stratified by genetic subgroup are presented in **Table 1**. Patients with sarcomeric HCM were ~15 years younger at diagnosis (median age 37.8 versus 53.7 years, p<0.001) and had higher, but still low, European Society of Cardiology (ESC) 5-year SCD risk scores (median 2.3% versus 1.8%, p <0.001). Patients with non-sarcomeric HCM were less likely to be female (OR 0.71 [CI, 0.64-0.79]), white (OR 0.71 [CI, 0.64-0.80]), or have a family history of sudden cardiac death (OR 0.33 [CI, 0.27-0.41]), but more likely to report significant symptoms at baseline (New York Heart Association [NYHA] functional class III-IV, OR 1.36 [CI, 1.14-1.61]).

**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 co-morbidities of hypertension (RR 1.87 [CI 1.75-2.00]), obesity (RR 1.44 [CI 1.32-1.57]), and obstructive physiology (gradient >30 mmHg; RR 1.51 [CI 1.43-1.60]). Patients with sarcomeric HCM were more likely to experience ventricular arrhythmias (RR for non-sustained ventricular tachycardias 1.40 [CI 1.27-1.53] and RR for composite VA 1.82 [CI 1.52-2.17]) and left ventricular systolic dysfunction (RR 1.68 [CI 1.42-1.98]).

**Cardiac Structure and Function in Sarcomeric versus Non-sarcomeric HCM**

Measures of cardiac function and remodeling were relatively similar between the two groups. However, patients with non-sarcomeric HCM had slightly higher LV ejection fraction (+1.6 %-points [CI: 1.1 to 2.1], p <0.001; **Table 1** and maximal LV gradients (+18.7 mmHg [CI: 16.6 to 20.7], p <0.001). Patients with sarcomeric HCM had slightly greater maximal LV wall thickness, both in absolute terms (+1.2 mm [CI: 0.9 to 1.5], p <0.001) and when converted to BSA-adjusted z-scores (+1.5 z [CI: 1.1 to 1.8], p <0.001).

**Incident events during longitudinal follow up**

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 1.51 (CI: 1.27-1.80) 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 atrial fibrillation, ventricular arrhythmias, and LV systolic dysfunction (**supplementary figures 2-3**). For atrial fibrillation the biggest relative differences in age-specific incidence was observed earlier in life (prior to age 45), and sarcomeric HCM was associated with an aHR of 1.32 (CI: 1.12 to 1.56, p=0.001) for developing atrial fibrillation (adjusted for age, sex, obesity, and hypertension). For the composite ventricular arrhythmia and the LV systolic dysfunction outcomes, the biggest relative difference in the age-specific incidences of the outcomes were observed in patients 65 years or older with an overall age-standardized incidence ratio of 1.30 (CI: 1.11 to 1.52, p <0.001) for ventricular arrhythmias, and 1.22 (CI: 1.07 to 1.39, p =0.003) for LV systolic dysfunction in sarcomeric HCM.

To evaluate the lifetime course of HCM, we evaluated the timing of onset of 6 adverse outcomes associated with HCM from birth: atrial fibrillation, New York Heart Association [NYHA] class III/IV symptoms, LV systolic dysfunction (LVEF<50%), composite ventricular arrhythmia outcome (cardiac arrest, SCD, appropriate ICD therapy), cardiac transplantation, and death. Results from this analysis are summarized in **Figure 2**, which shows the distribution of events according to age. In addition to being diagnosed at a younger age, the age-distribution of these adverse outcomes skewed earlier in life for patients with sarcomeric HCM, but the distribution of incident events was wide; spread over most of adulthood. In contrast, there was a narrower distribution of age at occurrence of these outcomes in patients with non-sarcomeric HCM, mostly centered around the time of diagnosis of HCM.

**Temporal patterns of cardiovascular events**

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

In this analysis, we found significant associations between 21 modifier-outcome pairs occurring in a specific temporal sequence (**Figure 3)**. Obesity was associated with a higher subsequent rate of developing obstructive physiology (HR 1.79 [CI 1.58-2.02]), atrial fibrillation (HR 1.49 [CI 1.28-1.73]) and NYHA class III-IV symptoms (HR 1.90 [CI 1.62-2.23]). Hypertension showed an association with incident LV obstruction (HR 1.41 [CI 1.24-1.61]). Obstruction was associated with higher rates of incident atrial fibrillation (HR 1.92 [CI 1.66-2.22]) and NYHA class III-IV symptoms (2.23 [CI 1.90-2.62]) but did not appear to increase risk of advanced heart failure, ventricular arrhythmias, stroke or death. Atrial fibrillation was found to lead to higher downstream rates of developing incident heart failure outcomes (HR 2.05 for NYHA III-IV symptoms, HR 2.71 for LVSD, and 8.2 for cardiac transplantation), ventricular arrhythmias (HR 3.21 [CI: 2.42-4.2]), stroke (HR 2.13 [CI: 1.57-2.88]) and all-cause mortality (HR 1.99 [CI: 1.68-2.36]). LV systolic dysfunction led to a higher incidence of NYHA class III-IV symptoms (HR 2.37 [CI 1.84-3.05]), ventricular arrhythmias (HR 3.81 [CI 2.75-5.3]), cardiac transplantation (HR 39 [CI: 26-59]) and all-cause mortality (HR 3.84 [CI 3.16-4.7],). Finally, ventricular arrhythmias were associated with and increased risk of incident atrial fibrillation (HR 1.86 [CI 1.44-2.40]), LV systolic dysfunction (HR 3.78 [CI 2.97-4.8]), cardiac transplantation (HR 7.2 [CI 4.8-11]) and all-cause mortality (HR 5.4 [CI 4.4-6.5]).

Interaction analysis indicated that genetic status modified the impact of modifier-outcome pairs (**Figure 4**). The largest interaction effects were found for atrial fibrillation increasing the risk of developing LV systolic dysfunction (effect ratio 2.06 [CI 1.49-2.84]), ventricular arrhythmias (effect ratio 1.99 [CI 1.27-3.11]), and death (effect ratio 1.73 [CI 1.35-2.22]) in sarcomeric HCM relative to non-sarcomeric HCM. LV obstruction was more likely to result in developing atrial fibrillation in sarcomeric HCM than non-sarcomeric HCM (effect ratio 1.58 [CI 1.29-1.95]).

In contrast, the effect of both obesity and hypertension had a greater impact on developing LV obstruction in non-sarcomeric HCM (effect ratio 2.20 [CI 1.79-2.69]) for obesity and 2.70 [CI 2.20-3.31 for hypertension).

Lastly, LV systolic dysfunction conferred higher risk in sarcomeric HCM regarding developing NYHA class III-IV symptoms (effect ratio 2.65 [CI 1.50-4.71]) and death (effect ratio 1.95 [CI 1.32-2.22]).

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

Finally, we investigated the timing and causes of death in patients with sarcomeric and non-sarcomeric HCM. A total of 591 (9.9%) patients died during follow-up, with similar all-cause mortality in patients with sarcomeric and non-sarcomeric HCM (10% and 9.6% respectively). However, the mean age at death was 8.1 years lower (CI: 5.6 to 10.5, p <0.0001) in sarcomeric HCM, resulting in a standardized incidence ratio 1.32 [CI: 1.18 to 1.48]) for all-cause mortality (**Supplementary Figure 4**), or a hazard ratio of 1.48 (CI: 1.25 to 1.75, p <0.0001) using age as the time-scale, 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 (19% versus 10% of deaths) and heart failure (26 versus 9% of deaths). Overall, having sarcomeric HCM was associated with an odds ratio of 2.76 (CI: 1.98 to 3.89, p<0.0001) 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 5**. Patients with sarcomeric HCM had a higher cumulative incidence of HCM-related death during follow-up (HR 1.75 [CI: 1.26 to 2.44, p <0.001]), and a significantly higher age-specific incidence in patients older than 45 years of age, with an overall standardized incidence ratio of 2.18 (CI: 1.83 to 2.57) for HCM-related death in patients with sarcomeric HCM.

**DISCUSSION:**

In this study, we systematically compared cardiac phenotypes and clinical trajectories in sarcomeric and non-sarcomeric HCM. Notably, sarcomeric HCM was characterized by a more severe phenotype with patients diagnosed at a younger age, exhibiting greater maximal LV wall thickness, and having a higher burden of cardiac arrhythmias and severe heart failure. Furthermore, the HCM-related mortality-rate was twice that of non-sarcomeric HCM. We also investigated temporal associations between various cardiovascular modifiers and HCM outcomes. Cardiovascular modifiers appeared to have greater impact on patients with sarcomeric HCM, associated with a higher risk of adverse outcomes that occurred earlier in life. These findings offer valuable insights into the clinical course of these major subtypes of HCM and have implications regarding risk stratification and management.

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

Consistent with prior studies, we found that patients with non-sarcomeric HCM were more likely to have obstructive physiology and common cardiovascular comorbidities (hypertension and obesity).3,9–11 Overall, the age-standardized incidence rate of an 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. Notably, while LV obstruction has previously been associated with a higher risk of ventricular arrhythmias, stroke and death,13 we did not find LV obstruction to be linked to these outcomes after adjustment for age and sex.

Hypertension and specifically elevated diastolic blood pressure has been identified as an important comorbidity for developing non-sarcomeric HCM.14,15 Congruent with this, the prevalence of hypertension was almost twice as high in non-sarcomeric HCM. Moreover, hypertension was much more likely to lead to the development of LV obstruction in patients with non-sarcomeric HCM.

**The impact of Comorbidities, Adverse Cardiovascular Outcomes, and HCM-Related Mortality are Higher in Sarcomeric HCM**

After performing age-specific analyses to account for the older age of non-sarcomeric HCM patients, patients with sarcomeric HCM had a higher prevalence of atrial and ventricular arrhythmias and LV systolic dysfunction. Overall, the age-standardized incidence rates were 22-34% higher in patients with sarcomeric HCM for each of these 3 outcomes. The downstream impact of these events also appeared to be more consequential. For example, after atrial fibrillation developed, the likelihood of LV systolic dysfunction, ventricular arrhythmias or death were each ~2-fold higher for patients with sarcomeric HCM. These findings suggests that healthcare providers should pay particular attention to these outcomes in patients with sarcomeric HCM, both because they merit aggressive management, but also because they suggest a poorer long-term prognosis16,17. Additionally, the cumulative incidence of ventricular arrhythmias was higher in sarcomeric HCM throughout adulthood, but particularly in patients older than 65 years. Thus, clinicians should be aware that while SCD risk decreases markedly after age 65 years in non-sarcomeric HCM, the same attenuation of risk does not seem to be present in sarcomeric HCM and attention to risk stratification may continue to be appropriate.

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 onwards. The largest relative difference in HCM-related mortality in patients between the age of 46 and 55, where mortality was 3.6 times higher in patients with sarcomeric HCM. Previous studies have identified sarcomeric HCM to associate with higher all-cause mortality rates3,5. However, no prior studies have investigated the difference in age-specific incidence of death, causes of death and may have been influenced by immortal time bias, leading to inflated effect estimates.

**Clinical Implications**

The 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 had less severe consequences of disease than patients with sarcomeric HCM. We hypothesize that hypertension and obesity 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 of HCM-- more likely to progress to advanced heart failure, experience arrhythmias, and die of HCM-related causes. Atrial fibrillation was both more prevalent and more consequential. 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.

**Limitations**

Several limitations should be acknowledged. First, our patients are followed at high-volume referral centers and are predominantly individuals with Caucasian ancestry. As such, findings may not be fully generalizable. Second, the study uses a pragmatic, real-world, 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**

Distinct differences in clinical characteristics, trajectory, and susceptibility to adverse events exist between patients with sarcomeric and non-sarcomeric HCM. Notably, patients with sarcomeric HCM had a significantly larger burden of heart failure and cardiac arrhythmias, both of which were associated with greater disease progression and adverse outcomes, including death. 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 patient care.

**ACKNOWLEDGEMENTS:**

The authors are grateful for the dedicated work of the site data managers. The authors express deep appreciation to the patients and families who live with HCM and partner with us in research.

**FUNDING SOURCES:**

SHaRe receives unrestricted research support from Bristol Myers Squib, Pfizer, and Cytokinetics. CSem is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (#1154992). JSW is supported by the Sir Jules Thorn Charitable Trust [21JTA], Medical Research Council (UK), British Heart Foundation [RE/18/4/34215], the National Institute for Health and Care Research (NIHR) Imperial College Biomedical Research Centre, and the NIHR Royal Brompton Cardiovascular Biomedical Research Unit. CRV was supported by grants from The Research Foundations at Rigshospitalet, Knud Højgaards Fond and Reinholdt W. Jorck og Hustrus Fond

**CONFLICT OF INTEREST AND DISCLOSURES:**

CRV, JCS, TDR and CSEM declare no relevant disclosures or competing interests.

CYH is a consultant for and/or receives research funding from Bristol Myers Squib, Pfizer, Cytokinetics, Tenaya, Biomarin, viz.AI and Lexicon. VNP receives research funding from BioMarin and consults for Nuevocor and Viz.ai. NKL is a consultant for Bristol Myers Squibb, Pfizer, Cytokinetics, Tenaya and Sarepta and receives research funding from Pfizer. SS isa consultant for Bristol Myers Squibb and Cytokinetics. MM is a consultant for Bristol Myers Squibb and Cytokinetics. JSW has consulted for MyoKardia (now Bristol Myers Squibb), Foresite Labs, and Pfizer. DJA is a consultant for Dinaqor.

**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. Helms Adam S., Thompson Andrea D., Glazier Amelia A., Hafeez Neha, Kabani Samat, Rodriguez Juliani, Yob Jaime M., Woolcock Helen, Mazzarotto Francesco, Lakdawala Neal K., et al. Spatial and Functional Distribution of MYBPC3 Pathogenic Variants and Clinical Outcomes in Patients with Hypertrophic Cardiomyopathy. *Circ. Genomic Precis. Med.* [Internet]. [cited 2020 Sep 9];0. Available from: https://www.ahajournals.org/doi/10.1161/CIRCGEN.120.002929

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. 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;

17. 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.

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= 2,999 | NON-SARCOMERIC HCM  N = 2,943 | p-value |
| --- | --- | --- | --- |
| **Demographic information** |  |  |  |
| Female | 1,293 (43%) | 1,030 (35%) | <0.001 |
| Age at HCM diagnosis | 37.8 (22.6 to 50.8) | 53.7 (42.0 to 63.2) | <0.001 |
| Age at first visit to a SHaRe site | 44 (29, 55) | 57 (46, 66) | <0.001 |
| Family proband | 2,429 (81%) | 2,834 (98%) | <0.001 |
| **Race** |  |  | <0.001 |
| White | 2,565 (86%) | 2,394 (81%) |  |
| Black | 84 (2.8%) | 145 (4.9%) |  |
| Asian | 113 (3.8%) | 131 (4.5%) |  |
| Other or Not Reported | 237 (7.9%) | 273 (9.3%) |  |
| **Clinical findings** |  |  |  |
| Systolic blood pressure | 120 (110, 131) | 130 (118, 140) | <0.001 |
| Diastolic blood pressure | 71 (65, 80) | 76 (70, 82) | <0.001 |
| Body mass index | 26.4 (23.1, 30.0) | 28.1 (25.1, 32.2) | <0.001 |
| Body surface area | 1.93 (1.74, 2.11) | 2.00 (1.83, 2.18) | <0.001 |
| **Echocardiography findings** |  |  |  |
| Maximal LV wall thickness | 18.0 (14.0 to 22.0) | 17.0 (14.0 to 20.0) | <0.001 |
| LV internal diameter in diastole | 43 (38, 47) | 44 (40, 49) | <0.001 |
| Indexed LV internal diameter in diastole | 22 (19, 25) | 22 (20, 25) | 0.3 |
| LV internal diameter in systole | 10 (8 to 27) | 14 (10 to 40) | <0.001 |
| Indexed LV internal diameter in systole | 6 (4 to 15) | 8 (4 to 20) | <0.001 |
| **Co-morbidities and medical history** |  |  |  |
| Hypertension | 576 (19%) | 1,189 (40%) | <0.001 |
| Atrial fibrillation | 380 (13%) | 384 (13%) | 0.7 |
| Syncope | 288 (9.6%) | 285 (9.7%) | >0.9 |
| Stroke | 80 (2.7%) | 93 (3.2%) | 0.3 |
| Family history of sudden cardiac death | 395 (13%) | 142 (4.8%) | <0.001 |
| History of cardiac arrest | 75 (2.5%) | 50 (1.7%) | 0.031 |
| New York Heart Association class III-IV | 215 (7.2%) | 258 (8.8%) | 0.023 |
| LV systolic dysfunction (LVEF<50%) | 111 (3.7%) | 51 (1.7%) | <0.001 |
| Severe LV systolic dysfunction (LVEF<35%) | 24 (0.8%) | 11 (0.4%) | 0.032 |
| **ESC risk score** |  |  | <0.001 |
| High (>6% per 5 years) | 148 (8.7%) | 64 (3.8%) |  |
| Moderate (4-6% per 5 years) | 216 (13%) | 128 (7.5%) |  |
| Low (<4% per 5 years) | 1,341 (79%) | 1,509 (89%) |  |
| Unknown | 1, 294 | 1,242 |  |
| n (%); Median (25% to 75%) | | | |
|  | | | |

| **Table 2:** All-cause and cause-specific mortality in sarcomeric and non-sarcomeric hypertrophic cardiomyopathy | | | |
| --- | --- | --- | --- |
| **CHARACTERISTIC** | **SARC(+)**, N = 2,999 | **SARC(-)**, N = 2,943 | **P-VALUE** |
| All-cause mortality | 308 (10%) | 283 (9.6%) | 0.4 |
| Causes of death |  |  | <0.001 |
| *Non-cardiovascular death* | 108 (35%) | 172 (61%) |  |
| *Heart failure* | 79 (26%) | 24 (8.5%) |  |
| *Sudden cardiac death* | 60 (19%) | 27 (9.5%) |  |
| *Not Recorded* | 32 (10%) | 21 (7.4%) |  |
| *Other cardiovascular death* | 21 (6.8%) | 24 (8.5%) |  |
| *Malignancy* | 8 (2.6%) | 15 (5.3%) |  |
|  |  |  |  |

**Figure 1:**

**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.

**Figure 2**



**Legend:** Density plots, showing the distribution of age (x-axis) at time of occurrence of each of six adverse outcomes associated with hypertrophic cardiomyopathy. Patients have been stratified into two groups according to whether they had sarcomeric (pink) or non-sarcomeric HCM (blue). The y-axis gives the raw number of patients associated with each outcome in a 5 year-period. The dots denote the median age of HCM diagnosis in the two groups.

**Figure 3:**



**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.

**Figure 4:**



**Legend**: Heatmaps showing the time-adjusted hazard ratios for the combined effect of each individual modifier (exposure, y-axis) and non-sarcomeric HCM (left panel) or sarcomeric HCM (right panel) on the hazard of the investigated outcomes (x-axis). 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 a significant interaction was found are included. The colors of the circles in the plots signify the relative significance of the association with darker red indicating a lower p-value.

**Figure 5**



**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.