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

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**ABSTRACT:**

***Background***: Rare variants in sarcomere genes are an important cause of hypertrophic cardiomyopathy (HCM). Clinical differences based on genetics have been identified in HCM but are underexplored, especially regarding the relative timing and sequence of events and the impact of cardiovascular comorbidities.

***Methods***: We conducted a longitudinal cohort study of genotyped HCM patients in the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Patients were classified as sarcomeric (pathogenic/likely pathogenic sarcomere gene variant present) or non-sarcomeric (genetically-elusive) HCM. The timing and influence of genetic status on the 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. The detrimental impact of atrial fibrillation and LV systolic dysfunction was greater in sarcomeric HCM compared to non-sarcomeric HCM. Additionally, patients with sarcomeric HCM had double the risk of sudden cardiac death, heart failure,stroke, or HCM-related death. Age-standardized incidence ratio for all-cause mortality was 1.32 (CI 1.18-1.48).

***Conclusions***: Sarcomeric and non-sarcomeric HCM have different clinical profiles. Obesity, hypertension and LV obstruction are central features of non-sarcomeric HCM, suggesting a role in the causal pathway for disease development, although not associated with an excess risk of adverse events. Atrial fibrillation and LV systolic dysfunction have a greater impact on sarcomeric HCM; associated with a higher risk of subsequent events and greater burden of severe heart failure and arrhythmias. Moreover, HCM-related mortality-rate is twice as high in sarcomeric versus 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 necessary 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 assessing the impact of comorbidities and 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:**

We studied 5,942 patients (39% female, 89% probands) with HCM in whom genetic testing had been performed and either identified a LP/P 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]) or white (OR 0.71 [CI, 0.64-0.80]), , 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]), obstructive physiology (gradient >30 mmHg; RR 1.51 [CI 1.43-1.60]) and undergo septal reduction therapy (RR \*\*\*). 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]).

Although slight differences could be detected, measures of cardiac function and LV wall thickness were similar between the two groups.

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**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 clinical course of HCM throughout life, 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 wider; spread over more of the lifespan. In contrast, there was a slightly narrower distribution of age at event in patients with non-sarcomeric HCM, mostly centered around the age HCM would be diagnosed.

**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 3** 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.

**Temporal patterns of cardiovascular events**

Our next objective was to evaluate whether adverse events occurred in a specific order and determine if timing differed 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 multiple modifier-outcome pairs, with one preceding the other (**Figure 3)**, i.e. the occurrence of one increased the occurrence of the other. Obesity was associated with a higher rate of subsequently 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 associated with the most subsequent events with 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 was then performed to determine how genetic status modified the impact of modifier-outcome pairs **Figure 4** shows the time-adjusted hazard ratios for modifier-outcome pairs, stratified by genotype. Effect ratios were calculated to determine the differential impact of the exposure in sarcomeric versus non-sarcomeric HCM. The impact of hypertension and obesity for subsequent development of LV obstruction was greater 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). The impact of obstruction, atrial fibrillation and ventricular arrhythmias for the development of subsequent adverse events was greater in sarcomeric HCM. The largest interaction effects were found for atrial fibrillation. In sarcomeric relative to non-sarcomeric HCM, atrial fibrillation increased 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]).

. 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]).

**Disease Trajectory**

To further characterize disease trajectory, we extended analysis to investigate the downstream occurrence of cardiovascular outcomes from the modifier-outcome pairs identified above. We identified trajectories in which the modifier-outcome pairing led to a significantly higher risk of a third outcome than either in isolation (**Table 2**). Although neither obesity nor LV obstruction was linked to stroke on their own (**Figure 3**), obesity leading to obstructive physiology was associated with a significantly higher risk of subsequent stroke (HR 1.68 [CI 1.14 to 2.49]). Atrial fibrillation leading to LV systolic dysfunction had a stronger temporal association with both stroke (HR 4.37 [CI 2.3 to 8.28]) and the composite VA outcome (HR 4.32 [CI 2.28 to 8.17]), than either outcome had on their own (no significant association between LV systolic dysfunction and stroke had been identified previously, **Figure 3**). Further results from this analysis are summarized in **Table 3**.

Next, we performed the analysis above separately for patients with sarcomeric HCM and non-sarcomeric HCM and identified different disease trajectories (**Supplementary Table 1** and **2**). Hypertension leading to obstruction was associated with subsequent stroke (HR 1.78 [CI 1.06 to 3]) in non-sarcomeric HCM but not in sarcomeric HCM. In contrast, the associations between obesity leading to LV obstruction and subsequent stroke was predominantly confined to sarcomeric HCM (HR 1.96 [CI 1.04 to 3.69]). In addition, the associations between atrial fibrillation leading to LV systolic dysfunction and subsequent stroke, or ventricular arrhythmia was also mostly features of sarcomeric HCM (HR of 5.53 and 4.87 respectively).

**DISCUSSION:**

In this study, we systematically compared cardiac phenotypes and clinical trajectories in sarcomeric and non-sarcomeric HCM. Sarcomeric HCM was characterized by a more severe phenotype with patients diagnosed at a younger age 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. Non-sarcomeric HCM was associated with a higher prevalence of obesity and hypertension. We also investigated the impact and temporal associations between various cardiovascular modifiers and HCM outcomes Atrial fibrillation and LV systolic dysfunction were significantly more impactful in sarcomeric HCM, conferring a greater risk of heart failure and death compared with non-sarcomeric HCM. \*\*\*Something here about the timeline/temporal sequence\*\*\*. Improved understanding of the clinical course of these major subtypes of HCM and will improve risk stratification and clinical management.

**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 obstructive physiology and common cardiovascular comorbidities (hypertension and obesity).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. 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 consistency of these findings support a hypothesis that hypertension and obesity may be in the causal pathway that lead to developing non-sarcomeric HCM.

**The Prevalence of and Impact of 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. From a clinical perspective, these findings suggest 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 worse 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 almost 4 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 atrial and ventricular 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**

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.

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**CONFLICT OF INTEREST AND DISCLOSURES:**

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

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**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 ejection fraction | 63.7±10.4 | 65.3±9.3 | <0.001 |
| Obstructive physiology | 467 (16%) | 849 (29%) | <0.001 |
| Left atrial diameter, mm | 40.2 ± 10.8 | 40.0 ± 10.3 | 0.5 |
| **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 |  |
| Absolute score in % per 5 years | 2.3 (1.5 to 3.6) | 1.8 (1.3 to 2.7) | <0.001 |
| n (%); Median (25% to 75%) | | | |
|  | | | |

**Table 2:** Disease trajectories

| **D1** | **D2** | **D3** | **D1 to D2 hazard ratio** | **D2 to D3 hazard ratio** |
| --- | --- | --- | --- | --- |
| Obesity | Obstruction | NYHA III-IV | 1.79 (1.58 to 2.02) | 2.80 (2.31 to 3.38) |
| Obesity | Obstruction | Stroke | 1.79 (1.58 to 2.02) | 1.68 (1.14 to 2.49) |
| Obesity | Atrial fibrillation | NYHA III-IV | 1.49 (1.28 to 1.73) | 3.00 (2.33 to 3.88) |
| Atrial fibrillation | LVSD | Composite VA | 2.71 (2.22 to 3.31) | 4.32 (2.28 to 8.17) |
| Atrial fibrillation | LVSD | Stroke | 2.71 (2.22 to 3.31) | 4.37 (2.3 to 8.28) |
| Atrial fibrillation | Composite VA | Stroke | 3.21 (2.42 to 4.24) | 2.97 (1.57 to 5.63) |
| LVSD | Atrial fibrillation | Stroke | 1.49 (1.13 to 1.97) | 2.63 (1.7 to 4.08) |

**Legend:** D1 signifies the first observed feature, D2 the second and D3 the third outcome. Only trajectories where the D2 to D3 hazard ratio is larger than that for either of the hazard ratios for the D1 or D2 features in simple analysis are included. *Abbreviations:* LVSD = left ventricular systolic dysfunction, NYHA = New York Heart Association functional class, VA = ventricular arrhythmia.

| **Table 3:** All-cause and cause-specific mortality in sarcomeric and non-sarcomeric hypertrophic cardiomyopathy | | | |
| --- | --- | --- | --- |
| **CHARACTERISTIC** | **Sarcomeric HCM**, N = 2,999 | **Non-sarcomeric HCM(-)**, 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. **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**



**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. **Abbreviations***:* *LVSD* = left ventricular systolic dysfunction, *NYHA* = New York Heart Association functional class, *VA* = ventricular arrhythmia.

**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. **Abbreviations***:* *LVSD* = left ventricular systolic dysfunction, *NYHA* = New York Heart Association functional class, *VA* = ventricular arrhythmia.

**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.