**Differences in Disease Trajectory, Comorbidities, and Mortality in Sarcomeric and Non-Sarcomeric Hypertrophic Cardiomyopathy**

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**ABSTRACT:**

***Background***: Sarcomere gene variants are a key cause of hypertrophic cardiomyopathy (HCM), and have been associated with worse prognosis. However, it is unclear whether the influence of comorbidities on clinical trajectories, the timing of clinical events, and causes of death differ between sarcomeric and non-sarcomeric HCM.

***Methods***: We conducted a multicenter longitudinal cohort study of genotyped children and adults in the Sarcomeric Human Cardiomyopathy Registry. 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), followed a median of 5.3 years, sarcomeric HCM (n=3,082) was associated with a younger age at diagnosis (median 38.1 versus 54.3 years, p<0.001), a higher proportion of females, and less obesity, hypertension and left ventricular (LV) obstruction. After age-standardization, sarcomeric HCM was associated with a higher burden of atrial fibrillation (age-standardized incidence [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]) than non-sarcomeric HCM.

All-cause mortality was similar (10.4% vs. 9.4%, p=0.20), however patients with sarcomeric HCM died younger (mean -7.8 years, p<0.001), with model-based survival-analysis estimating an average of 3.5 life-years lost between ages 44-85. Sarcomerc HCM was also associated with higher HCM-related mortality (HR 1.61 [CI 1.18-2.20]).

Temporal analysis identified atrial fibrillation as the strongest disease-modifier, increasing the 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 groups. Genotype-interaction analyses demonstrated a larger impact of atrial fibrillation and LV systolic dysfunction on adverse outcomes in sarcomeric versus non-sarcomeric HCM, with effect ratios up to 1.97 for severe heart failure and 1.86 for mortality (both p<0.01).

***Conclusions***: Genetic findings can refine risk stratification and inform clinical management in HCM. Sarcomeric HCM is associated with worse prognosis and may benefit from more vigilant surveillance for arrhythmias and systolic dysfunction, with a lower threshold for advanced therapies. Comorbidities, including hypertension and obesity, may be modifiable risk factors for patients with non-sarcomeric HCM.

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

**CLINICAL PERSPECTIVE**

**What is new?**

* Sarcomeric HCM had a worse clinical trajectory than non-sarcomeric HCM, with earlier disease onset, more arrhythmias (both atrial and ventricular), and a higher burden of heart failure.
* Non-sarcomeric HCM was associated with a higher prevalence of hypertension and obesity, suggesting that these comorbidities, in conjunction with other factors (e.g., 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, particularly 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, including sudden death and progressive heart failure, thus more vigilant surveillance 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 with disease development and emphasizing the importance of aggressive management of blood pressure and weight as a potential opportunity to modify disease severity and trajectory.

**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

VUS = Variant of uncertain significance

**INTRODUCTION**

Hypertrophic cardiomyopathy (HCM) is a complex cardiovascular disorder characterized by left ventricular hypertrophy (LVH), 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*1–3, but at least half of HCM patients do not have a clear monogenic etiology. Patients with HCM due to pathogenic sarcomere variants (sarcomeric HCM) are more likely to be female, to have a younger age at diagnosis of HCM, higher lifetime burden of adverse events, and less left ventricular outflow obstruction, compared to patients in whom a genetic etiology remains elusive despite genetic testing (non-sarcomeric HCM)4–8. However, how comorbidities influence clinical outcomes in sarcomeric versus non-sarcomeric HCM is less well understood. Such information would help to optimize the care of individual patients and their families.

With this study, we aimed to contrast disease trajectories in patients with sarcomeric and non-sarcomeric HCM, focusing on assessing the impact of comorbidities on the longitudinal sequence of events.

**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.4 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 – such as lysosomal and glycogen storage disorder (e.g., Fabry, Pompe,. Danon), and infiltrative cardiomyopathies (e.g, cardiac amyloidosis) – were excluded, as were individuals with variants of uncertain significance (VUS), or those without genetic testing. Genetic variants were classified based on criteria of the American College of Medical Genetics and Genomics and Association for Molecular Pathology.9,10 Variants with conflicting classification were reviewed by the SHaRe variant curation committee (led by J.I.) and assigned a consensus SHaRe-based classification.

***Clinical Features:***

Clinical characteristics and outcomes of interest were selected based on their potential 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 (with a gradient >30 mmHg defined as obstruction) 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 or 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.

To quantify survival differences, we calculated the restricted mean survival time (RMST) from age 44 (mean age at HCM diagnosis) up to the highest age at which at least 100 individuals remained under observation (to ensure reliable survival estimates). RMST was defined as the area under the Kaplan–Meier survival curve within this age interval and represents the average number of years lived. Group differences in RMST was computed non-parametrically and 95% confidence intervals were obtained by bootstrap resampling (1000 iterations).

We assessed the clinical course of HCM by examining the relative timing of developing 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 and LV systolic dysfunction. 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 online11.

**RESULTS:**

Among the 11,335 individuals with HCM in the SHARE registry, we included 6,120 (including n = 725, 12% with HCM diagnosed <age 18 years) 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). Reasons for exclusion included that no genetic testing had been performed (n = 3940), genetic testing only identified a VUS (n = 887), or identified a genocopy of HCM (n = 322). Overall 40% were female and 87% were probands. 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). 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 (median 2.3% versus 1.8%, p <0.001). They were also more likely to be female (OR 1.35 [CI, 1.22-1.50]) and self-report as white (OR 1.28 [CI, 1.09-1.50]), but less likely to report advanced symptoms at first visit (NYHA functional class III-IV, OR 0.74 [CI, 0.61-0.86]).

**Figure 1** depicts the relative risk of cardiovascular co-morbidities and adverse events in patients with non-sarcomeric versus sarcomeric HCM. Patients with sarcomeric HCM were less likely to have hypertension (RR 0.51 [CI 0.48-0.55]), obesity (RR 0.72 [CI 0.67-0.79]), obstructive physiology (RR 0.68 [CI 0.65-0.72]) and to have undergone septal reduction therapy (RR 0.86 [CI 0.78-0.96]). These differences remained significant after adjusting for age and sex in logistic regression. Obstructive physiology was also associated with obesity (OR 1.92 [CI, 1.71-2.16]), hypertension (OR 1.47 [CI, 1-31-1.65]), female sex (OR 1.22 [CI, 1.09-1.36]), older age at HCM diagnosis (OR 1.10 per 10 years [CI, 1.07-1.47]) and being a proband (OR 2.18 [CI, 1.85-2.58]), all with p<0.001. In multivariate logistic regression correcting for these factors, patients with sarcomeric HCM remained less likely to have obstructive physiology (OR 0.54 [CI, 0.47-0.61], p<0.001).

Regarding adverse events, 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 2.44 [CI 1.81-3.29]).

Since sex and age are important factors a

**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 atrial fibrillation, LV systolic dysfunction and the composite ventricular arrhythmia outcome in patients without these outcomes at first visit (**Figure 2**). Sarcomeric HCM was associated with a higher age-standardized incidence (ASI) of atrial fibrillation (ASI ratio 1.28 (CI: 1.16 to 1.40, p<0.001) and LV systolic dysfuntion (ASI ratio 1.31 [CI: 1.15 to 1.48], p =0.003). The biggest relative differences in age-specific incidence of atrial fibrillation was observed earlier in life (prior to age 45 years, **Figure 2B**). Patients with sarcomeric HCM also 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 <0.00, **Figure 2D**).

**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 (**Table 2**; 10.4% and 9.4% respectively, p=0.20), but causes of death differed between groups (**Table 2**). Cardiovascular mortality was significantly higher in sarcomeric , with cardiovascular mortality accounting for 51% (n=162 of 320 deaths) of deaths in sarcomeric HCM, compared with 24% (n=67 of 285 deaths) in non-sarcomeric HCM. Patients with sarcomeric HCM were more likely to die from sudden cardiac death (20% versus 9% of deaths, p<0.001) and heart failure (25 versus 8% of deaths, p<0.001). Overall, the odds of dying of either heart failure, sudden cardiac death or stroke was 2.51 times higher (CI: 1.86 to 3.44, p<0.001) in sarcomeric HCM, compared with non-sarcomeric HCM.

The cumulative incidence and age-specific incidence of HCM-related death (heart failure, stroke or SCD) were 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 duration as the time-scale), and incidence rates diverged significantly after 45 years of age. Between ages 46–55, the rate of HCM-related death was more than three-fold higher in sarcomeric HCM, and the overall standardized incidence ratio was 2.34 (CI: 1.98 to 2.75).

While all-cause mortality was similar in sarcomeric and non-sarcomeric HCM, patients with sarcomeric HCM died at a significantly younger age. Among those who died, the mean age at death was 7.8 years younger (CI: 5.4 to 10.2, p <0.001) in sarcomeric HCM. To account for censoring and delayed study entry, we estimated the restricted mean survival time (RMST) from 44 years of age (mean age at HCM diagnosis) to 85 years of age (oldest age at which at least 100 persons remained under observation). Patients with sarcomeric HCM lived, on average, 3.5 fewer years over this interval compared with those with non-sarcomeric HCM (RMST: 28.8 vs. 32.4 years; difference: 3.51 years; 95% CI: 1.74 to 4.84) (**Figure 4**).

Consistent with these findings, the age-adjusted standardized incidence ratio for all-cause mortality was 1.35 [CI: 1.21 to 1.51]), and the corresponding hazard ratio using age as the timescale (left-truncated at first SHaRe visit was 1.52 (CI: 1.29 to 1.80, p <0.001). Results remained consistent in sensitivity analysis including sex as a covariate.

**Temporal patterns of cardiovascular events**

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 5**), on the overall cohort of both 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]). LV 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 highest number of subsequent events with higher downstream rates of developing incident heart failure (HR 2.22 for NYHA III-IV symptoms, 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],). Since septal reduction therapy could potentially modify these outcomes we performed sensitivity analysis including septal reduction therapy as a time-varying covariate with consistent results to those reported above (see supplementary figure X).

Interaction analyses were performed to determine how genetic status modified the impact of disease modifiers on outcomes. **Figure 6** 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 compared with non-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, nearly a decade 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.4,12–14 Overall, the prevalence of obstructive physiology was twice as high in non-sarcomeric HCM. Obesity was associated with an 70% higher risk of obstruction as seen previously15. In a previous study, LV obstruction was linked to a higher risk of sudden cardiac death, stroke and death in HCM16. In our study, LV obstruction was not independently associated with these outcomes. This discrepancy may be explained by confounding by age and sex, which we now adjust for, and more aggressive anticoagulation.

Hypertension and specifically elevated diastolic blood pressure has been identified as an important comorbidity associated with non-sarcomeric HCM in Mendelian randomization analyses.17,18 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 be causal factors in the development of non-sarcomeric HCM.

**Sarcomeric HCM is Associated with a Higher Burden and Consequences of Adverse Cardiovascular Outcomes, including HCM-Related Mortality**

After age-adjustment, we found a higher risk of atrial and ventricular arrhythmias and LV systolic dysfunction in patients with sarcomeric HCM. Age-standardized incidence rates for these outcomes were 28-37% higher than in non-sarcomeric HCM. For atrial fibrillation, this was primarily due to its emergence at a younger age in those with sarcomeric HCM, while the risk of ventricular arrhythmias was similar in youth but persisted into old age in sarcomeric but not non-sarcomeric HCM.

Moreover, the downstream impact of atrial fibrillation and LV systolic dysfunction was more consequential in sarcomeric HCM. Once atrial fibrillation occurred, subsequent rates of LV systolic dysfunction, ventricular arrhythmias and death were each ~2-fold higher in patients with sarcomeric compared to non-sarcomeric HCM.

Finally, sarcomeric HCM had twice the HCM-related mortality rate of non-sarcomeric HCM. HCM-related mortality diverged from age 45 onward, and a three-fold excess mortality was found between ages 46–55. The crude difference in mean lifespan of decedents between the groups was 7.8 years. In model-based age-specific survival analysis accounting for censoring, delayed study entry and correcting for survivor effects, patients with sarcomeric HCM had a 3.5-year shorter restricted mean survival time between ages 44 and 85. This quantifies the average number of life-years lost attributable to sarcomeric disease within a clinically relevant age window.

Previous studies have identified sarcomeric HCM to associate with higher all-cause mortality rates, but did not examine the age-specific incidences of death or causes of death and were vulnerable to immortal-time bias – namely, counting survival time before diagnosis of HCM as exposure time – leading to inflated effect estimates.4,6We minimized these limitations by using age as time-scale and performing left-truncation at the first SHaRe visit, allowing us to better isolate biologically driven excess mortality risk.

**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 risk factor management for potential benefit on disease modification. On the other hand, patients with sarcomeric HCM appeared to be more susceptible to adverse outcomes related to HCM (i.e. advanced heart failure, atrial and ventricular arrhythmias, HCM-related mortality) independent of comorbidities. Although risk factor management remains essential for best care, these findings suggest that sarcomeric HCM may be driven more intrinsically by the underlying genetic variant. 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 outcomes is an important avenue of further research. Sudden cardiac death risk was also higher in sarcomeric HCM and persisted to older ages. As such, patients with sarcomeric HCM, may benefit from more intensive surveillance and management of ventricular and atrial arrhythmias and LV systolic dysfunction.19–21

Current risk stratification algorithms for sudden cardiac death in HCM do not account for genetic substrate.22–24 However, in this study, the presence of 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. Thus, a portion of sudden death risk that is not currently explained by existing algorithms may be accounted for in polygenic or Mendelian risk. Including 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 predominantly self-identify as white. As such, findings may not be fully generalizable to those followed in community settings 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. Sarcomeric HCM was associated with earlier disease onset, a greater burden of heart failure and cardiac arrhythmias, persisting into old age, and a shorter lifespan. Non-sarcomeric HCM was associated with greater background obesity and hypertension, suggesting a role in disease etiology, likely in combination with polygenic risk. Genetic characterization can help guide therapy in HCM, with vigilant longitudinal surveillance for arrhythmias and systolic dysfunction in sarcomeric HCM and aggressive management of comorbidities to potentially modify disease in non-sarcomeric HCM.

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**CONFLICT OF INTEREST AND DISCLOSURES:**

CRV, JCS, and TDR 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= 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*** | ***132 (41% of deaths)*** | ***200 (70% of deaths)*** | ***<0.001*** |
| *Malignancy* | 8 (6%) | 15 (8%) |  |
| *Other non-cardiovascular* | 124 (94%) | 185 (92%) |  |
| ***Cardiovascular death*** | ***162 (51% of deaths)*** | ***67 (24% of deaths)*** | ***<0.001*** |
| *Heart failure* | 79 (49%) | 24 (36%) |  |
| *Sudden cardiac death* | 63 (39%) | 26 (39%) |  |
| *Stroke* | 5 (3%) | 9 (13%) |  |
| *Other cardiovascular death* | 15 (9%) | 8 (12%) |  |
| ***Unknown*** | ***26* (8*% of deaths)*** | ***18 (*6.3*% of deaths)*** | ***0.29*** |

**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 four rows indicates the percentage of the entire cohort who died. The remaining rows reflect the distribution of causes among those who died in each group and the percentages refers to the proportion of deaths attributed to each cause.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:**



**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

AI-genereret indhold kan være ukorrekt.]()

**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

AI-genereret indhold kan være ukorrekt.

**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:**

**Et billede, der indeholder tekst, Kurve, skærmbillede, Font/skrifttype

AI-genereret indhold kan være ukorrekt.**

**Legend:** Survival curves and restricted mean survival time (RMST) difference between sarcomeric and non-sarcomeric HCM. Kaplan–Meier curves showing age-specific survival from age 44 to 85 for individuals with sarcomeric (pink) and non-sarcomeric (blue) hypertrophic cardiomyopathy. The shaded area between the curves represents the difference in restricted mean survival time, quantifying the average number of life-years lost between the two groups over this age range.

**Figure 5:**

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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 6:**

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

AI-genereret indhold kan være ukorrekt.**

**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 italic). 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.