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

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

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**ABSTRACT:**

***Background***: Rare variants in sarcomere genes are a common cause of hypertrophic cardiomyopathy (HCM), however, genetic testing does not identify a monogenic cause in most patients. Previous research suggests clinical differences between patients with and without sarcomere variants, but comprehensive comparison has not been performed. \*ALSO ADD SOMETHING ABOUT TEMPORAL SEQUENCE, ETC\*\*

***Methods***: We conducted a longitudinal cohort study including patients with HCM from 12 international, high-volume cardiomyopathy clinics in the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Inclusion required genetic testing that identified pathogenic or likely pathogenic variants (LP/P) in the 8 classic sarcomere genes (sarcomeric HCM) or genetically-elusive (non-sarcomeric) HCM. Clinical characteristics and outcomes were compared between these groups.

***Results***: We analyzed 5,454 patients (38% female, 89% probands, 50% sarcomeric HCM). Patients with sarcomeric HCM were ~13 years younger at diagnosis (median age 36.7 versus 49.6 years) and had a lower burden of cardiovascular comorbidities (obesity, hypertension). Non-sarcomeric HCM was associated with higher left ventricular (LV) ejection fraction (+1.6 % [CI: 1.0-2.1]) and LV gradient (+19.7 mmHg [CI: 17.4-22.0]), but less LV hypertrophy (maximal LV wall thickness -1.3 mm [CI: 0.9 to 1.6]). Although obstructive physiology was twice as frequent in patients with non-sarcomeric HCM, it did not impact prognosis. Atrial fibrillation, LV systolic dysfunction and ventricular arrhythmias were more frequent in sarcomeric HCM, with age-adjusted incidence rates approximately 33% higher than in non-sarcomeric HCM. Time-to-event analysis revealed greater additive effect of cardiovascular co-morbidities on developing atrial fibrillation, ventricular arrhythmias, heart failure outcomes and death in patients with sarcomeric HCM Although all-cause mortality was similar in both groups (~10%), patients with sarcomeric HCM were younger at death and twice as likely to die from HCM-related death (sudden cardiac death, heart failure or stroke).

***Conclusions***: Sarcomeric and non-sarcomeric HCM differ in clinical characteristics, cardiac phenotypes, and outcomes. Sarcomeric HCM is associated with a younger age at diagnosis and lower burden of cardiovascular comorbidites, but higher incidence of atrial and ventricular arrhythmias, heart failure, and higher disease-related mortality. These distinctions have implications for risk stratification and management.

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

**CLINICAL PERSPECTIVE**

**What is new?**

* Although hypertension, obesity and obstructive physiology are more common in non-sarcomeric HCM, these features are not associated with excess risk of advanced heart failure or sudden cardiac death.
* Patients with sarcomeric HCM had a higher risk of cardiac arrhythmias and LV systolic dysfunction and double the risk of HCM-related mortality compared with patients with non-sarcomeric HCM.
* Atrial fibrillation and LV systolic dysfunction were important predictors of ventricular arrhythmias and advanced heart failure in both sarcomeric and non-sarcomeric HCM, but with a greater additive effect in sarcomeric HCM.

**What are the clinical implications?**

* Patients with sarcomeric HCM are at higher risk for disease-related adverse outcomes, including death, thus more intensive surveillance for cardiac arrhythmias and LV dysfunction may be appropriate.
* Integrating genetic testing results may improve clinical risk stratification algorithms and predictive models for cardiovascular 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 characterized 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, such as *MYH7*, *MYBPC3*, *TNNT2*, and others.1,2 Previous studies have investigated the impact of specific genetic mutations and sarcomere variants overall on HCM phenotypes and outcomes.3,4 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 risk factors, and outcomes between these two groups is crucial for optimizing the care of individual patients and for informing personalized treatment strategies. In light of these gaps in the literature, our study aims to contrast the prognosis and outcomes 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 progression, risk stratification, and providing 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 initial visit at a SHaRe site, demographics, clinical characteristics, echocardiographic measurements, genetic testing results, cardiovascular comorbidities, and longitudinal, prospective assessment 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 patients who had undergone clinical evaluation and genetic testing for sarcomere gene variants at a SHaRe site. Patients were stratified into two groups based on the presence or absence 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.5,6 Patients carrying LP/P sarcomere variants were defined to have sarcomeric HCM, while patients negative for sarcomere variants were defined to have non-sarcomeric HCM.

***Clinical Features:***

Features of interest were selected based on their clinical relevance and potential impact on patients' 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, non-sustained ventricular tachycardia (VT), cardiac arrest, composite ventricular arrhythmia (VA) outcome (including sudden cardiac death, aborted sudden cardiac death, sustained ventricular tachycardia and appropriate implantable cardioverter-defibrillator [ICD] therapy), and atrial fibrillation.
5. Stroke.
6. Mortality: All-cause and HCM-related mortality (sudden cardiac death [SCD], heart failure and stroke).

These phenotypic 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 and the potential influence of genetic etiology on disease progression and management.

***Statistical Analyses*:**

SHaRedata through June 2022 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. For the analysis of cardiac function and remodeling, we report results from both simple linear regression and multivariable linear regression to adjust for age, sex, and body surface area. Linear mixed-effects regression was performed when investigating results from cardiopulmonary exercise testing.

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, a composite ventricular arrhythmia outcome, stroke, cardiac transplantation, LVAD implantation, and death. We used Cox proportional hazards modeling with age as the time-scale, left-truncated at the time of the first SHaRe visit. Time-varying covariates (exposures) included obesity, hypertension, LV obstruction, atrial fibrillation, onset of NYHA class III-IV symptoms, LV systolic dysfunction, and a composite ventricular arrhythmia outcome. We corrected for sex and age at diagnosis with HCM. Our analysis also investigated potential interactions between the exposures and genetic status (non-sarcomeric versus sarcomeric HCM) for all outcomes. Results from this analysis are reported from a combined model that includes both patients with sarcomeric and non-sarcomeric HCM (stratified for genetic status if an interaction was identified). We also applied a Bonferroni correction for multiple testing. In case of a significant interaction, we also investigated and reported the combined effect of genetic status and the exposures.

Finally causes of death were compared between patients with sarcomeric and non-sarcomeric HCM.

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 online7.

**RESULTS:**

This study focused on 5,454 patients (38% female, 89% probands) diagnosed with HCM in whom genetic testing had been performed and either identified a LP/P genetic sarcomere variant (sarcomeric HCM, n= 2715) or was negative (non-sarcomeric HCM, n= 2739). Median age at time of HCM diagnosis was 46.1 years (IQR: 30.4 to 58.3) and age at initial visit to a SHaRe site was 50 years (IQR: 35 to 62). At initial SHaRe visit, hypertension was prevalent or had been diagnosed in 29%, atrial fibrillation in 13%, stroke in 2.8%; 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 ~13 years younger at diagnosis (median age 36.7 versus 49.6 years, p<0.001) and had higher European Society of Cardiology (ESC) 5-year SCD risk scores (median 2.5% versus 1.9%, p <0.001). Patients with non-sarcomeric HCM were less likely to be female (OR 0.71 [CI, 0.64-0.80]), white (OR 0.71 [CI, 0.64-0.80]), or have a family history of sudden cardiac death (OR 0.36 [CI, 0.30-0.42]), but more likely to report significant symptoms at baseline (New York Heart Association [NYHA] functional class III-IV).

**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 classic cardiovascular co-morbidities (RR for hypertension 1.83 [CI 1.72-1.97]; RR for obesity 1.46 [CI 1.34-1.60]) and obstructive physiology (gradient >30 mmHg; RR 1.51 [CI 1.42-1.60]). Patients with sarcomeric HCM were more likely to experience cardiac arrhythmias (RR for atrial fibrillation 1.12 [CI 1.02-1.22] and RR for composite VA 1.92 [CI 1.60-2.31]) and left ventricular systolic dysfunction (RR 1.72 [CI 1.45-2.04]).

**Sarcomeric versus Non-sarcomeric HCM**

*Cardiac Structure and Function*

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: 1.0 to 2.1], p <0.001; **Table 1**), remaining significant after correction for age and sex (+2.2 %-points [CI: 1.6 to 2.8], p <0.001). Patients with sarcomeric HCM had greater maximal LV wall thickness, both in absolute terms (+1.3 mm [CI: 0.9 to 1.6], p <0.001) and when converted to BSA-adjusted z-scores (+1.5 z [CI: 1.1 to 1.9], p <0.001).

We investigated the peak oxygen uptake from 2895 cardiopulmonary exercise tests, performed in 1537 patients (50% with sarcomeric HCM) and found that carrying a sarcomere variant was associated with a lower peak oxygen uptake (unadjusted -0.6 ml O2/kg/min [CI: -1.3 to 0.1], p = 0.083 ; adjusted for age, sex, BMI, presence of atrial fibrillation and effort [highest achieved respiratory exchange ratio] -1.9 ml O2/kg/min [CI: -2.7 to -1.1], p <0.001). For further information on clinical characteristics, see **Table 1**.

*LV obstruction*

Non-sarcomeric HCM patients had higher LV gradient at baseline (+19.7 mmHg [CI: 17.4 to 22.0], p <0.001). During 17,154 person-years of follow-up in 2456 patients, the cumulative incidence of LV obstruction was almost twice as high in patients with non-sarcomeric HCM versus sarcomeric HCM (**Supplementary Figure 1A**). Age-specific incidences of LV obstruction was higher in patients with non-sarcomeric HCM across all age-groups (**Supplementary Figure 1B**). Since patients with non-sarcomeric HCM had a higher burden of cardiovascular risk factors, we performed Cox regression adjusted for age at HCM diagnosis, sex, presence of hypertension or obesity and being a proband. Patients with non-sarcomeric HCM had an adjusted HR of 1.59 (CI: 1.32-1.92) for the presence of obstructive physiology.

*Cardiac arrhythmias*

The incidence of atrial fibrillation was evaluated over 29,923 person-years of follow-up in 4270 patients without atrial fibrillation at baseline. The cumulative incidence of atrial fibrillation was similar in non-sarcomeric and sarcomeric HCM during follow-up (log-rank p =0.078) (**Figure 2a**). To account, for factors associated with developing atrial fibrillation, we performed multiple Cox proportional hazards models adjusting for age, obesity and hypertension. In this analysis, having sarcomeric HCM was associated with a HR of 1.41 (CI: 1.18 to 1.67, p=0.0001) for developing atrial fibrillation. Next, we calculated the age-specific incidence of atrial fibrillation and found this to be significantly higher in patients with sarcomeric HCM across all evaluated age-groups (**Figure 2c**), with an age-standardized incidence ratio of 1.34 (CI: 1.21 to 1.47, p <0.0001) for atrial fibrillation in sarcomeric HCM (27 [CI 24-30] versus 21 [CI: 19-24] per 1000 person-years).

The incidence of the composite ventricular arrhythmia outcome was evaluated over 35,703 person-years of follow-up in 4726 patients, without ventricular arrhythmias at baseline. The cumulative incidence was higher in sarcomeric HCM during follow-up (p =0.004) (**Figure 2b**). The age-specific incidence of the composite ventricular arrhythmia outcome was numerically higher in patients with sarcomeric HCM, across all evaluated age-groups (**Figure 2d**), with the most pronounced difference in patients older than 65 years. Overall, the age-standardized incidence rate in sarcomeric and non-sarcomeric HCM was 7.6 (CI 6.4-8.9) versus 5.4 (CI: 4.1-7.0) per 1000 person-years. This corresponds to a standardized incidence ratio of 1.35 (CI: 1.15 to 1.59, p <0.001) for ventricular arrhythmias in sarcomeric HCM.

*Left ventricular systolic dysfunction*

The incidence of LV systolic dysfunction was evaluated over 38,410 person-years of follow-up in 4939 patients with LVEF>50% at baseline. The cumulative incidence of LV systolic dysfunction was similar during follow-up (p =0.120) (**Supplementary Figure 2a**). However, the age-specific incidence rates of LV systolic dysfunction were numerically higher in patients with sarcomeric HCM (**Supplementary Figure 2b**) with an age-standardized incidence rate of LV systolic dysfunction of 14 (CI 12-16) versus 10 (CI: 8-12) per 1000 person-years. This corresponds to a standardized incidence ratio of 1.33 (CI: 1.17 to 1.50, p <0.001) in sarcomeric HCM.

**Incident events during longitudinal follow up**

To evaluate the longitudinal course of HCM, we evaluated the timing of onset of 6 adverse outcomes associated with HCM: atrial fibrillation, New York Heart Association [NYHA] class III/IV symptoms, LV systolic dysfunction (LVEF<50%), composite ventricular arrhythmias, cardiac transplantation, and death. Results from this analysis are summarized in **Figure 3**, which shows the distribution of events according to age. Consistent with a younger age at diagnosis of HCM, the age-distribution of investigated outcomes skewed earlier in life for patients with sarcomeric HCM. In addition, we observed a sharper peak in the distribution of age at occurrence of these outcomes in patients with non-sarcomeric HCM, mostly centered around the time of diagnosis of HCM. This contrasts with a wider distribution of incident events in sarcomeric HCM; spread over most of adulthood (**Figure 3**).

**Temporal patterns of cardiovascular events and genetic modifiers**

Our next objective was to evaluate the co-occurrence of cardiovascular features and assess the likelihood of their occurrence in a specific temporal pattern (i.e., one feature preceding the occurrence of another feature). In addition, we sought to assess if these associations were modified by genetic findings. To do this, we performed Cox proportional hazards modelling, including time-varying effects of key exposures and adjusted for sex. A summary of results from this analysis are shown in **Figure 4**. Hypertension and obesity showed an association with incident LV obstruction (HR 1.40 and 1.78 respectively). However, the effect of these exposures were modified by genetic status, with a large effect in non-sarcomeric HCM and no effect observed in sarcomeric HCM (**Supplementary Figure 3**). Obstruction and obesity were also associated with developing atrial fibrillation (obstruction, HR 1.74 and obesity, HR 1.54) and NYHA III-IV symptoms (obstruction, HR 2.13 and obesity, HR 1.92). Atrial fibrillation was found to have a strong association with incident heart failure outcomes (HR 2.03 for NYHA III-IV symptoms, HR 2.76 for LVSD, and 7.6 for cardiac transplantation all p <0.001), ventricular arrhythmias (HR 3.13 [CI: 2.34-4.2], p<0.001), stroke (HR 2.27 [CI: 1.66-3.12], p<0.001) and death (HR 1.95 [CI: 1.63-2.33], p<0.001). Interaction analysis found that sarcomere status modified the effect of atrial fibrillation on developing NYHA III-IV functional limitations, LVSD, ventricular arrhythmias, and death, with a larger additive effect of this exposure in patients carrying sarcomere variants (**Supplementary Figure 3)**. LVSD was associated with NYHA III-IV functional limitations (HR 2.15 [CI: 1.65-2.80], p <0.001), cardiac transplantation (HR 37 [CI: 25-56], p <0.001), ventricular arrhythmias (HR 3.82 [CI 2.73-5.3] p <0.001) and death (HR 3.8 [CI 3.09-4.7], p <0.001). For outcomes in which a significant interaction was found between an exposure and sarcomere variant status, the combined effect can be seen according to sarcomere variant status in **Supplementary Figure 3**.

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

Finally, we investigated the timing and causes of death in patients with sarcomeric and non-sarcomeric HCM. At the end of follow-up, 541 (9.9%) patients had died, with similar all-cause mortality in patients with sarcomeric and non-sarcomeric HCM (10% and 9.5% respectively). The mean age at time of death was lower among patients with sarcomeric HCM (63 versus 70 years, p <0.0001). Additionally, patients with sarcomeric HCM had a higher likelihood of dying from sudden cardiac death (21 versus 11% of deaths) and heart failure (27 versus 9.2% of deaths). Overall, having sarcomeric HCM was associated with an odds ratio of 2.70 (CI: 1.94 to 3.82, p<0.0001) of dying of either heart failure or sudden cardiac death. A summary of the causes of death in our cohort can be seen in **Table 2**. Next, we sought to investigate the cumulative incidence of HCM-related death (heart failure , stroke or SCD), from time of inclusion in SHaRe and the age-specific incidence of HCM-related death in patients with sarcomeric and non-sarcomeric HCM. Results from this analysis can be seen in **Figure 5**, which shows a higher cumulative incidence of HCM-related death during follow-up (corresponding to a hazard ratio of 1.69 [CI: 1.22 to 2.35, p =0.002] in Cox modelling), and a significantly higher age-specific incidence in patients older than 45 years of age, with an overall standardized incidence ratio of 2.3 (CI: 1.9 to 2.7) for HCM-related death in patients with sarcomeric HCM. Patients with sarcomere variants were also found to have a higher age-standardized incidence of cardiovascular death (SIR 1.90 [CI: 1.61 to 2.23) and all-cause mortality (SIR 1.27 [CI: 1.13 to 1.43]) (**Supplementary Figure 4**)

**DISCUSSION:**

We describe differential cardiac phenotypes and clinical outcomes in sarcomeric and non-sarcomeric HCM in a large observational cohort. Notably, patients with sarcomeric HCM were younger at diagnosis, had more substantial LVH, had a higher burden of cardiac arrhythmias, severe heart failure, and an HCM-related mortality-rate twice that of their non-sarcomeric counterparts. While non-sarcomeric HCM was associated with more obesity, hypertension, and LV obstruction. Atrial fibrillation and LV systolic dysfunction were significant precursors of severe cardiovascular outcomes associated with twice the rates of ventricular arrhythmias and advanced heart failure outcomes in sarcomeric and non-sarcomeric HCM. These findings offer valuable insights into the clinical course of these two major subtypes of HCM and have potential implications regarding risk stratification and management.

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

Clinical characteristics and objective measures of cardiac function and remodeling associated with sarcomeric and non-sarcomeric HCM have been characterized in prior genotype-phenotype studies. These studies have reported differences in sex, age at diagnosis, presence of co-morbidities, LV wall thickness and LV gradient, consistent with those reported here.3,8–10 We additionally provide new information regarding differences in cardiopulmonary exercise testing. Overall, patients had a mild to moderate reduction in exercise capacity. Although the difference in maximum oxygen uptake was insignificant in unadjusted analysis, when adjusted for age, sex, body-size and effort, 11,12 patients with sarcomeric HCM had a 10% lower exercise capacity compared to patients with non-sarcomeric HCM. This could suggest that while the overall functional limitation might appear similar between these two groups, inherent biological differences lead to a differential impact on the ability to respond to the increased demands during physical exertion and could contribute to more pronounced exercise limitation in sarcomeric HCM.

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

Consistent with prior studies, we observed that patients with non-sarcomeric HCM were more likely to have classic cardiovascular comorbidities and an obstructive phenotype.3,8,9,19 However, we add to this knowledge base by providing detailed information on the timing and downstream effect of LV obstruction. We found that the age-specific incidence of LV obstruction in non-sarcomeric HCM to be at least 40% higher than in sarcomeric HCM across all examined age-groups. Overall, the age-standardized incidence rate was twice as high in non-sarcomeric HCM. We confirm that obesity is an independent risk factor for developing obstructive physiology, with an 80% higher rate of obstruction in obese patients and a larger effect in patients with non-sarcomeric HCM.20 Notably, while LV obstruction has previously been associated with an higher risk of ventricular arrhythmias, stroke and death, 21 we did not find LV obstruction to be linked to these outcome after adjustment for age and sex. However, we did find a strong association between LV obstruction and emergence of NYHA class III/IV symptoms irrespective of genetic substrate with HCM.

Hypertension and specifically elevated diastolic blood pressure has been identified as an important exposure leading to HCM in patients with non-sarcomeric disease. 22,23 In accordance with this, the prevalence of hypertension was almost twice as high in non-sarcomeric HCM. However, the impact of hypertension on progression of HCM has not been investigated previously. In this study, hypertension was associated with developing LV obstruction but no significant associations with other adverse cardiovascular outcomes in time-to-event analysis was found after adjusting for age and sex.

**Adverse Cardiovascular Outcomes and HCM-Related Mortality are Higher in Sarcomeric HCM**

Patients with sarcomeric HCM had a higher prevalence of atrial and ventricular arrhythmias and LV systolic dysfunction. Even though the cumulative incidence of LV systolic dysfunction and atrial fibrillation were similar in sarcomeric and non-sarcomeric when monitored from the first visit at a SHaRe site, the age-specific incidence was consistently higher in sarcomeric HCM across all age-groups. Overall, the age-standardized incidence rates were approximately 33% higher in patients with sarcomeric HCM for both atrial fibrillation, ventricular arrhythmias and LVSD. Notably, both atrial fibrillation and LV systolic dysfunction were important precursors of adverse cardiovascular outcomes, and with a larger disease modifying effect in patients with sarcomeric HCM. This suggests that healthcare providers should pay particular attention to these outcomes, especially in patients with sarcomeric HCM, both since they are amenable to medical intervention but also since they suggest a poorer long-term prognosis24,25.

The cumulative incidence of the composite ventricular arrhythmia outcome was higher in sarcomeric HCM during follow-up. Investigation of age-specific incidence rates revealed that the largest relative difference in incidence was observed in patients older than 65.

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 the rate is 3.7 times higher in patients with sarcomeric HCM.

**Clinical Implications**

The findings from this study have important implications for clinical practice and future research in HCM. Non-sarcomeric HCM was characterized by a higher burden of cardiovascular risk factors and LV obstruction, and these patients may benefit from aggressive management targeting hypertension control and risk factor modification. On the other hand, patients with sarcomeric HCM were more likely to die of HCM-related causes, progress to LV systolic dysfunction and experience cardiac arrhythmias.

Patients with sarcomeric HCM, may benefit from more intensive screening for and surveillance of ventricular and atrial arrhythmias and LV dysfunction, particularly given the adverse nature of these outcomes.12,24,25 Current risk stratification algorithms for sudden cardiac death in HCM do not include genetic information26–28. However, in this study carrying a LP/P genetic variant in a sarcomere gene was associated with a standardized incidence ratio of 1.35 for a composite ventricular arrhythmia outcome, and notably with the highest relative and absolute difference in elderly patients (>65 years). Furthermore, LV systolic dysfunction was also identified to be a risk factor for ventricular arrhythmias with a HR> 2 in both sarcomeric and non-sarcomeric HCM. These findings suggest that implementing information regarding genetic substrate and LV ejection fraction into future models could improve model performance and better guide management decisions regarding primary prevention ICD. Future research should aim to further investigate the underlying mechanisms contributing to the observed differences in disease progression and outcomes between patients with sarcomeric and non-sarcomeric HCM. Advancements in comprehensive genetic profiling and comprehensive phenotyping may provide further insights into the complex interplay between genetic variants, clinical characteristics, and disease progression in HCM.

**Limitations**

Several limitations should be acknowledged in this study. First, our sample was limited to patients followed at high-volume referral centers, and our cohort primarily consists of probands and individuals with Caucasian ancestry and does not fully represent the general population of patients with HCM. Second, the study had a pragmatic, real-world, partially retrospective observational design, and therefore, is subject to a potential selection and information bias. Third, although we attempted to control for potential confounders through various adjustments, there may be residual confounding that could impact the results of the study. Fourth, in time-to-event analysis we chose to use age (left-truncated at time of first SHaRe visit) as the time-scale. Using standard follow-up from time of first visit as the time-scale would yield different results in assessing associations between different exposures and downstream outcomes. Finally, we did not have comprehensive data on the use of guideline-directed medical therapy and the potential impact of drugs on cardiovascular co-morbidities or occurrence of outcomes could not be evaluated.

**Conclusion**

In conclusion, our study provides insights into the clinical characteristics and natural history in patients with sarcomeric and non-sarcomeric HCM, contributing to our understanding of the heterogeneity within HCM. We identified distinct differences in clinical characteristics, temporal progression, and outcomes which underscore 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 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 time of initial SHaRe visit.

| Characteristic | SARCOMERIC HCM N= 2,715 | NON-SARCOMERIC HCM  N = 2,739 | p-value |
| --- | --- | --- | --- |
| **Demographic information** |  |  |  |
| Female | 1,144 (42%) | 939 (34%) | <0.001 |
| Age at HCM diagnosis | 37.5 (22.5 to 50.5) | 53.2 (41.2 to 63.0) | <0.001 |
| Age at initial visit to a SHaRe site | 43 (28, 55) | 56 (45, 66) | <0.001 |
| Family proband | 2,154 (80%) | 2,627 (98%) | <0.001 |
| **Race** |  |  | <0.001 |
| White | 2,356 (87%) | 2,227 (81%) |  |
| Black | 72 (2.7%) | 134 (4.9%) |  |
| Asian | 82 (3.0%) | 98 (3.6%) |  |
| Other or Not Reported | 205 (7.6%) | 280 (10%) |  |
| **Clinical findings** |  |  |  |
| Systolic blood pressure | 120 (110 to 130) | 130 (118 to 140) | <0.001 |
| Diastolic blood pressure | 71 (65 to 80) | 76 (70 to 82) | <0.001 |
| Body mass index | 26.3 (23.1 to 30.0) | 28.1 (25.0 to 32.3) | <0.001 |
| Body surface area | 1.92 (1.73 to 2.11) | 2.00 (1.83 to 2.18) | <0.001 |
| **Echocardiography findings** |  |  |  |
| Maximal LV wall thickness | 18.0 (14.5 to 22.0) | 17.0 (14.0 to 20.0) | <0.001 |
| LV internal diameter in diastole | 43 (39 to 48) | 45 (40 to 49) | <0.001 |
| Indexed LV internal diameter in diastole | 22.7 (20.0 to 25.4) | 22.2 (19.8 to 24.9) | 0.001 |
| LV internal diameter in systole | 26 (22 to 30) | 27 (22 to 31) | <0.001 |
| Indexed LV internal diameter in systole | 13.5 (11.3 to 16.1) | 13.2 (11.2 to 15.4) | 0.003 |
| **Cardiopulmonary exercise testing** | N = 762 | N = 775 |  |
| Peak oxygen uptake (ml O2/kg/min) | 21.7 (16.5 to 28.6) | 21.1 (16.6 to 28.1) | 0.37 |
| Peak oxygen uptake (% of predicted) | 75 (61 to 91) | 83 (69 to 100) | <0.001 |
| **Co-morbidities and medical history** |  |  |  |
| Hypertension | 518 (19%) | 1,054 (38%) | <0.001 |
| Atrial fibrillation | 357 (13%) | 357 (13%) | 0.9 |
| Syncope | 282 (10%) | 263 (9.6%) | 0.3 |
| Stroke | 68 (2.5%) | 85 (3.1%) | 0.2 |
| Family history of sudden cardiac death | 486 (18%) | 197 (7.2%) | <0.001 |
| History of cardiac arrest | 70 (2.6%) | 45 (1.6%) | 0.016 |
| New York Heart Association class III-IV | 196 (7.2%) | 244 (8.9%) | 0.022 |
| LV systolic dysfunction (LVEF<50%) | 101 (3.7%) | 48 (1.8%) | <0.001 |
| Severe LV systolic dysfunction (LVEF<35%) | 22 (0.8%) | 10 (0.4%) | 0.031 |
| **ESC risk score** |  |  | <0.001 |
| High (>6% per 5 years) | 172 (11%) | 76 (4.8%) |  |
| Moderate (4-6% per 5 years) | 215 (13%) | 122 (7.8%) |  |
| Low (<4% per 5 years) | 1,216 (76%) | 1,374 (87%) |  |
| Unknown | 1,112 | 1,167 |  |
| n (%); Median (25% to 75%) | | | |
|  | | | |

| **Table 2:** All-cause and cause-specific mortality in sarcomeric and non-sarcomeric hypertrophic cardiomyopathy | | | |
| --- | --- | --- | --- |
| **CHARACTERISTIC** | **SARC(+)**, N = 2,715 | **SARC(-)**, N = 2,739 | **P-VALUE** |
| All-cause mortality | 281 (10%) | 260 (9.5%) | 0.3 |
| Causes of death |  |  | <0.001 |
| *Non-cardiovascular death* | 93 (33%) | 147 (57%) |  |
| *Heart failure* | 77 (27%) | 24 (9.2%) |  |
| *Sudden cardiac death* | 58 (21%) | 28 (11%) |  |
| *Not Recorded* | 25 (8.9%) | 22 (8.5%) |  |
| *Other cardiovascular death* | 21 (7.5%) | 25 (9.6%) |  |
| *Malignancy* | 7 (2.5%) | 14 (5.4%) |  |

**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**

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**Legend:** Incidence of arrhythmias in sarcomeric versus non-sarcomeric HCM, excluding patients diagnosed with these events prior to or at initial 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 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 (shown in grey area). 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**



**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 4:**



**Legend:** Heatmap showing the time-adjusted hazard ratios of being diagnosed with one of 8 cardiovascular features (x-axis) predicated on of the presence of one of the 7 pre-defined exposures (y-axis). Hazard ratios larger than 1 are shown with Bonferroni corrected 95% confidence intervals if Bonferroni corrected p <0.05 (i.e. uncorrected p <0.0009). Colors indicate if an interaction with genetic subgroup was found and if non-sarcomeric HCM status attenuated the effect (blue) or sarcomeric HCM status did (pink). Hazard ratios are adjusted for sex and if a significant interaction was observed stratified analysis was performed.

**Figure 5**

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

**Supplementary Figure 1**



**Legend:** Incidence of obstruction in patients who are genotype-positive versus -negative for sarcomere variants. **A.** Cumulative incidence of obstruction since first SHaRe evaluation, including numbers at risk by year. **B.** Age-specific incidence rates of obstruction, including total person-years at risk in each age-group.

**Supplementary Figure 2**



**Legend:** Incidence of left ventricular systolic dysfunction in patients who are genotype-positive versus -negative for sarcomere variants. **A.** Cumulative incidence of obstruction since first SHaRe evaluation, including numbers at risk by year. **B.** Age-specific incidence rates of obstruction, including total person-years at risk in each age-group.

**Supplementary Figure 3:**



**Legend**: Heatmaps showing the time-adjusted hazard ratios for the combined effect of each individual exposure and non-sarcomeric HCM (left panel) or sarcomeric HCM (right panel) on the hazard of investigated outcomes. All hazard ratios are adjusted for sex and computed using age as the time-scale 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 effect of genetic status on the disease-modifying effect of the exposure on the outcome. Darker blue colors signify a larger additive effect of having non-sarcomeric HCM, while darker pink is used for a larger additive effect of sarcomeric HCM.

**Supplementary Figure 4**



**Legend:** Incidence of cardiovascular mortality in patients who are genotype-positive (pink) versus -negative (blue) for sarcomere variants. Panel **A.** Cumulative incidence since first SHaRe evaluation, including numbers at risk by year. Panel **B.** Age-specific incidence rates, including total person-years at risk in each age-group. The age-standardized incidence rate (ASI) has been added as the final group. The standardized incidence ratio (SIR) has been added for each age-group at the bottom of the plot.