**Associations between female sex, sarcomere variants and clinical outcomes in hypertrophic cardiomyopathy**

**Running Title**: Lakdawala. Sex differences in HCM

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**ABSTRACT**

**Background**: The impact of sex on phenotypic expression in hypertrophic cardiomyopathy (HCM) has not been well characterized in genotyped cohorts.

**Methods:** Retrospective cohort study from an international registry of patients receiving care at experienced HCM centers. Sex-based differences in baseline characteristics and clinical outcomes were assessed.

**Results:** Of 5,873 patients (3,788 genotyped), 2,226 (37.9%) were women. At baseline, women were older (49.0±19.9 vs. 42.9±18.4 years, p<0.001) and more likely to have pathogenic/likely-pathogenic sarcomeric variants (SARC+; 51% vs 43%, p<0.001) despite equivalent utilization of genetic testing. Age at diagnosis varied by sex and genotype despite similar distribution of causal genes. Women were 3.6 to 7.1 years older at diagnosis (p<0.02) except for patients with *MYH7* variants where age at diagnosis was comparable for women and men (n=492; 34.8±19.2 vs 33.3±16.8 years, p=0.39). Over 7.7 median years of follow up, NYHA III-IV heart failure (HF) was more common in women (HR 1.87, CI 1.48-2.36, p<0.001), after controlling for their higher burden of symptoms and outflow tract obstruction at baseline, reduced ejection fraction, SARC+, age and hypertension. All-cause mortality was increased in women (HR 1.50, CI 1.13-1.99, p<0.01), but neither ICD utilization nor ventricular arrhythmia varied by sex.

**Conclusions:**  In HCM, women are older at diagnosis, partly modified by genetic substrate. Regardless of genotype, women were at higher risk of mortality and developing severe HF symptoms. This points to a sex-effect on long-term myocardial performance in HCM, which should be investigated further.

**Key Words:** Hypertrophic Cardiomyopathy, women, sarcomere

**NON-STANDARD ABBREVIATIONS AND ACRONYMS**

HF: Heart failure

HFpEF: Heart failure with preserved ejection fraction

HCM: Hypertrophic cardiomyopathy

SHaRe: Sarcomeric Human Cardiomyopathy Registry

ICD: Implantable cardioverter defibrillator

MYBPC3: The gene which encodes myosin binding protein C

MYH7: The gene which encodes beta-myosin heavy chain

SARC-: HCM patients without a sarcomere mutation

Sarc+: HCM patients with a sarcomere mutation

LV: Left ventricle, left ventricular

LVEF: Left ventricular ejection fraction

LVOTO: Left ventricular outflow tract obstruction

e’: Peak early diastolic septal tissue Doppler velocity

E: Peak velocity of early diastolic inflow

LVAD: Left ventricular assist device

SCD: Sudden cardiac death

**INTRODUCTION**

Sex-based differences in clinical presentation, natural history, and management are increasingly appreciated across cardiovascular medicine, including heart failure (HF) and cardiomyopathies. Women with HF are diagnosed at an older age and have different clinical profiles and etiologies compared to men, including a greater burden of HF with preserved ejection fraction (HFpEF)1. Hypertrophic cardiomyopathy (HCM) is an important cause of HF and is often caused by autosomal dominant variants in sarcomere genes2,3. Women have been underrepresented in published HCM cohorts, comprising between 26-45%4–6 of patients in referral centers. Nevertheless, they appear to present at a more advanced stage of disease, be older at diagnosis, have a higher symptom burden, and carry greater risk for HF and mortality4,7, compared with men. The reasons underlying sex-related differences in phenotypic manifestations and clinical outcomes remain unclear. Disparities in diagnosis and management have been cited as possible explanations for differences in clinical outcomes4,5. Alternatively, the effects of sex hormones on cardiac remodeling have been invoked and studied in model systems with conflicting findings8,9. Finally, the penetrance of sarcomere variants may be lower in women10–12, providing a possible biological rationale for relative underrepresentation in HCM cohorts and different outcomes. However, prior clinical studies have not thoroughly examined whether the expression of sarcomere variants differs by sex and may account for different clinical trajectories.

In this study, we examined how women with HCM differ from men with respect to presenting characteristics and subsequent clinical outcomes by analyzing the Sarcomeric Human Cardiomyopathy Registry (SHaRe), a large international database of patients with primary cardiomyopathies3. The scale of SHaRe, in combination with robust genetic assessment, enables examination of sex-related differences in the penetrance and expression of sarcomere variants. We compared age of diagnosis, a surrogate for penetrance, and incident occurrence of key outcomes between men and women with different genetic substrates. To determine whether provision of care varied by sex, we examined the use of invasive septal reduction therapies and implantable cardioverter defibrillator (ICD) placement.

**METHODS**

Institutional review board and ethics approval was obtained in accordance with policies applicable to each SHaRe site. The data that support the findings of this study are available from the corresponding author upon reasonable request. A full description of methods, including study population, genetic testing, outcomes definitions, and statistical analysis are available in the **supplemental materials**.

**RESULTS**

Genetics and Baseline characteristics

 A total of 5,873 HCM patients were included in this study, of whom 2,226 (37.9%) were women. Demographic, genetic, clinical and echocardiographic characteristics of men and women at the time of their first SHaRe site visit are presented in **Table 1**. Baseline NYHA functional class was available for 84% of patients and revealed that class III-IV symptoms were present in 21% of women versus 9% of men (p<0.001). Women were also more likely to have obstructive physiology (31.3% vs. 25.2%, p<0.001)

Genetic testing was performed in 3,788 (65%) patients, with a similar proportion of men and women. However, females were 17% more likely than males to have a sarcomere mutation (SARC+) (p<0.001) (**Figure 1A**). In SARC+ patients, the distribution of disease genes did not vary significantly between women and men (p=0.06), and most commonly involved *MYBPC3* (52.0% and 59.9%) and *MYH7* (31.2% vs. 26.8%), excluding patients with multiple variants. There was also no significant difference in the proportion of female and male patients with two or more pathogenic/likely pathogenic sarcomere variants (1.6% vs. 1.6%, p=0.79) or a VUS (7.4% vs. 9.8%, p=0.22).

Age of diagnosis varied with sex, genotype, and disease gene. In the overall cohort, women were ~5.4 years older (mean) than men (p<0.001) at the time of HCM diagnosis (**Figure 1B)**. As shown in **Table 2**, the difference in age at diagnosis was most pronounced in patients without sarcomere mutations (SARC-) (women 7.1 years older). SARC+ women were 3.6 years older than SARC+ men. Specifically, in patients with *MYBPC3* (n=972) and thin filament pathogenic/likely-pathogenic variants (n=170), women were ~4.8 and ~6.7 years older at the time of diagnosis respectively. In contrast, men and women with *MYH7* variants (n=492) had a similar age at diagnosis (33.3±16.8 vs 34.8±19.2 years, p=0.4).

Since sarcomeric HCM is an autosomal dominant disease, an equal number of male and female patients would be anticipated. However, women comprised only 38% of this cohort. Therefore, we examined whether geographic region, era of care, or reason for referral were associated with the relative underrepresentation of women in SHaRe. The frequency of women varied significantly by site (p<0.05) and was higher in the United States versus European sites as depicted in **Supplemental** **Figure 1**. This difference remained significant in the subset of 2,030 patients with sarcomeric HCM, and if analyses were restricted to probands only. Additionally, the relatively low frequency of women has not changed over time; either by decade since 1990, nor after the first major publication (20055) examining sex-differences in HCM (36.6% vs. 38.2%, p=0.34) and women were demonstrated to be more symptomatic than men at presentation.

 Several echocardiographic features differed significantly between men and women. As shown in table 1, absolute maximal wall thickness, left ventricular (LV) cavity size and left atrial diameter were significantly larger in men, while LV ejection fraction (LVEF) was higher in women. However, after controlling for body surface area, women had significantly *greater* wall thickness, left atrial diameter and LV cavity size compared with men. Obstructive physiology (defined as LV outflow tract obstruction (LVOTO)≥30 mmHg at rest or with provocation) and maximal LVOT gradient (at rest or with the Valsalva maneuver) were greater in women (47±45 vs. 36±38 mmHg, p<0.001). This finding may be related to smaller LV cavity size in women because after controlling for LV end diastolic diameter, the sex-based difference in LVOTO did not persist (p=0.17). Echocardiographic assessments of diastolic function were available for a subset of the cohort (n=1,364 with tissue Doppler and spectral Doppler, n=2,488 with only spectral Doppler). Although peak early diastolic septal tissue Doppler velocity (e’) was lower (6.1±2.6 vs. 7.0±2.7, p<0.0001), and the peak velocity of early diastolic inflow (E wave; 83.5±32.7 vs. 75.0±23.7, p<0.0001) and the ratio of E/e’ (15.6±9.2 vs. 11.9±6.3, p<0.0001) were higher in females, these differences were not significant after controlling for age and hypertension.

 When the analysis was restricted to only SARC+ or SARC- patients, differences in baseline symptom burden and echocardiographic findings at diagnosis were similar to those in the overall HCM population **(Supplemental Table 1**).

Clinical outcomes

 Follow up duration was similar for women and men (median time from first to last encounter 7.8 vs 7.7 years, p=0.75). Women were more likely than men to undergo invasive septal reduction therapies (myectomy or alcohol septal ablation; 20.8% vs. 15.8%, p<0.001) (**Table 3, Figure 2A**). Additionally, myectomy was performed ~6 months sooner after the index visit in women versus men (0.59 years (IQR: 0.47, 0.96) versus 1.08 years (IQR: 0.83, 1.31), p=0.048. Sex-based differences in the utilization and timing of septal reduction therapies did not persist after controlling for maximal outflow tract gradient and/or NYHA functional class. However, amongst patients undergoing septal reduction therapies, alcohol septal ablation was performed more frequently in women than men (24.9 vs. 17.6%, p<0.01). In a multivariable model (**Table 4**), the proportionally greater utilization of septal ablation amongst women (HR 2.33; 95% CI 1.44, 3.77, p<0.001) persisted after controlling for age, maximal wall thickness, and severity of outflow tract obstruction.

Amongst patients with NYHA class I-II symptoms at index presentation, women were significantly more likely to progress to NYHA III-IV symptoms (HR 1.89, 95% CI 1.6-2.23, p<0.001; **Figure 2B**) during follow up. This difference persisted (HR 1.87, 95% CI 1.48-2.36, p<0.001) after controlling for age, sarcomere variant status, the presence of obstructive physiology, history of hypertension, and baseline LVEF (**Table 4**). Progression to systolic dysfunction (defined as LVEF <50%) was rare (incidence <1%/year) and did not differ by sex overall. However, amongst *MYBPC3* variant carriers, the risk of systolic dysfunction was higher in males (HR 1.53, 95% CI 1.03-2.26, p=0.03). Cardiac transplantation and/or LV assist device (LVAD) implantation was an infrequent outcome (n=62) and no significant sex-based differences could be identified.

In contrast to HF, ventricular arrhythmias were not more prevalent in women (**Figure 2C**). Utilization of ICDs was comparable in women and men in unadjusted analysis (HR for women 1.11, 95% CI 0.96-1.28, p=0.18), and after controlling for genetic status and ESC risk score category (HR for women 1.15, 95% CI 0.98-1.34, p=0.08). Women were at modestly increased risk of incident atrial fibrillation (HR 1.21, 95% CI 1.01-1.46, p=0.04) in a multivariable model which included age, left atrial diameter and hypertension. The risk of stroke was higher in women (HR 1.48, 95% CI 1.11-1.98, p=0.007) after controlling for age, hypertension and history of atrial fibrillation.

Women had greater all-cause mortality than men following index visit (**Figure 2D, Table 3 and 4**). Overall, 43% of deaths were HCM-related, (caused by HF, sudden death, or stroke) with similar frequency of causes in women and men. In a multivariable analysis controlling for age, sarcomere mutation status, systolic dysfunction (LVEF<50%) and left atrial diameter, women remained at increased risk for death (HR 1.50, 95% CI 1.13-1.99, p<0.01). This excess hazard persisted after excluding patients with NYHA III-IV symptoms at the initial evaluation.

**DISCUSSION**

 In this study, we report sex-based differences in presenting characteristics and clinical outcomes of HCM in a large international cohort. The major findings are: 1) Women were more likely than men to have sarcomere pathogenic/likely-pathogenic variants; 2) Women were diagnosed at an older age across genotypes except in patients with *MYH7* variants 3) Women had 50% higher mortality, 50% higher risk of stroke and a greater burden of prevalent and incident HF, even after controlling for their more prevalent outflow tract obstruction; 5) Women were older and more symptomatic when presenting for specialty care, but HCM-specific management thereafter, including genetic testing, overall septal reduction therapies and ICD implantation was not significantly different based on sex.

Sex based differences in age at diagnosis with HCM

Similar to smaller prior studies4,5, women were under-represented in this study, comprising <40% of our cohort. Women were also older at diagnosis and presentation than men, despite worse symptoms at initial evaluation. However, in this study, we were able to leverage the genetic characterization and greater scale of the SHaRe cohort to gain novel insights into these observations. The sex-based difference in the age of diagnosis was more pronounced in genetically tested patients with non-sarcomeric HCM (women 7.1 years older at diagnosis) compared to sarcomeric HCM (women 3.6 years older at diagnosis). Moreover, amongst patients with sarcomeric HCM, there were gene-specific differences in age of diagnosis. Women with disease caused by *MYBPC3* and thin filament variants were 4.8 and 6.7 years older than men at diagnosis, respectively (p<0.02). Although reduced/delayed penetrance of HCM in women with sarcomeric variants has been noted, predominantly in individuals with *MYBPC3* variants,10–14disease appears to develop at similar ages in women and men with HCM caused by *MYH7* variants (table 2). Using age of diagnosis as a surrogate for penetrance, our findings newly suggest that sex does not appear to modify the penetrance of pathogenic *MYH7* variants as much as variants in other sarcomeric genes.

Sex-based differences in HCM outcomes

While age of diagnosis or disease penetrance may be delayed, HF and mortality appear to be worse in women with HCM. The increased burden of HF in women with HCM may be related to differences in LVOTO and/or diastolic function, but not systolic dysfunction, as this was infrequent and not more common in women. Indeed, we found that women with *MYBPC3* variants were 35% less likely to develop systolic dysfunction than males. The increased frequency and severity of LVOTO in women has been previously noted4–6 and may be related to their relatively smaller LV cavity size15 as noted in this analysis. Further studies are needed to determine if the other important determinants of LVOTO, including mitral leaflet area, relative position of the papillary muscles, also vary by sex.

Notably, incident HF was 87% more common in women even after controlling for obstruction, systolic dysfunction, hypertension and age, suggesting diastolic dysfunction as a contributor to excess HF in women. We found relatively impaired diastolic function in women amongst the subset of patients who underwent spectral and tissue Doppler imaging at baseline evaluation. Indeed, sarcomere variants which cause HCM have been shown to impair relaxation In model systems spanning the spectrum from isolated sarcomere filaments to human sarcomere mutation carriers without overt HCM16. Prior investigation into sex-based differences of sarcomere variants on diastolic function in HCM are limited but support our findings. In a clinicopathologic study of 71 patients with sarcomeric HCM who underwent septal myectomy, women had worse diastolic function assessed by echocardiography, more interstitial fibrosis on histology, and lower expression of calcium handling proteins (PLN and SERCA2)8. Baseline echocardiographic features of diastolic dysfunction were also more common in women in a Mayo clinic HCM cohort with a high frequency of LVOTO4. As in HFpEF17, these findings suggest that diastolic abnormalities are more prominent in women with HCM and may underlie their greater burden of HF.

The underlying mechanisms for sex-based differences in the penetrance and expression of sarcomeric HCM are not well understood. Rodent models of HCM have revealed sex-based differences in hypertrophy signaling pathways, cardiomyocyte calcium sensitivity and ultimately ventricular remodeling9,18. However, murine studies have not pointed to a consistent effect of sex hormones on HCM development. Future human studies should interrogate the impact of sex-specific differences in cardiac physiology and female reproductive health on HCM outcomes, including age at menarche/menopause, pregnancy and associated complications including pre-eclampsia.19

 In our cohort, mortality was 50% higher in women. The increased risk of mortality observed in women is similar to recent publications from a Mayo Clinic4 and a collaborative European cohort7. However, this study provides new insights. Increased mortality was not simply a reflection of the greater prevalence of sarcomeric HCM, known to be associated with worse outcomes3, in women as it persisted after controlling for genotype. Additionally, the excess mortality seen in women was not secondary to stroke or sudden death. Thus, excess HF is the most plausible HCM-specific mechanism contributing to decreased survival in women.

Societal Factors and HCM

Although in the minority in all centers despite more prominent obstructive physiology and symptoms at presentation, the proportion of women in US centers was 14% higher than in European centers. This observation suggests that societal and cultural factors may influence referral to specialized HCM centers, including provider delay in cardiology referral or patient reporting of symptoms. Although not previously studied in HCM, disparate utilization of advanced cardiac therapies adversely affecting the care of female patients has been previously documented in acute myocardial infarction20, end stage HF21 and atrial fibrillation22. Additionally, healthcare provider sex and gender and patient perceptions about the cause of their symptoms can both negatively influence referral for cardiac testing in women23,24 However, after care was initiated at SHaRe sites, we generally did not identify sex-based differences in HCM-specific management. Overall utilization of septal reduction therapies and ICD implantation were similar in men and women after controlling for factors which influence these decisions, severity of LVOTO and sudden cardiac death (SCD) risk factors respectively. However, amongst patients undergoing septal reduction, women were proportionally more likely to undergo alcohol septal ablation, even after controlling for their older age.

Limitations

A central question asked in this study was whether the decreased frequency of female patients in HCM cohorts is related to decreased penetrance of sarcomeric variants or decreased access to specialty HCM care. Our observational and retrospective study design does not resolve this question. Additionally, female reproductive history and pubertal status were not available in this study; limiting investigation into the impact of sex-hormones on our findings.

Conclusions

Women are underrepresented in HCM specialty centers despite a higher burden of presenting symptoms and obstructive physiology. There appear to be sex-gene interactions that affect penetrance, such that disease development is initially slower in females, particularly in non-sarcomeric HCM, but similar in males and females with disease caused by *MYH7* variants. However, once clinical HCM is present, disease severity, particularly HF and mortality, appears to be greater in women Further study is needed to better characterize the underlying biological and non-biological factors that contribute to disparate disease experiences in males and females.

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**DISCLOSURES**

Drs. Day, Ho, Lakdawala, Olivotto and Saberi have received consulting income from MyoKardia. Drs. Leinwand and Seidman are Founders and Shareholders of MyoKardia and Dr. Leinwald has a sponsored research agreement with MyoKardia.

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**TABLES**

**Table 1. Baseline characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** | **Female** | **Male** | **P-value\*** |
| **N = 5,873** | **N = 2,226 (37.9%)** | **N = 3,647 (62.1%)** |
|  |  |  |
| Age at Diagnosis, years, median (IQR) | 44.9(33.9, 61.2) | 49.0(36.8, 65.3) | 42.9(32.4, 58.6) | < 0.001 |
| Follow-up Time, years, median (IQR) | 7.7 (3.1, 15.4) | 7.8 (3.3, 15.3) | 7.7 (3.0, 15.6) | 0.75 |
| Race |  |  |  |  |
|   White | 4,888 (87.0%) | 1,840 (86.6%) | 3,048 (87.3%) | 0.16 |
|   Black | 223 (4.0%) | 82 (3.9%) | 141 (4.0%) |
| Family Proband, N (%) | 5,306 (91.1%) | 2,009 (90.7%) | 3,297 (91.4%) | 0.74 |
| Genetic testing, N (%) | 3,788 (64.5%) | 1,410 (63.3%) | 2,378 (65.2%) | 0.16 |
| SARC+, N (% of those genotyped) | 1,747 (46.1%) | 717 (50.9%) | 1,030 (43.3%) | < 0.001 |
| Body Mass Index (kg/m2) ± SD  | 27.8 ± 5.9 | 27.7 ± 6.9 | 27.8 ± 5.3 | 0.72 |
| Hypertension, N (%) | 548 (9.3%) | 242 (10.9%) | 306 (8.4%) | 0.002 |
|  Systolic BP (mmHg) | 124.6 ± 18.7 | 124.2 ± 20.8 | 124.8 ± 17.2 | 0.48 |
|  Diastolic BP (mmHg) | 74.0 ± 10.8 | 72.5 ± 11.2 | 74.9 ± 10.5 | < 0.001 |
| NYHA Class III or IV, N\* (%) | 407 (13.8) | 237 (21.6) | 171 (9.3) | < 0.001  |
| Maximal Wall Thickness, mm ± SD  | 18.2 ± 5.8 | 17.8 ± 5.8 | 18.5 ± 5.9 | < 0.001 |
| Maximal Wall Thickness index, mm/m2 ± SD | 9.7 ± 3.8 | 10.3 ± 3.8 | 9.4 ± 3.8 | < 0.001 |
| LV end diastolic diameter, mm ± SD  | 43.7 ± 7.4 | 41.3 ± 7.1 | 45.2 ± 7.3 | < 0.001 |
| LV end diastolic diameter index, mm/m2 ± SD | 23.0 ± 5.3 | 23.5 ± 5.3 | 22.7 ± 5.3 | < 0.001 |
| LV ejection fraction, % ± SD  | 65.1 ± 9.5 | 66.0 ± 9.7 | 64.6 ± 9.3 | < 0.001 |
| Obstructive physiology by echo, (N) % | 1,616 (27.5) | 696 (31.3) | 920 (25.2) | < 0.001  |
| LV outflow tract gradient at rest, mm Hg ± SD  | 30.0 ± 33.8 | 35.5 ± 37.1 | 26.6 ± 31.1 | < 0.001 |
| Left atrium anterior-posterior diameter, mm ± SD  | 42.7 ± 11.0 | 41.5 ± 11.1 | 43.4 ± 10.9 | < 0.001 |
| Left atrial diameter index, mm/m2 ± SD | 23.0 ± 5.8  | 24.1 ± 6.5 | 22.3 ± 5.3 | < 0.001 |
| ESC Risk Score, median (IQR) | 2.1 (1.5, 3.2) | 2 (1.4, 3.1) | 2.2 (1.6, 3.3) | 0.06 |
| ESC Risk Score, N (%) < 4% 4-6% >6% | 2,563 (83.9)148 (4.8)344 (11.3) | 952 (85.4)59 (5.3)104 (9.3) | 1,611 (83.0)89 (4.6)240 (12.4) | 0.03 |

\* p-values were calculated using Student’s t-test for continuous variables and Fisher’s exact test for discrete variables

**Table 2. Age of diagnosis in men and women by sarcomere status and disease gene**

|  |  |  |  |
| --- | --- | --- | --- |
|   | Female | Male | p-value\* |
|   | N | Age (SD) | N | Age (SD) |   |
| Sarc -  | 549 | 53.0 (18.6) | 1039 | 45.9 (17.3) | <0.0001 |
| Sarc +  | 701 | 38.7 (18.3) | 1016 | 35.1 (16.7) | <0.0001 |
| MYBPC3 | 363 | 41.5 (16.8) | 609 | 36.8 (16.0) | <0.0001 |
| MYH7 | 220 | 34.8 (19.2) | 272 | 33.3 (16.8) | 0.387 |
| Thin filament | 84 | 37.6 (18.3) | 86 | 30.9 (19.4) | 0.021 |

Analysis restricted to patients who underwent genetic testing and with age of diagnosis available, excluding patients with multiple pathogenic or likely pathogenic variants. The bottom three columns represent only SARC+ patients.

\*p-values were calculated from Fisher’s exact test

**Table 3. Incident outcomes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** | **Female** | **Male** |  |
|  | **N = 5,873** | **N = 2,226** | **N = 3,647** | **P-value\*** |
| **Outcomes** |  |  |  |  |
| Alcohol Septal Ablation | 227 (3.9%) | 122 (5.5%) | 105 (2.9%) | < 0.001 |
| Myectomy | 857 (14.6%) | 367 (16.5%) | 490 (13.4%) | 0.002 |
| Cardiac Transplantation | 83 (1.5%) | 40 (2.0%) | 43 (1.3%) | 0.07 |
| Atrial Fibrillation | 1,273 (21.7%) | 488 (21.9%) | 785 (21.5%) | 0.74 |
| Stroke | 235 (4.0%) | 110 (4.9%) | 125 (3.4%) | 0.005 |
| Cardiac Arrest | 150(2.6%) | 59(2.7%) | 91(2.5%) | 0.78 |
| ICD implantation | 1,244 (21.2%) | 492 (22.1%) | 752 (20.6%) | 0.19 |
| Death | 462 (7.9%) | 213 (9.6%) | 249 (6.8%) | <0.001 |
| **Composite Outcomes**  |  |  |  |  |
| Heart Failure Composite† | 1,111 (18.9%) | 593 (26.6%) | 518 (14.2%) | < 0.001 |
| Ventricular Arrhythmia Composite‡ | 313 (5.3%) | 111 (5.0%) | 202 (5.5%) | 0.39 |

\*p-values were calculated using Fisher’s exact test, †Heart Failure (HF) Composite: first occurrence of cardiac transplantation, left ventricular assist device (LVAD) implantation, or New York Heart Association (NYHA) functional class III-IV symptoms, ‡ Ventricular Arrhythmic Composite: first occurrence of sudden cardiac death (SCD), resuscitated cardiac arrest, or appropriate implantable cardioverter-defibrillator (ICD) therapy.

**Table 4. Multivariable Models**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Heart failure composite\*** |  |  |  |  |
| **Covariate** | **Hazard Ratio** | **Lower 95%** | **Upper 95%** | **p value**‡ |
| Female | 1.85 | 1.48 | 2.32 | <0.001 |
| Obstruction**†** | 2.07 | 1.64 | 2.63 | <0.001 |
| LVEF<50% | 1.95 | 1 | 3.83 | 0.05 |
| Hypertension | 2.23 | 1.61 | 3.09 | <0.001 |
| Sarc(+) | 0.83 | 0.64 | 1.07 | 0.15 |
| Age | 1 | 0.99 | 1.01 | 0.87 |
|  |  |  |  |  |
|  |  |  |  |  |
| **NYHA III-IV** |  |  |  |  |
| **Covariate** | **Hazard Ratio** | **Lower 95%** | **Upper 95%** | **p value**‡ |
| Female | 1.87 | 1.48 | 2.36 | <0.001 |
| Obstruction\* | 2.11 | 1.65 | 2.7 | <0.001 |
| LVEF<50% | 1.73 | 0.85 | 3.54 | 0.13 |
| Hypertension | 2.08 | 1.49 | 2.89 | <0.001 |
| Sarc(+) | 0.86 | 0.66 | 1.12 | 0.25 |
| Age | 1 | 1 | 1.01 | 0.19 |
|  |  |  |  |  |
| **Mortality** |  |  |  |  |
| **Covariate** | **Hazard Ratio** | **Lower 95%** | **Upper 95%** | **p value**‡ |
| Female | 1.45 | 1.16 | 1.82 | 0.001 |
| Sarc(+) | 1.12 | 0.83 | 1.51 | 0.47 |
| Age, years | 1.02 | 1.01 | 1.03 | <0.001 |
| LVEF<50% | 2.45 | 1.46 | 4.11 | <0.001 |
| Left atrial diameter, mm | 1.05 | 1.04 | 1.06 | <0.001 |

\* Heart Failure (HF) Composite: first occurrence of cardiac transplantation, left ventricular assist device (LVAD) implantation, or New York Heart Association (NYHA) functional class III-IV symptoms.

**†** Obstruction as a dichotomous variable defined as ≥30 mm Hg at rest or with provocation.

‡ p-values were calculated from Cox proportional hazards regressions

**FIGURE LEGENDS**

**Figure 1. Women are older than men at the time of HCM diagnosis and were more likely to have a sarcomere mutation.**

1. Frequency of pathogenic/likely-pathogenic sarcomere variants in patients who had undergone genetic testing, excluding patients with multiple variants.
2. Age at HCM diagnosis for all women (shaded pink) and men (shaded blue), irrespective of sarcomere variant status. Where age of diagnosis overlapped, the frequency of female patients is represented by the darker color. Mean age of diagnosis labeled and indicated by line.

**Figure 2. Time to event curves dichotomized by sex**

1. Invasive septal reduction therapy
2. Incident severe HF (NYHA III-IV), excluding patients with severe HF at baseline
3. Ventricular arrhythmia composite (first occurrence of sudden cardiac death, resuscitated cardiac arrest, or appropriate ICD therapy).
4. Mortality

The pink and blue lines represent the event curves in women and men respectively.

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