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ORIGINAL ARTICLE

Associations Between Female Sex, Sarcomere Variants, and Clinical Outcomes in Hypertrophic Cardiomyopathy

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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 5873 patients (3788 genotyped), 2226 (37.9%) were women. At baseline, women were older (49.0±19.9 versus 42.9±18.4 years, $P<0.001$) and more likely to have pathogenic/likely pathogenic sarcomeric variants (HCM patients with a sarcomere mutation; 51% versus 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 versus 33.3±16.8 years, $P=0.39$). Over 7.7 median years of follow-up, New York Heart Association III-IV heart failure was more common in women (hazard ratio, 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, HCM patients with a sarcomere mutation, age, and hypertension. All-cause mortality was increased in women (hazard ratio, 1.50 [CI, 1.13–1.99], $P<0.01$) but neither implantable cardioverter-defibrillator 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 heart failure symptoms. This points to a sex-effect on long-term myocardial performance in HCM, which should be investigated further.

Key Words: cardiomyopathy, hypertrophic ■ genetics ■ heart failure ■ sarcomeres ■ women

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 causes compared with men, including a greater burden of HF with preserved ejection fraction.[1] Hypertrophic cardiomyopathy (HCM) is an important cause of HF and is often caused by autosomal dominant variants in sarcomere genes.[2,3] Women have been underrepresented in published HCM cohorts, comprising between 26% and

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Nonstandard Abbreviations and Acronyms

E	peak velocity of early diastolic inflow
e′	peak early diastolic septal tissue Doppler velocity
HCM	hypertrophic cardiomyopathy
HF	heart failure
ICD	implantable cardioverter-defibrillator
LV	left ventricle
LVEF	left ventricular ejection fraction
LVOTO	left ventricular outflow tract obstruction
NYHA	New York Heart Association
SARC–	HCM patients without a sarcomere mutation
SARC+	HCM patients with a sarcomere mutation
SHaRe	Sarcomeric Human Cardiomyopathy Registry

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 mortality,[4,7] 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 outcomes.[4,5] Alternatively, the effects of sex hormones on cardiac remodeling have been invoked and studied in model systems with conflicting findings.[8,9] Finally, the penetrance of sarcomere variants may be lower in women,[10–12] 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 cardiomyopathies.[3] 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 Data Supplement.

RESULTS

Genetics and Baseline Characteristics

A total of 5873 patients with HCM were included in this study, of whom 2226 (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 New York Heart Association (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% versus 25.2%, $P<0.001$).

Genetic testing was performed in 3788 (65%) patients, with a similar proportion of men and women. However, females were 17% more likely than males to have a sarcomere mutation (HCM patients with 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% versus 26.8%), excluding patients with multiple variants. There was also no significant difference in the proportion of female and male patients with 2 or more pathogenic/likely pathogenic sarcomere variants (1.6% versus 1.6%, $P=0.79$) or a sarcomere variant of unknown significance (7.4% versus 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 versus 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

Table 1. Baseline Characteristics

	Total	Female	Male	
	N=5873	N=2226 (37.9%)	N=3647 (62.1%)	*P* value*
Age at diagnosis, y, 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, y, median (IQR)	7.7 (3.1–15.4)	7.8 (3.3–15.3)	7.7 (3.0–15.6)	0.75
Race				
White	4888 (87.0%)	1840 (86.6%)	3048 (87.3%)	0.16
Black	223 (4.0%)	82 (3.9%)	141 (4.0%)	0.16
Family proband, N (%)	5306 (91.1)	2009 (90.7)	3297 (91.4)	0.74
Genetic testing, N (%)	3788 (64.5)	1410 (63.3)	2378 (65.2)	0.16
SARC+, N (% of those genotyped)	1747 (46.1)	717 (50.9)	1030 (43.3)	< 0.001
Body mass index, kg/m^2, ± 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, mm Hg	124.6±18.7	124.2±20.8	124.8±17.2	0.48
Diastolic BP, mm Hg	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/m^2±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/m^2±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 echocardiography, N (%)	1616 (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/m^2±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%	2563 (83.9)	952 (85.4)	1611 (83.0)	0.03
4–6%	148 (4.8)	59 (5.3)	89 (4.6)	
>6%	344 (11.3)	104 (9.3)	240 (12.4)	

BP indicates blood pressure; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LV, left ventricle; NYHA, New York Heart Association; and SARC+, HCM patients with a sarcomere mutation.

*P values were calculated using Student *t* test for continuous variables and Fisher exact test for discrete variables.

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 Figure I in the Data Supplement. This difference remained significant in the subset of 2030 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 (2005[5]) examining sex differences in HCM (36.6% versus 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 mm Hg at rest or with provocation) and maximal LVOT gradient (at rest or with the valsalva maneuver) were greater in women (47±45 versus 36±38 mm Hg, $P<0.001$). 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=1364 with tissue Doppler and spectral Doppler, n=2488 with only spectral Doppler). Although peak early diastolic septal tissue Doppler velocity (e′) was lower (6.1±2.6 versus 7.0±2.7, $P<0.0001$), and the peak velocity of early diastolic inflow (E wave; 83.5±32.7 versus 75.0±23.7, $P<0.0001$) and the ratio of E/e′ (15.6±9.2 versus 11.9±6.3, $P<0.0001$) were higher in females, these differences were not significant after controlling for age and hypertension.

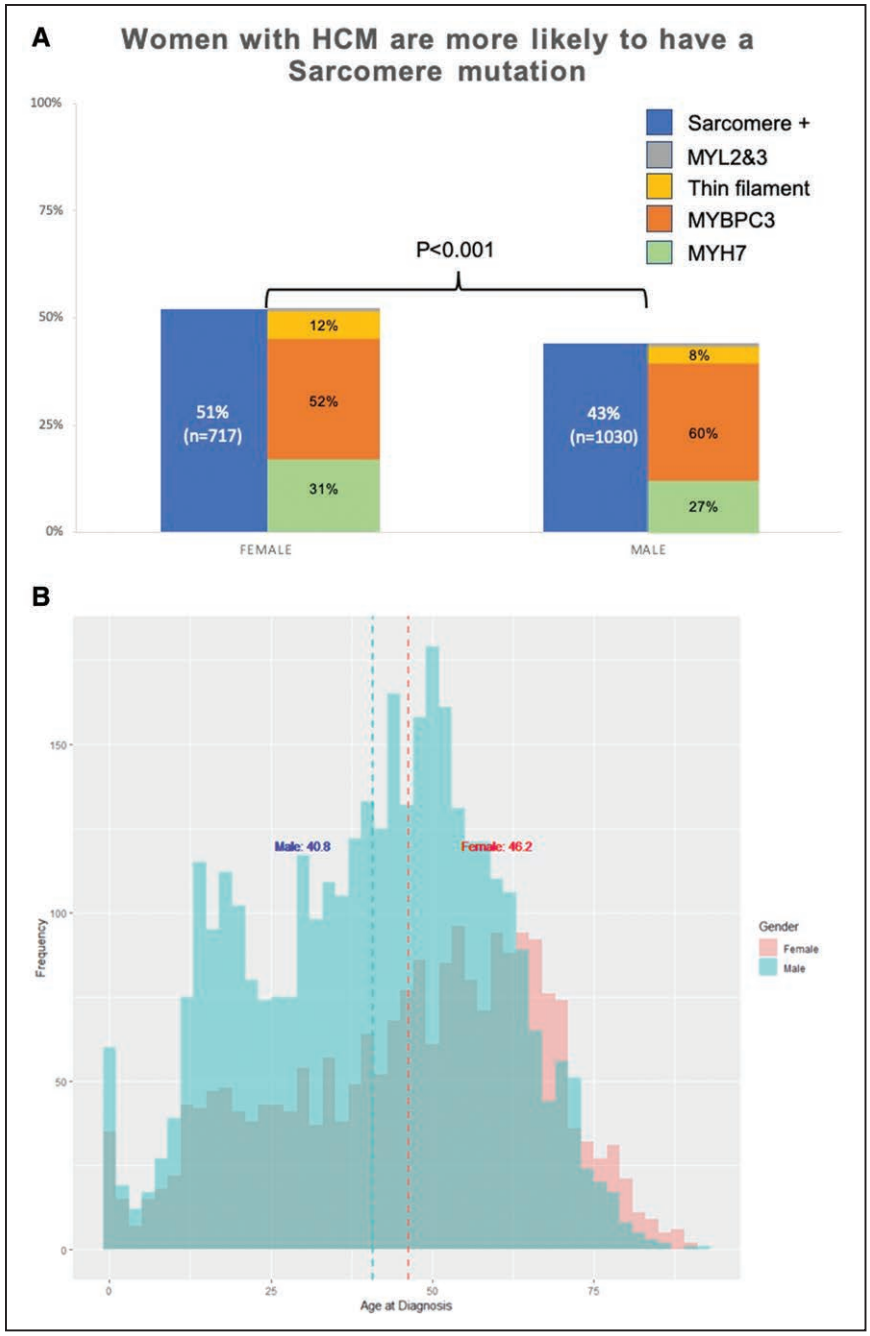

Figure 1. Women are older than men at the time of hypertrophic cardiomyopathy (HCM) diagnosis and were more likely to have a sarcomere mutation.
A, Frequency of pathogenic/likely pathogenic sarcomere variants in patients who had undergone genetic testing, excluding patients with multiple variants. **B**, 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.

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 (Table I in the Data Supplement).

Clinical Outcomes

Follow-up duration was similar for women and men (median time from first to last encounter 7.8 versus 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% versus 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 (interquartile range: 0.47–0.96) versus 1.08 years (interquartile range: 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 NYHA functional class. However, among patients undergoing septal reduction therapies, alcohol septal ablation was performed more frequently in women than men (24.9% versus 17.6%, *P*<0.01). In a multivariable model (Table 4), the proportionally greater utilization of septal ablation among women (hazard ratio [HR] 2.33 [95% CI, 1.44–3.77], *P*<0.001) persisted after controlling for age, maximal wall thickness, and severity of OTO.

Table 2. Age of Diagnosis in Men and Women by Sarcomere Status and Disease Gene

	Female		Male		
	N	Age (SD)	N	Age (SD)	*P* value*
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 3 columns represent only SARC+ patients. HCM indicates hypertrophic cardiomyopathy; MYBPC3, myosin-binding protein C; MYH7, myosin heavy chain; SARC–, HCM patients without a sarcomere mutation; SARC+, HCM patients with a sarcomere mutation.

**P* values were calculated from Fisher exact test.

Among 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%/y) and did not differ by sex overall. However, among *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 or LV assist device 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 European Society of Cardiology 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, Tables 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

Table 3. Incident Outcomes

	Total	Female	Male	
	N=5873	N=2226	N=3647	*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	1273 (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	1244 (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†	1111 (18.9%)	593 (26.6%)	518 (14.2%)	< 0.001
Ventricular arrhythmia composite‡	313 (5.3%)	111 (5.0%)	202 (5.5%)	0.39

ICD indicates implantable cardioverter-defibrillator.

**P* values were calculated using Fisher exact test.

†Heart failure composite: first occurrence of cardiac transplantation, left ventricular assist device implantation, or New York Heart Association functional class III-IV symptoms.

‡Ventricular arrhythmic composite: first occurrence of sudden cardiac death, resuscitated cardiac arrest, or appropriate ICD therapy.

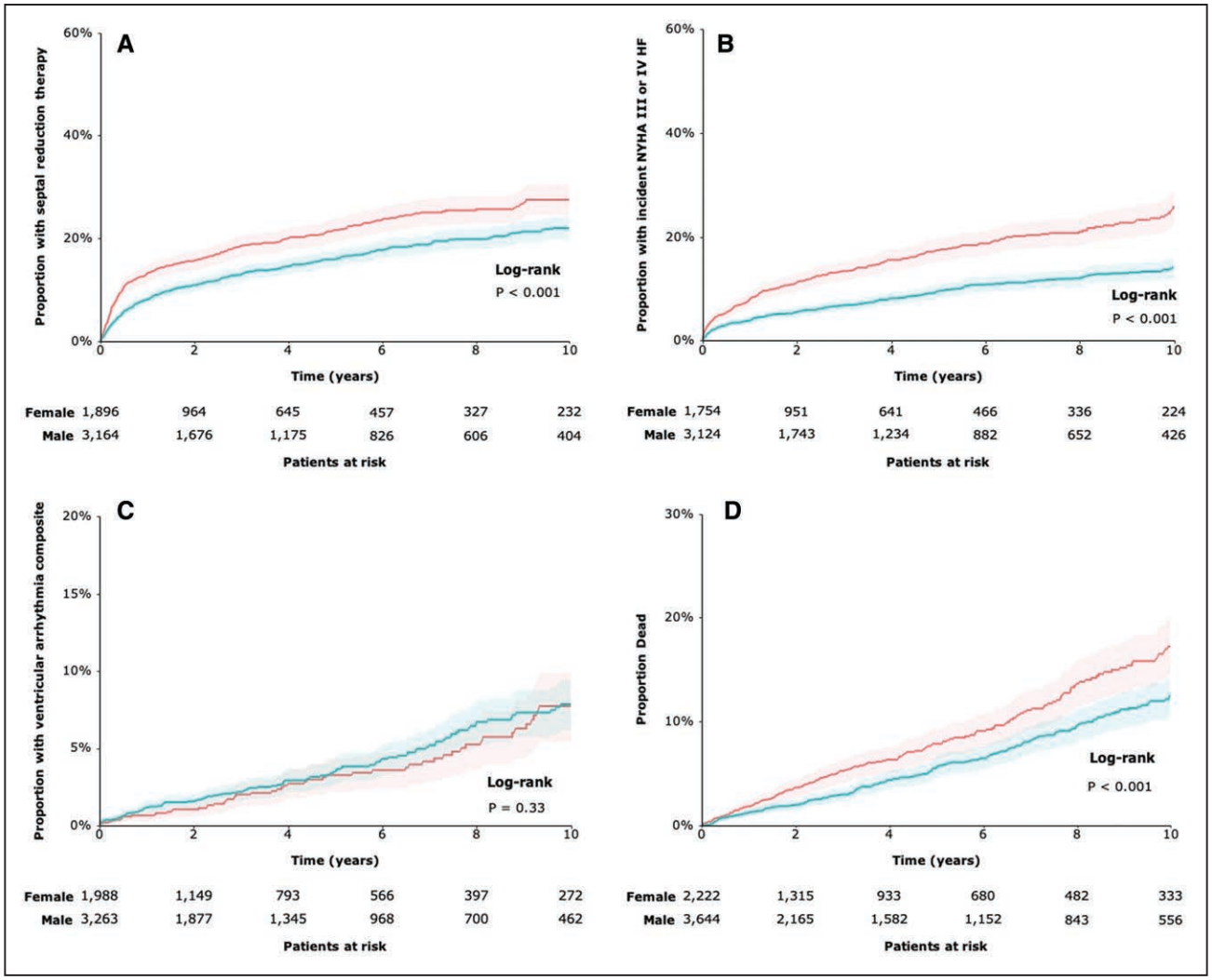

Figure 2. Time to event curves dichotomized by sex.
A, Invasive septal reduction therapy. **B**, Incident severe heart failure (HF; New York Heart Association [NYHA] III-IV), excluding patients with severe HF at baseline. **C**, Ventricular arrhythmia composite (first occurrence of sudden cardiac death, resuscitated cardiac arrest, or appropriate ICD therapy). **D**, Mortality. The pink and blue lines represent the event curves in women and men, respectively.

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 as follows: (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 OTO; and (4) 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 studies,[4,5] women were underrepresented 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 nonsarcomeric HCM (women 7.1 years older at diagnosis) compared with sarcomeric HCM (women 3.6 years older at diagnosis). Moreover, among patients with sarcomeric

Table 4. Multivariable Models

Covariate	Hazard ratio	Lower 95%	Upper 95%	*P* value*
Heart failure composite†				
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				
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				
Female	1.45	1.16	1.82	0.001
SARC(+)	1.12	0.83	1.51	0.47
Age, y	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

LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; and SARC+, HCM patients with a sarcomere mutation.

**P* values were calculated from Cox proportional hazards regressions.

†Heart failure composite: first occurrence of cardiac transplantation, left ventricular assist device implantation, or NYHA functional class III-IV symptoms.

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

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,[10–14] disease 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 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 noted[4–6] and may be related to their relatively smaller LV cavity size[15] 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 among 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 HCM.[16] 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 genes (*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 LVOTO.[4] As in HF with preserved ejection fraction,[17] 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 remodeling.[9,18] 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 preeclampsia.[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 Clinic[4] and a collaborative European cohort.[7] 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 outcomes,[3] 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 infarction,[20] end-stage HF,[21] and atrial fibrillation.[22] Additionally, health care provider sex and gender and patient perceptions about the cause of their symptoms can both negatively influence referral for cardiac testing in women.[23,24] 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 risk factors, respectively. However, among 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 nonsarcomeric 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 nonbiological factors that contribute to disparate disease experiences in males and females.

ARTICLE INFORMATION

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