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ORIGINAL ARTICLE

Sex-Specific Clinical and Genetic Factors Associated With Adverse Outcomes in Hypertrophic Cardiomyopathy

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BACKGROUND: Females with hypertrophic cardiomyopathy present at a more advanced stage of the disease and have a higher risk of heart failure and death. The factors behind these differences are unclear. We aimed to investigate sex-related differences in clinical and genetic factors affecting adverse outcomes in the Sarcomeric Human Cardiomyopathy Registry.

METHODS: Cox proportional hazard models were fit with a sex interaction term to determine if significant sex differences existed in the association between risk factors and outcomes. Models were fit separately for females and males to find the sex-specific hazard ratio (HR).

RESULTS: After a mean follow-up of 6.4 years, females had a higher risk of heart failure (HR, 1.51 [95% CI, 1.21–1.88]; P=0.0003) but a lower risk of atrial fibrillation (HR, 0.74 [95% CI, 0.59–0.93]; P<0.0001) and ventricular arrhythmia (HR, 0.60 [95% CI, 0.38–0.94]; P=0.027) than males. No sex difference was observed for death (P=0.84). Sarcomere-positive males had higher heart failure (HR, 1.34 [95% CI, 1.06–1.69]) and death risks (HR, 1.48 [95% CI, 1.08–2.04]) not seen in females (HR, 0.85 [95% CI, 0.66–1.08] versus HR, 0.86 [95% CI, 0.71–1.21]). *MYBPC3* variants lowered heart failure risk in females (HR, 0.56 [95% CI, 0.41–0.77]) but not in males (HR, 1.29 [95% CI, 0.99–1.67]). A sex difference appeared in moderate (4% to <6%) versus low risk (<4%) European Society of Cardiology hypertrophic cardiomyopathy risk score, with females at moderate risk more prone to ventricular arrhythmia (HR, 3.57 [95% CI, 1.70–7.49]), unobserved in males (HR, 1.13 [95% CI, 0.63–2.03]).

CONCLUSIONS: We found that clinical and genetic factors contributing to adverse outcomes in hypertrophic cardiomyopathy affect females and males differently. Thus, research to inform sex-specific management of hypertrophic cardiomyopathy could improve outcomes for both sexes.

Key Words: cardiomyopathy, hypertrophic ■ female ■ heart failure ■ male ■ sex

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease, affecting at least 1 of 500 in the general population.[1] HCM is a heterogeneous condition, with approximately half of cases due to likely pathogenic or pathogenic (LP/P) autosomal dominant variants in genes encoding

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BMI	body mass index
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
LA	left atrial
LV	left ventricular
LP/P	likely pathogenic/pathogenic

sarcomere proteins (sarcomere-positive), critical for cardiomyocyte contractile function. The 2 most common genes implicated are *MYBPC3* (myosin-binding protein C) and *MYH7* (β-myosin heavy chain), which account for ≈75% of all patients with HCM with causative variants.[2] Despite the inheritance pattern conveying 50% risk to first-degree relatives, incomplete penetrance is common, and not all carriers of causative variants will develop the disease.[3,4] There is increasing evidence that ≈40% have a non-Mendelian subtype, where the underlying disease mechanism is likely due to a combination of polygenic risk and comorbidities (sarcomere-negative).[5–8]

Published HCM cohorts are disproportionately male, with women accounting for only 30% to 45% of published study populations,[9] despite this being considered an autosomal dominant disease. This might be explained by decreased disease penetrance in women, with male sex previously associated with 3× the risk of developing HCM among individuals with sarcomere gene variants.[3] Additionally, differences in clinical recognition due to the lack of sex-specific diagnostic criteria in clinical guidelines[10] and unequal access to care also likely play a role.[11] Indeed, multiple studies have shown that women have a higher risk of adverse events, including heart failure and death.[11–14] Women with HCM are more likely to have an LP/P sarcomere variant, while men are more likely to be sarcomere-negative.[5,11] Compared with men, women are older at diagnosis, present at an advanced stage of disease, have a higher prevalence of obstruction, and heart failure symptoms (New York Heart Association III–IV), worse exercise capacity, and worse diastolic function.

We expand on previous work by evaluating sex-specific differences in risk factors for adverse outcomes in men and women with HCM. Early detection and management of cardiovascular risk factors remain vital for improving women's cardiovascular health.[15] We hypothesized that clinical and genetic factors contributing to adverse outcomes in HCM might be influenced differently by sex. Understanding the underlying factors contributing to these sex differences in outcomes of HCM is essential if we are to improve health outcomes and care for both men and women with HCM.

METHODS

Each participating site has received ethics approval in accordance with local policies, as per the following: ethical approval requiring informed consent was obtained from Cincinnati Children's Hospital; Children's Hospital of Philadelphia; Michigan Medical; Yale-New Haven Hospital Medical; Royal Brompton Hospital, United Kingdom; Erasmus University Medical Center, The Netherlands; Florence Centre for Cardiomyopathies, Italy; and Sydney Local Health District, Royal Prince Alfred Hospital, Australia; InCor, Heart Institute, University of Sao Paulo, Brazil ethics committees. Waiver of consent was granted by Stanford School of Medicine; Brigham and Women's Hospital; Boston Children's Hospital; Pennsylvania University Medical Center; and Sydney Local Health District, Royal Prince Alfred Hospital, Australia ethics committees. 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 design, study population, genetic testing, outcomes definitions, and statistical analysis, is available in the Supplemental Data.

RESULTS

Demographic and Baseline Clinical Characteristics

There were 7315 patients with HCM seen between 1960 and 2020, and after excluding 768 family members, 6647 probands were included in the study (Figure 1A). There were 2538 (38%) females, with an overall mean follow-up time from the first to the last encounter of 6.4±7.1 years (Table 1).

At diagnosis, females were ≈6.0 years older than males (47.5±20.6 versus 41.6±18.4; $P<0.0001$). At baseline, New York Heart Association class III to IV symptoms were present in 455 (23%) of females, compared with only 337 (11%) of males ($P<0.0001$). Additionally, 895 (47%) females had left ventricular (LV) outflow tract obstruction (defined as ≥30 mm Hg at rest or with provocation) compared with 1086 males (36%; $P<0.0001$). Subsequently, females also had a significantly higher LV outflow tract gradient (37.1±38.4 versus 26.9±31.4; $P<0.0001$). LV ejection fraction was greater in females, although not clinically significant (65.6±9.8 versus 64.4±9.0; $P<0.0001$). After adjusting for body surface area, females had significantly greater absolute maximum LV wall thickness, LV cavity diameter, and left atrial (LA) diameter (Table 1).

Genetic testing was performed in 4182 (63%) probands, with a total of 2630 (64%) males and 1552 (61%) females undergoing genetic testing ($P=0.019$; Table 1). Sarcomere status differed by sex; a total of 728 (47%) females and 1047 (40%) males were sarcomere-positive ($P<0.0001$). Among the sarcomere-positive group, most had *MYBPC3* variants, although males were proportionately even more likely to have *MYBPC3* variants ($P=0.001$). Proportionately, more females had variants in *MYH7* and other sarcomere genes compared with males ($P=0.001$; Figure 1B).

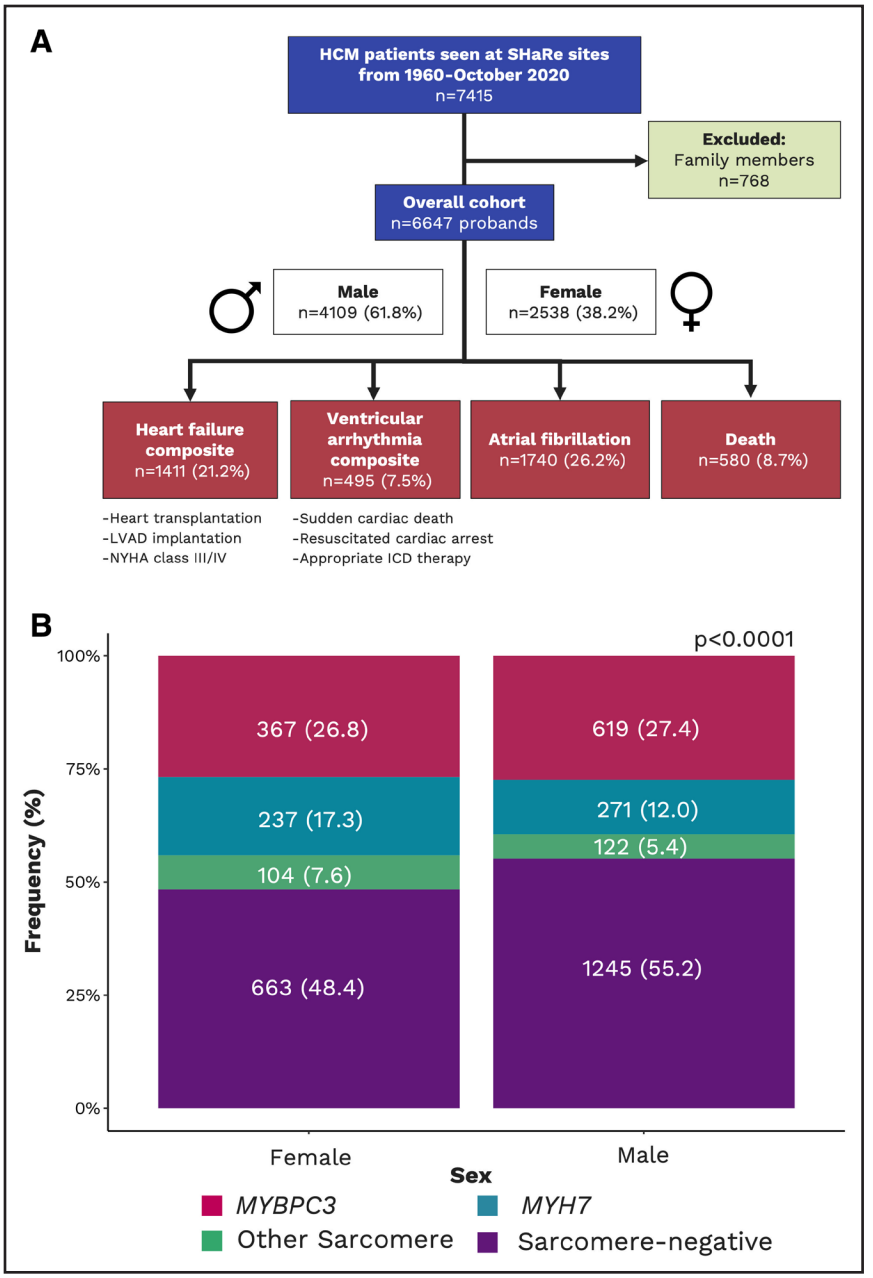

Figure 1. Study outcomes and genetic findings.
A, Flow diagram of study participants. B, Sarcomere variant gene distribution including sarcomere-negative probands. ICD indicates implantable cardioverter defibrillator; HCM, hypertrophic cardiomyopathy; LVAD, left ventricular assist device; NYHA, New York Heart Association; and SHaRe, Sarcomeric Human Cardiomyopathy Registry.

Overall Use of Medications and Interventions

Table 2 shows the overall medication use and interventions among the cohort. Compared with males, females were more likely to be prescribed β-blockers (1495 [63%] females versus 2294 [59%]; *P*=0.001), calcium channel blockers (529 [22%] versus 682 [18%]; *P*<0.0001), disopyramide (240 [11%] versus 236 [7%]; *P*<0.0001), and loop diuretics (157 [15%] versus 151 [8%]; *P*<0.0001), though noting data missingness for these variables (missing, 5%–14%), especially loop diuretics (55%). There was no sex difference in the prescription of antiarrhythmic drugs (*P*=0.953). The prevalence of implantable cardioverter defibrillator insertion was similar between the sexes (*P*=0.386). In patients with obstruction, females were significantly more likely than males to undergo alcohol septal ablation (102/895 [11%] versus 80/1082 [7%]; *P*=0.002); however, there was no significant sex difference for septal myectomy (331/895 [37%] versus 361/1086 [33%]; *P*=0.08).

Adverse Clinical Outcomes

During the follow-up period, a total of 1411 heart failure composite events were recorded (729, 51.7% women), 495 ventricular arrhythmia composite events (175, 35.4% women), 1740 AF events (1740, 39.1% women), and 580 deaths (289, 49.8% women; Table 2). Multivariable Cox models were fit to test if sex is an independent

Table 1. Demographic and Baseline Characteristics of Hypertrophic Cardiomyopathy Probands by Sex

	Total cohort	Female	Male	
	6647	2538 (38.2)	4109 (61.8)	*P* value
Age at diagnosis, y	43.9±19.5	47.5±20.6	41.6±18.4	<0.0001
Follow-up time, y	6.4±7.1	6.3±6.8	6.5±7.2	0.412
Race (self-reported)				0.300
White	5465 (91.8)	2114 (92.2)	3351 (91.6)	
Black	269 (4.5)	92 (4.0)	177 (4.8)	
Asian	217 (3.7)	87 (3.8)	130 (3.6)	
Genetic testing	4182 (62.9)	1552 (61.2)	2630 (64.0)	0.019
Sarcomere status				<0.0001
Positive	1775 (42.4)	728 (46.9)	1047 (39.8)	
VUS	499 (11.9)	161 (10.4)	338 (12.9)	
Negative	1908 (45.6)	663 (42.7)	1245 (47.3)	
Gene status				0.001
MYBPC3	986 (57.3)	367 (51.8)	619 (61.2)	
MYH7	508 (29.5)	237 (33.5)	271 (26.8)	
Other sarcomere gene	226 (13.1)	104 (14.7)	122 (12.1)	
Hypertension	2690 (40.5)	1091 (43.0)	1599 (38.9)	0.001
Body mass index, kg/m^2	27.5±6.2	27.3±7.0	27.7±5.7	0.080
NYHA III–IV	792 (15.3)	455 (22.9)	337 (10.5)	<0.0001
Syncope	1008 (15.6)	432 (17.5)	576 (14.4)	0.001
Echo characteristics				
Indexed max LV wall thickness, mm*	9.9±2.3	10.4±4.3	9.5±4.2	<0.0001
Indexed LV end diastolic diameter, mm*	23.6±6.6	24.2±6.7	23.2±6.6	<0.0001
Indexed end-systolic diameter, mm*	14.3±5.2	14.5±2.9	14.2±5.4	0.071
LV ejection fraction, %	64.9±9.3	65.6±9.8	64.5±9.0	<0.0001
LV outflow tract obstruction	1981 (40.2)	895 (46.9)	1086 (36.0)	<0.0001
LV outflow tract gradient at rest, mm Hg	30.8±34.6	37.1±38.4	26.9±31.4	<0.0001
Mitral regurgitation	3737 (64.6)	1527 (68.6)	2210 (62.2)	<0.0001
Indexed left atrial diameter, mm*	22.6±6.2	23.9±6.5	21.7±5.8	<0.0001
ESC HCM risk score				
Low risk (<4%)	4220 (87.0)	1627 (89.2)	293 (85.7)	0.0002
Moderate risk (4% to <6%)	415 (8.6)	117 (6.4)	298 (9.9)	
High risk (≥6%)	216 (4.5)	81 (4.4)	135 (4.5)	

Data shown as n (%) or mean±SD. ESC indicates European Society of Cardiology; HCM, hypertrophic cardiomyopathy; LV, left ventricular; NYHA, New York Heart Association; and VUS, variant of unknown significance.

*Adjusted for body surface area.

predictor of key outcomes (Table S1). Women had a higher risk of heart failure (HR, 1.51 [95% CI, 1.21–1.88]; *P*=0.0003). However, female sex did not remain a significant predictor of death in a model adjusted for age, sarcomere status, baseline LV ejection fraction <50%, baseline indexed LA size, and baseline LV outflow tract obstruction (HR, 0.96 [95% CI, 0.66–1.41]; *P*=0.843). Additionally, in adjusted models, women had a reduced risk of atrial fibrillation (AF; HR, 0.74 [95% CI, 0.59–0.93]; *P*<0.0001) and ventricular arrhythmia (HR, 0.60 [95% CI, 0.38–0.94]; *P*=0.027) compared with men.

Sex-Specific Clinical and Genetic Factors for Heart Failure Composite

Sex differences existed for the associations between the heart failure composite and sarcomere-positive status, LP/P variants in *MYBPC3*, and baseline indexed LA diameter after adjusting for age at first encounter

Table 2. Overall Medication Use, Interventions, and Outcomes by Sex

	Total cohort	Female	Male	*P* value
Medications	6647	2538 (38.2)	4109 (61.8)	
β-blocker	3789 (60.1)	1495 (62.2)	2294 (58.8)	0.001
Anti-arrhythmic	718 (13.7)	275 (13.8)	443 (13.7)	0.953
Calcium channel blocker	1211 (19.3)	529 (22.0)	682 (17.6)	<0.0001
Disopyramide	476 (8.4)	240 (11.0)	236 (6.7)	<0.0001
Loop diuretic	308 (10.4)	157 (14.7)	151 (7.9)	<0.0001
Interventions				
ICD implantation	1697 (25.5)	633 (24.9)	1064 (25.9)	0.386
Alcohol septal ablation	295 (4.5)	160 (6.3)	135 (3.3)	<0.0001
Septal myectomy	1124 (16.9)	505 (19.9)	619 (15.1)	<0.0001
Outcomes				
Heart failure composite	1411 (21.2)	729 (28.7)	682 (16.6)	
Ventricular arrhythmia composite	495 (7.5)	175 (6.9)	320 (7.8)	
Atrial fibrillation	1740 (26.2)	681 (26.8)	1059 (25.8)	
Death	580 (8.7)	289 (11.4)	291 (7.1)	

Data shown as n (%) or mean±SD. 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. ICD indicates implantable cardioverter defibrillator.

(Figure 2). In males, sarcomere-positive status was associated with an increased risk of the heart failure composite compared with sarcomere-negative patients (HR, 1.34 [95% CI, 1.06–1.69]), while for females, there was no significant change in risk by sarcomere status (HR, 0.85 [95% CI, 0.66–1.08]; $P_{heterogeneity}$=0.006). However, having an LP/P variant in *MYBPC3* was associated with a lower risk of the heart failure composite for females compared with sarcomere-negative HCM (HR, 0.56 [95% CI, 0.41–0.77]), with no significant change for males (HR, 1.29 [95% CI, 0.99–1.67]; $P_{heterogeneity}$<0.0001).

Greater indexed LA diameter (per cm increase) was associated with an increased risk of the heart failure composite in both females and males, but slightly more so in males (HR, 1.50 [95% CI, 1.36–1.65] compared with females (HR, 1.25 [95% CI, 1.13–1.39]; $P_{heterogeneity}$=0.007).

While Black race, LP/P variants in *MYH7*, larger baseline indexed maximum LV wall thickness, larger baseline indexed LV end-systolic diameter, baseline LV outflow tract obstruction, LV ejection fraction <50%, greater body mass index (BMI), and AF all increased the risk of the heart failure composite in the cohort, there was no evidence of heterogeneity by sex for any of these associations ($P_{heterogeneity}$>0.05).

Sex-Specific Clinical and Genetic Factors for Death

Sex differences existed for the associations between death and sarcomere-positive status, greater BMI, and the heart failure composite after adjusting for age at first encounter (Figure 3). Compared with sarcomere-negative HCM, sarcomere-positive status increased the risk of death in males (HR, 1.48 [95% CI, 1.08–2.04]) but not in females (HR, 0.86 [95% CI, 0.71–1.21]; $P_{heterogeneity}$=0.035). Greater BMI increased the risk of death in females (HR, 1.18 [95% CI, 1.05–1.31]) but not in males (HR, 0.96 [95% CI, 0.82–1.12]; $P_{heterogeneity}$=0.031). Heart failure increased the risk of death to a greater extent in males (HR, 2.18 [95% CI, 1.72–2.78]) than in females (HR, 1.45 [95% CI, 1.14–1.83]; $P_{heterogeneity}$=0.013).

The risk of death was increased for both sexes for the associations between baseline LV outflow tract obstruction, baseline indexed LA diameter, and ventricular arrhythmia composite. Hypertension was consistently associated with a lowered risk of death in both sexes (all $P_{heterogeneity}$>0.05).

Sex-Specific Clinical and Genetic Factors for AF

No evidence of heterogeneity by sex was observed in associations between risk factors and AF after adjusting for age at first encounter (Figure S1). Sarcomere-positive status, disease-causing variants in *MYH7*, larger baseline indexed maximum LV wall thickness, baseline LV outflow tract obstruction, mitral regurgitation, baseline indexed LA diameter, and greater BMI were all associated with an increased risk of AF in both sexes ($P_{heterogeneity}$>0.05).

Sex-Specific Clinical and Genetic Factors for Ventricular Arrhythmia Composite

Sex differences were identified for the associations between the ventricular arrhythmia composite and European Society of Cardiology (ESC) HCM risk score and greater baseline BMI after adjusting for age at first encounter (Figure 4). There was a sex difference in the association between moderate ESC HCM risk (4% to <6%) compared with low risk (<4%), with females at moderate risk more likely to experience ventricular arrhythmia (HR, 3.57 [95% CI, 1.70–7.49]), and this was not observed in males (HR, 1.13 [95% CI, 0.63–2.03]; $P_{heterogeneity}$=0.019). Males had a 1.3-fold increased risk of ventricular arrhythmia composite for every 5 kg/m^2 increase in BMI above the mean (HR, 1.29 [95% CI, 1.14–1.48]) with no significant change for females (HR, 1.04 [95% CI, 0.87–1.24]; $P_{heterogeneity}$=0.030).

The risk of ventricular arrhythmia was increased for both sexes for the associations between high ESC HCM risk score (>6%), nonsustained ventricular tachycardia, and syncopal events, with no evidence of heterogeneity by sex ($P_{heterogeneity}$>0.05).

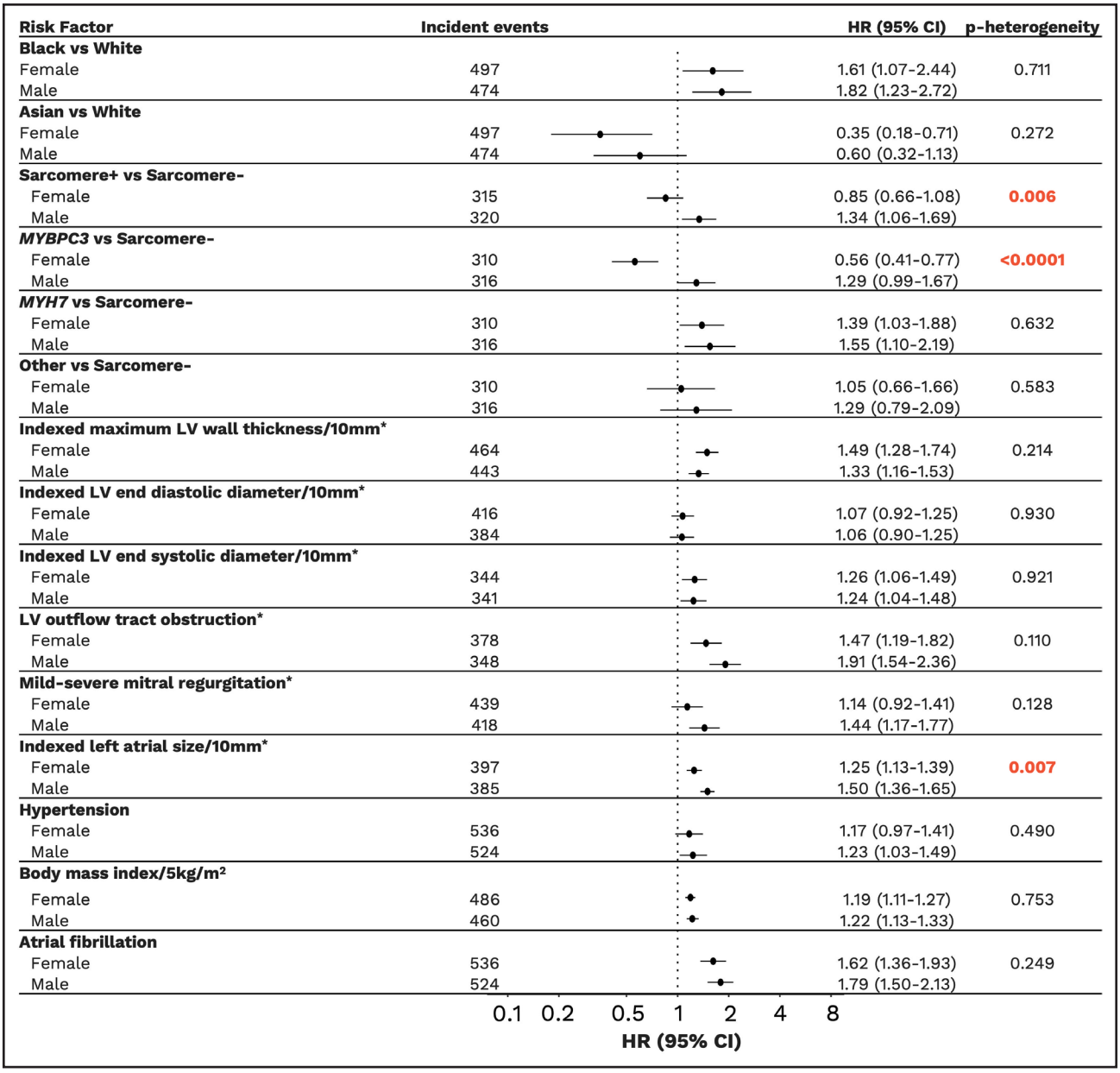

Figure 2. Sex-disaggregated analysis showing clinical and genetic features for heart failure.
Cox regression models were fit for females and males, and the heterogeneity of association was tested by adding a sex interaction term into the model. All models were adjusted for age at first evaluation. *Echocardiogram measurements adjusted for body surface area. HR indicates hazard ratio; and LV, left ventricular.

Increased Risk of Events Over Time for Sarcomere-Negative Females

To further explore why genotype is a sex-specific risk factor, Kaplan-Meier survival analysis with log-rank comparison was used to evaluate time to event for each sex descriptively. While sarcomere-negative males and females were initially less likely to develop heart failure than sarcomere-positive individuals, this difference diminished over time in females but persisted in males (Figure 5A). However, the risk remained higher in males and females with *MYH7* variants and men with *MYBPC3* variants (Figure 5B). Regarding death, for both sexes, those who are sarcomere-positive, on average, die at a younger age than sarcomere-negative individuals (Figure 5C). A comparison of the baseline characteristics, medications, and interventions between sarcomere-positive and sarcomere-negative patients by sex can be found in Tables S2 and S3.

DISCUSSION

Clinical evidence informing the management of HCM is predominantly based on studies involving men.[9,16]

Risk Factor	Incident events	HR (95% CI)	p-heterogeneity
Black vs White			
Female	273	1.25 (0.62-2.55)	0.613
Male	265	1.60 (0.82-3.13)	
Asian vs White			
Female	273	0.92 (0.47-1.80)	0.704
Male	265	0.71 z90.31-1.59)	
Sarcomere+ vs Sarcomere-			
Female	153	0.86 (0.71-1.21)	**0.035**
Male	177	1.48 (1.08-2.04)	
***MYBPC3* vs Sarcomere-**			
Female	151	0.94 (0.63-1.39)	0.083
Male	176	1.59 (1.13-2.24)	
***MYH7* vs Sarcomere-**			
Female	151	0.74 (0.42-1.27)	0.153
Male	176	1.27 (0.74-2.19)	
Other vs Sarcomere-			
Female	151	0.81 (0.38-1.71)	0.305
Male	176	1.39 (0.73-2.65)	
Indexed maximum LV wall thickness /10mm*			
Female	190	0.92 (0.70-1.20)	0.225
Male	206	1.14 (0.91-1.44)	
Indexed LV end diastolic diameter/10mm*			
Female	155	1.19 (0.92-1.54)	0.683
Male	166	1.09 (0.85-1.41)	
Indexed LV end systolic diameter/10mm*			
Female	127	1.40 (1.09-1.80)	0.516
Male	146	1.30 (0.99-1.70)	
LV outflow tract obstruction*			
Female	146	1.56 (1.10-2.22)	0.863
Male	151	1.51 (1.09-2.11)	
LV ejection fraction<50*			
Female	171	1.53 (0.96-2.43)	0.073
Male	180	2.75 (1.85-4.09)	
LV ejection fraction<35*			
Female	171	1.75 (0.83-3.68)	0.268
Male	180	3.47 (1.59-7.60)	
Mitral regurgitation*			
Female	170	1.41 (0.98-2.03)	0.604
Male	170	1.33 (0.69-2.57)	
Indexed left atrial size/10mm*			
Female	156	1.39 (1.18-1.64)	0.615
Male	169	1.48 (1.29-1.70)	
Hypertension			
Female	285	0.59 (0.46-0.76)	0.230
Male	284	0.97 (0.96-0.98)	
Body mass index/5kg/m2			
Female	207	1.18 (1.05-1.31)	**0.031**
Male	218	0.96 (0.82-1.12)	
Heart failure composite			
Female	285	1.45 (1.14-1.83)	**0.013**
Male	284	2.18 (1.72-2.78)	
Ventricular arrhythmia composite			
Female	285	3.69 (0.81-1.31)	0.853
Male	284	3.59 (2.75-4.68)	
Atrial fibrillation			
Female	285	1.03 (0.81-1.31)	0.875
Male	284	0.96 (0.75-1.23)	

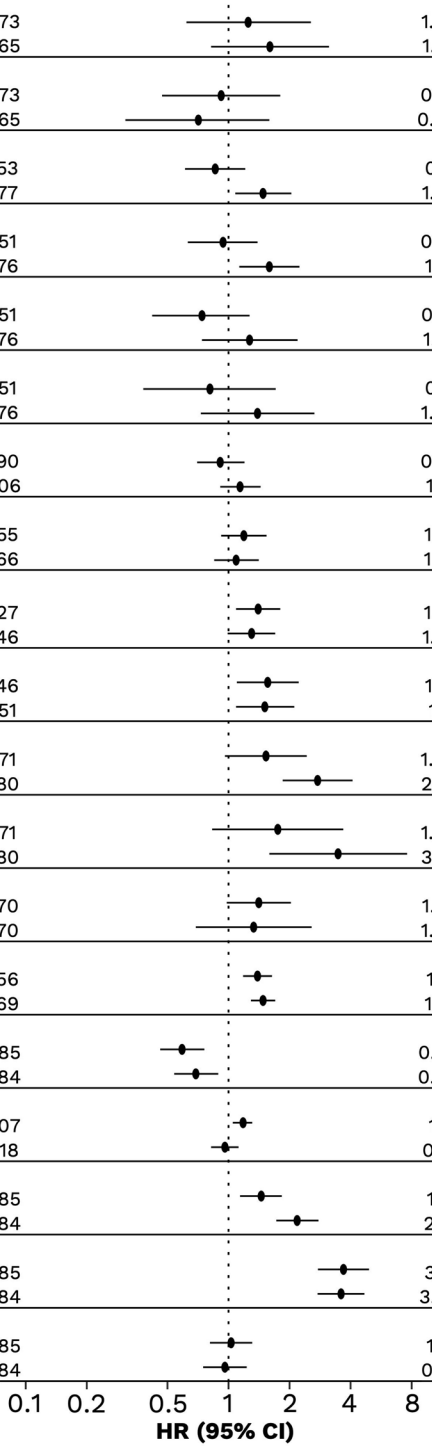

Figure 3. Sex-disaggregated analysis showing clinical and genetic features for death.
Age-adjusted Cox regression models were fit for females and males, and the heterogeneity of association was tested by adding a sex interaction term into the model. All models were adjusted for age at first evaluation. *Echocardiogram measurements adjusted for body surface area. HR indicates hazard ratio; and LV, left ventricular.

It is, therefore, essential to gain a more comprehensive understanding of the social, clinical, and biological factors that differentiate between sexes. A critical first step in addressing sex disparities is reporting sex-disaggregated statistics.[10,17–19] We show important sex differences in risk factors associated with heart

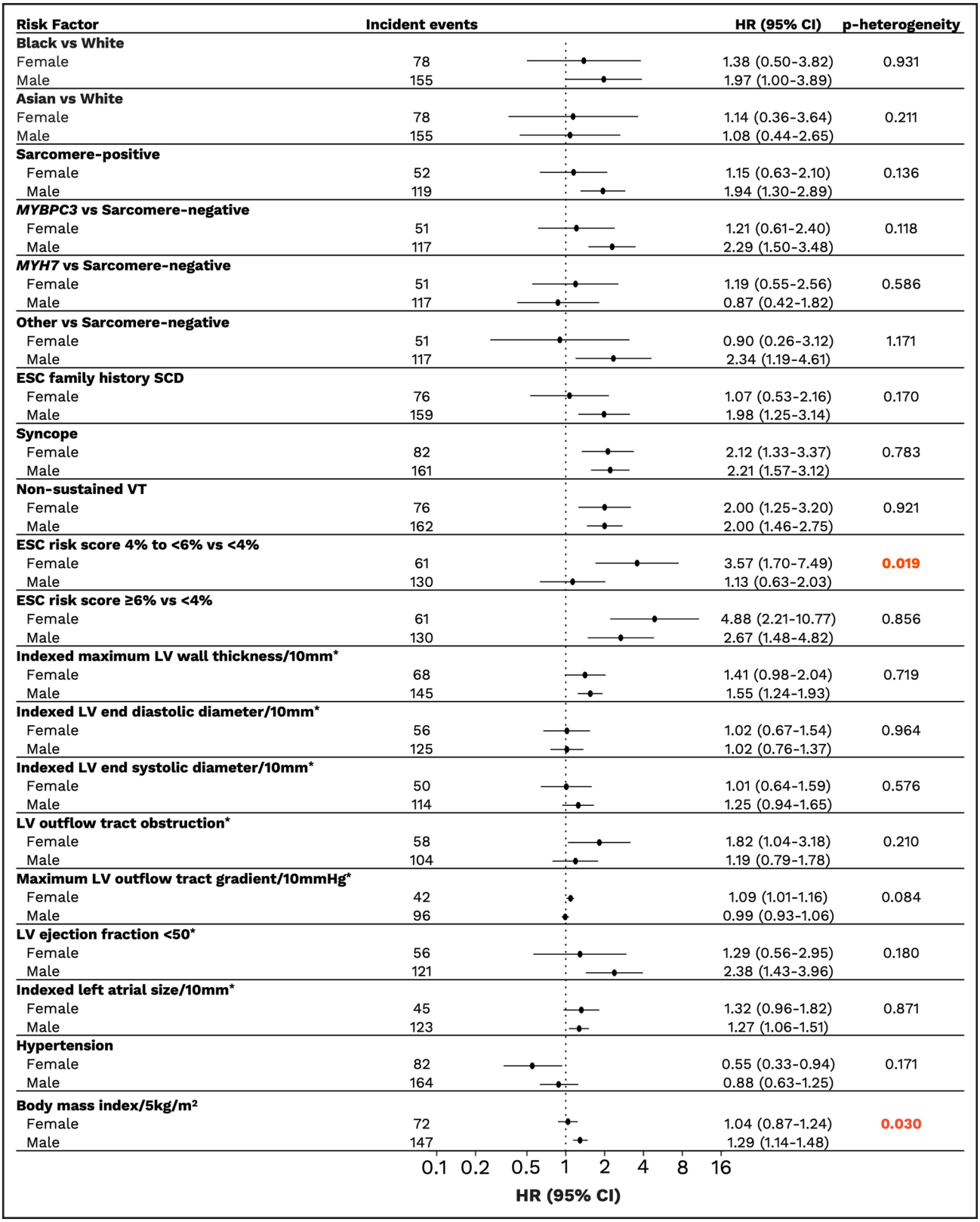

Figure 4. Sex-disaggregated analysis showing associations of clinical and genetic features with ventricular arrhythmia. Age-adjusted Cox regression models were fit for females and males, and the heterogeneity of association was tested by adding a sex interaction term into the model. All models were adjusted for age at first evaluation. *Echo measurements adjusted for body surface area. ESC indicates European Society of Cardiology; HR; hazard ratio; LV, left ventricular; SCD, sudden cardiac death; and VT, ventricular tachycardia.

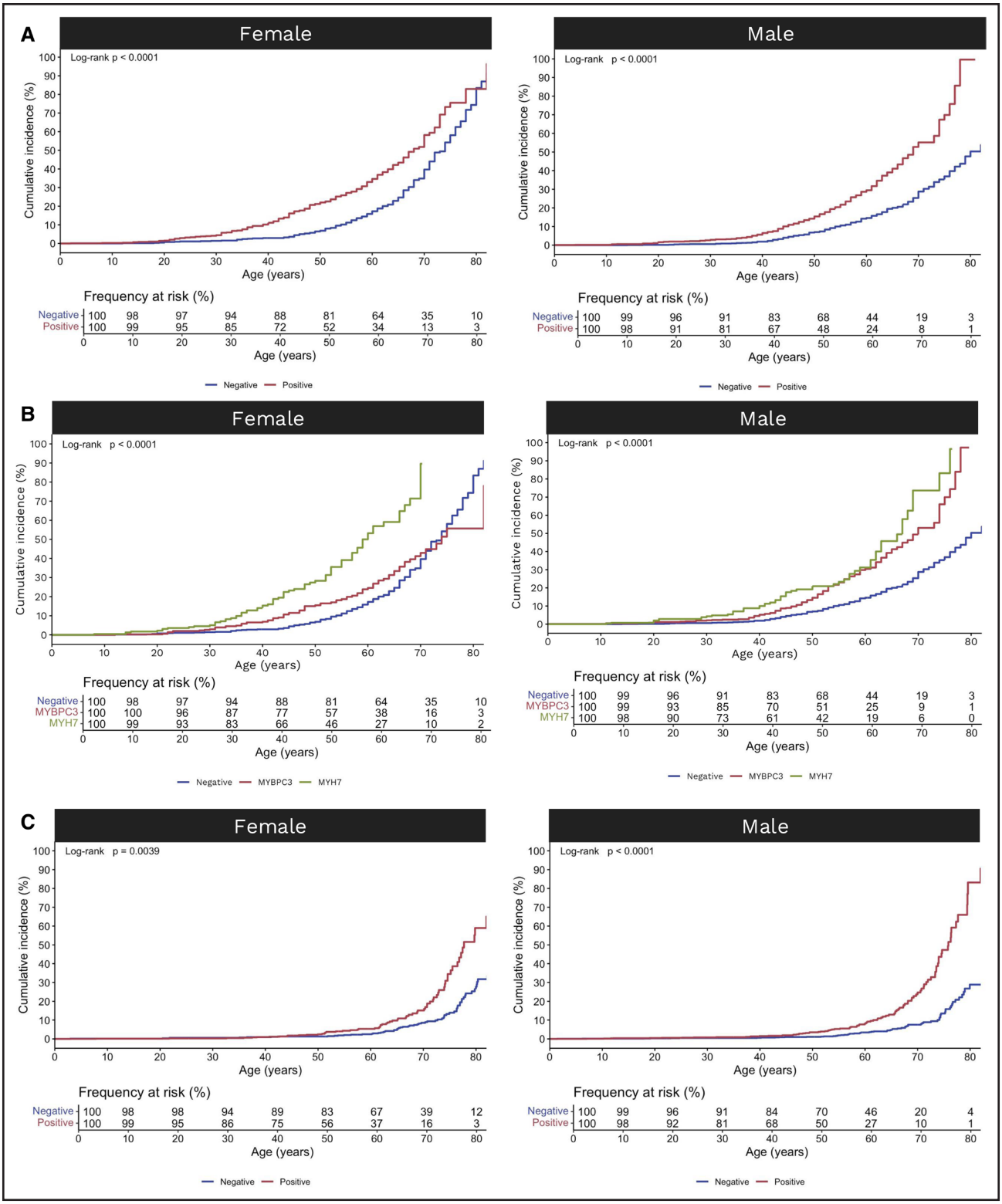

Figure 5. Kaplan-Meier survival analysis showing the difference in lifetime risk. (A) heart failure composite for males and females by sarcomere status; (B) heart failure composite for males and females by gene status; and (C) death by sarcomere status for females and males.

failure, death, and ventricular arrhythmia in HCM, but not AF (Figure 6). Notably, we observed that although sarcomere-negative males and females were initially less susceptible to developing heart failure compared with sarcomere-positive individuals, sarcomere-negative females had an increased risk of heart failure later in life

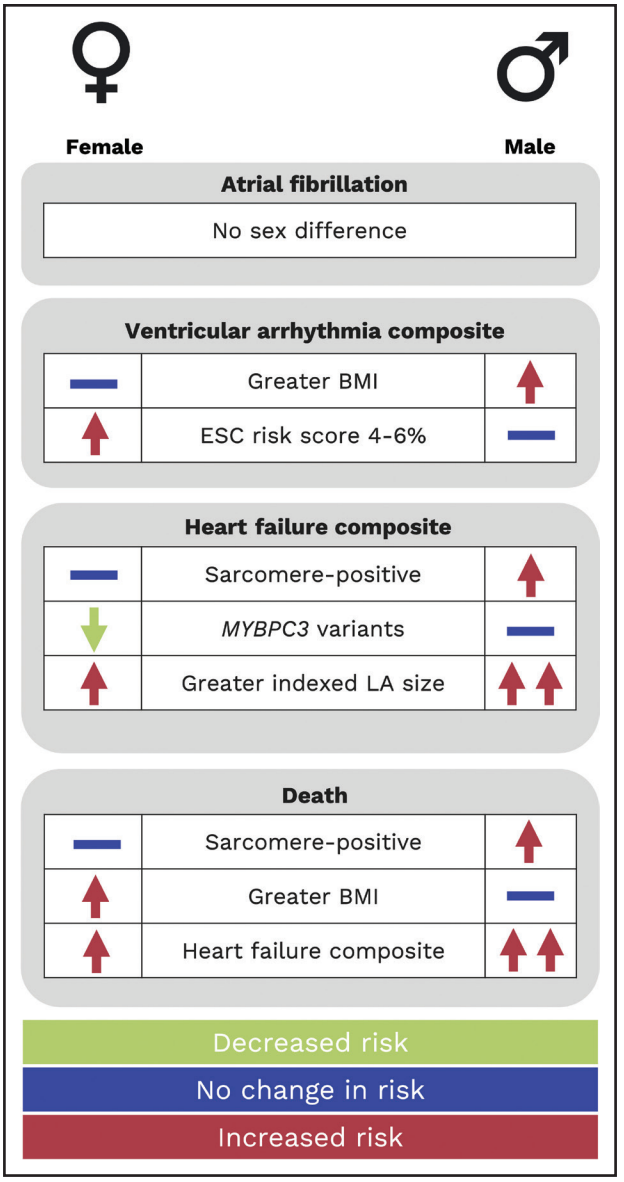

Figure 6. Sex-specific risk factors for adverse outcomes in hypertrophic cardiomyopathy.
BMI indicates body mass index; ESC, European Society of Cardiology; and LA, left atrial.

(≈70 years and older), which may be explained by the trends observed in heart failure with preserved ejection fraction in the general female population.[20–23] Additionally, younger females with *MYBPC3* variants had a lower risk of heart failure compared with males with *MYBPC3* variants of the same age, suggesting sex-based mechanistic differences. Importantly, the impact of AF, BMI, LV wall thickness, and obstruction on heart failure, and to a large extent, death, were by similar sex. We show sex differences in ESC HCM risk score in predicting the risk of ventricular arrhythmia, whereby females with moderate ESC HCM risk had an increased risk of ventricular arrhythmia compared with females at low ESC HCM risk. No significant difference in risk was observed for males. As the risk score does not consider sex, this may indicate risk for females is not adequately predicted using this tool. Our findings underscore the need for prespecified sex-disaggregated analyses to elucidate sex differences and suggest the potential value of sex-specific medical management recommendations that may improve outcomes. Further research, validation of our findings, and a better understanding of the role of genetics in predicting sex-based risk will inform a precision-based approach to care that benefits both males and females.

The importance of recognizing and addressing sex differences in cardiovascular research and clinical practice cannot be overstated. The prevailing clinical evidence for managing HCM has predominantly relied on studies involving males.[9] This raises concern regarding the applicability of these findings to females who may experience distinct social, clinical, and biological factors affecting their cardiovascular health.[10,18,19] An established method for the analysis and reporting of sex differences among cardiovascular risk factors has recently been published, with this work predominantly using UK Biobank datasets.[17,24–27] As an increasingly accepted methodology for identifying sex-specific differences in risk factors, we followed this analysis approach in our work.

The underlying genetic basis of HCM has a differential impact on adverse outcomes across the sexes. We demonstrated that LP/P variants in sarcomere genes increased the risk of heart failure and death for males; this trend was not observed in females. Unlike sarcomere-negative males, sarcomere-negative females had an increased risk of heart failure and death in later life, likely mirroring the increasing risk of heart failure in females seen in the general population in later life.[20] In fact, the prevalence of heart failure increases with age for both sexes in the general population. Still, by the age of 79 years, more females than males have heart failure, with more associated comorbidities but better survival than males.[28–30] Sarcomere-negative males had a lower lifetime risk of both heart failure and death compared with sarcomere-positive males, consistent with previous reports in the general HCM literature, suggesting a more benign clinical course compared with sarcomere-positive males with HCM.[5–7] Recent work to understand the underlying disease cause in this group has shown an important polygenic basis, and diastolic blood pressure has been demonstrated as an independent contributor to disease development in sarcomere-negative HCM.[31,32] Interestingly, important sex differences exist for blood pressure in the general population, with males having a greater prevalence of hypertension overall, but females experiencing steeper increases in measures earlier in life, hypothesized to contribute to cardiovascular disease risk in later life for females.[33,34] The observed sex differences among sarcomere-negative patients in our study and known differences in modifiable risk factors such

as hypertension signal a critical need for future studies to report sex-disaggregated data and consider clinical implications for each sex.

LP/P variants in *MYH7* and *MYBPC3* account for most sarcomere-positive HCM, and we highlight important sex differences at the gene level. Males and females with *MYH7* variants had a greater risk of heart failure than those with sarcomere-negative HCM. However, among females, LP/P variants in *MYBPC3* did not similarly increase risk. Although subtle genotype-phenotype associations exist in HCM, such as LP/P variants in *MYH7* associated with a younger age at presentation[35] and greater risk of AF,[36,37] the overall marked phenotypic and genetic heterogeneity in HCM limits the clinical utility of this information. Variants in *MYBPC3* are frequently truncations, with a proportion being founder variants.[38] Founder variants, which must withstand negative selection pressure to be inherited over generations, were initially considered to cause less penetrant or milder disease. However, more recent data suggest they do not confer a more benign prognosis,[38,39] with recent Sarcomeric Human Cardiomyopathy Registry data showing founder truncating variants have an identical effect as nonfounder truncating variants.[39] Therefore, the significance of this finding in our study is unclear. Nevertheless, it raises interesting questions about the impact of the underlying biological cause of disease and its potential modification by sex.

Other adverse outcomes, including ventricular arrhythmia, AF, and death, were also evaluated in this study. We showed a sex-specific difference in risk of ventricular arrhythmia between females and males with a moderate ESC HCM risk score compared with those with a low risk. Considering the key variables comprising the score, which do not include sex, this finding suggests the risk calculator might not adequately discriminate between those at high and low risk of sudden cardiac death in females. Males with greater BMI had an increased risk of the ventricular arrhythmia composite, while no difference was seen for females. Studies investigating sudden cardiac death in the general population have reported this association previously. However, there is disagreement on whether this is due to increased myocardial hypertrophy and fibrosis, which could potentially be a mechanism for ventricular arrhythmia.[40,41] Comorbidities and other modifiable risk factors significantly contribute to cardiovascular disease risk in both males and females in the general population.[15] Although these data were limited in our HCM dataset, a more extensive investigation of both traditional, sex-specific, and nontraditional risk factors in HCM could provide even greater clarity on sex differences. Given the potential role of sex-specific hormones in modulating disease, gathering female-specific data, such as menarche, pregnancy, menopause, and reproductive-associated variables, could be particularly important.

While the development of heart failure is a true finding, the fact that more females have worse heart failure at the initial visit may be partly due to referral bias. Females are often sicker at presentation because they are not referred for evaluation, particularly to specialty centers, as early as males.[42–44] Females typically have smaller hearts than males. Consequently, females require a more significant degree of hypertrophy to fulfill the diagnostic criteria of maximal wall thickness of at least 15 mm (or 13 mm in first-degree relatives). This underlying difference in biology has been postulated to contribute to the delay in diagnosis and the higher initial diagnosis of peak LV outflow gradient observed in females.[45] A general assumption that males are more at risk of cardiovascular disease, leading to reduced awareness and prioritization among females, must also be considered. The Heart Foundation of Australia reported that only 39% of females aged ≥45 years had undergone a heart risk assessment by a health care professional in the previous 2 years.[46] Indeed, physician bias contributes to reduced screening and prevention efforts for females compared with males.[47] Our results show equal access and utilization of medical therapy and interventions by sex when treated in a Sarcomeric Human Cardiomyopathy Registry center. Investigation of why females are referred to specialist centers later than males is warranted.

Limitations

The use of the heart failure composite outcome provides an incomplete measure of heart failure burden in HCM. New York Heart Association class III to IV symptoms could be attributed to LV obstruction rather than systolic dysfunction, which is supported by the higher prevalence of LV obstruction in women. We had incomplete and limited information about comorbidities and could not interrogate the impact of menarche, pregnancy, or reproductive history. Further research is necessary to determine the effects of these factors on adverse outcomes in HCM, including more specific analyses to understand at which age women become more at risk. Finally, all patients come from specialized HCM clinics that have been shown to lack ancestral diversity.[48]

Conclusions

Sex-specific differences in risk factors for poor outcomes in HCM primarily relate to heart failure or death. Although patients with sarcomere-negative HCM tend to have a milder course, sarcomere-negative females have an increased risk of heart failure later in life, which may be similar to that reported in the general female population. Furthermore, females with *MYBPC3* variants have a lower risk of heart failure than males with similar variants, the mechanism for which is currently unclear. Additionally, we show sex-specific differences in the performance

of the ESC HCM risk score. Further work to explore sex differences in the risk of heart failure and death in HCM includes the collection of female-specific variables such as menarche, pregnancy, and menopause, and more detailed comorbidity data. Reporting sex-disaggregated data is a critical first step in addressing sex disparities and informing sex-specific management strategies.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
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