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Gender-Related Differences in the Clinical Presentation and Outcome of Hypertrophic Cardiomyopathy

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OBJECTIVES The goal of this study was to assess gender-related differences in a multicenter population with hypertrophic cardiomyopathy (HCM).

BACKGROUND Little is known regarding the impact of gender on the heterogeneous clinical profile and clinical course of HCM.

METHODS We studied 969 consecutive HCM patients from Italy and the U.S. followed over 6.2 ± 6.1 years.

RESULTS Male patients had a 3:2 predominance (59%), similar in Italy and the U.S. ($p = 0.24$). At initial evaluation, female patients were older and more symptomatic than male patients (47 ± 23 years vs. 38 ± 18 years; $p < 0.001$; mean New York Heart Association [NYHA] functional class 1.8 ± 0.8 vs. 1.4 ± 0.6; $p < 0.001$), and more frequently showed left ventricular outflow obstruction (37% vs. 23%; $p < 0.001$). Moreover, female patients were less often diagnosed fortuitously by routine medical examination (23% vs. 41% in male patients, $p < 0.001$). Female gender was independently associated with the risk of symptom progression to NYHA functional classes III/IV or death from heart failure or stroke compared with male gender (independent relative hazard 1.5; $p < 0.001$), particularly patients ≥50 years of age and with resting outflow obstruction ($p < 0.005$). Hypertrophic cardiomyopathy-related mortality and risk of sudden death were similar in men and women.

CONCLUSIONS Women with HCM were under-represented, older, and more symptomatic than men, and showed higher risk of progression to advanced heart failure or death, often associated with outflow obstruction. These gender-specific differences suggest that social, endocrine, or genetic factors may affect the diagnosis and clinical course of HCM. A heightened suspicion for HCM in women may allow for timely implementation of treatment strategies, including relief of obstruction and prevention of sudden death or stroke. (J Am Coll Cardiol 2005;46: 480–7) © 2005 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by extreme heterogeneity in clinical expression and natural history (1–5). This diversity has periodically constituted an obstacle to a full understanding of the clinical spectrum and the consequences of the disease (2). We and others (2–11) have previously investigated a large number of demographic and disease-related variables that potentially impact diagnosis, risk stratification, and prognosis in HCM patients, but differences between the genders with regard to clinical expression and outcome remain largely unresolved.

Gender has proved important in the characterization and management of a variety of acquired cardiovascular conditions, including coronary artery disease and heart failure (12–17), aortic stenosis (18), atrial fibrillation (19), and sustained ventricular arrhythmias (20). Because of the potential relevance of these considerations to genetic diseases such as HCM (21), in the present investigation we have targeted the impact that gender may have on presentation and clinical course in a large cohort of HCM patients.

METHODS

Study population. A total of 969 consecutive patients with HCM were enrolled at three institutions: Azienda Ospedaliera Careggi, Florence, Italy; Minneapolis Heart Institute, Minneapolis, Minnesota; and Tufts-New England Medical Center, Boston, Massachusetts. Initial evaluation (i.e., study entry) was defined as the time of the first clinical assessment at each institution. Duration of follow-up to the most recent evaluation (or death) was 6.2 ± 6.1 years.

Echocardiography. Standard echocardiographic studies were performed with commercially available instruments. Magnitude and distribution of left ventricular (LV) hypertrophy was assessed, as previously described (22); LV outflow obstruction was considered to be present when a peak instantaneous subaortic gradient ≥30 mm Hg was estimated with continuous wave Doppler echocardiography under basal (resting) conditions (10).

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Abbreviations and Acronyms

HCM = hypertrophic cardiomyopathy
ICD = implanted cardioverter-defibrillator
LV = left ventricle/ventricular
NYHA = New York Heart Association

Definitions. HCM. Diagnosis was based on two-dimensional echocardiographic evidence of a hypertrophied, non-dilated LV (maximum wall thickness ≥13 mm, or the equivalent relative to body surface area in children), in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident (1–4,22).

SUDDEN CARDIAC DEATH. Sudden and unexpected collapse due to HCM occurring <1 h from the onset of symptoms in patients previously experiencing a relatively stable or uneventful clinical course (23). Potentially lethal cardiovascular events in which patients were either successfully resuscitated from cardiac arrest or received appropriate defibrillation shocks from an implanted cardioverter-defibrillator (ICD) were regarded as equivalent to sudden death in the present analysis (23).

HEART FAILURE-RELATED DEATH. Hypertrophic cardiomyopathy-related events occurring in the context of cardiac decompensation and progressive disease course, including when complicated by pulmonary edema or evolution to the end-stage phase (24), or fatal embolic stroke (9). Patients with advanced refractory heart failure who received heart transplantation were considered equivalent to HCM-related heart failure deaths (23).

Statistical methods. Data were expressed as mean ± SD. An unpaired Student *t* test was employed for comparison of normally distributed data. The chi-square test was utilized to compare non-continuous variables expressed as proportions. Relative risks and 95% confidence intervals were calculated using univariate and multivariate Cox proportional hazard regression models. Multivariate analyses were performed with a stepwise forward regression model, in which each variable with a p value of ≤0.05 (based on univariate analysis) was entered into the model. Survival curves were constructed according to the Kaplan-Meier method, and comparisons were performed using the log-rank test. The p values are two-sided and considered significant when <0.05. Calculations were performed with SPSS 8.0 software (SPSS Inc., Chicago, Illinois).

The clinical end points used in this study were death from any cause, all deaths related to HCM, sudden cardiac death alone, as well as the combined end point including symptomatic progression to New York Heart Association (NYHA) functional classes III or IV or death from heart failure or embolic stroke (10). Deaths from all causes and all deaths related to HCM were analyzed within the overall study group of 969 patients, whereas sudden deaths alone and the combined end point were assessed only in the 867 patients in NYHA functional classes I to II (after excluding 102 patients who were already in NYHA classes III to IV at study entry).

RESULTS

Prevalence. Among the 969 HCM study patients, there was a predominance of male patients (n = 576; 59%) compared with female patients (n = 393; 41%), which was similar in Italy and the U.S. (Table 1). This relationship did not change over the period of patient enrollment (Fig. 1). Male predominance occurred from adolescence to mid-life, with reversed female predominance evident only among patients >60 years old (Fig. 1).

Baseline characteristics. CLINICAL FEATURES. At the time of initial evaluation, female patients were 51 ± 22 years, an average of 9 years older than male patients (42 ± 18 years, $p < 0.001$); a similar age difference of nine years was also present at the time of the first diagnosis of HCM (Table 1). Female patients also had experienced more advanced heart failure symptoms of exertional dyspnea, as well as chest pain or syncope (Table 1). Specifically, 57% of women (n = 225) were symptomatic in NYHA functional classes II to IV at initial evaluation, compared with only 39% of men (n = 223; $p < 0.001$).

MORPHOLOGY. Female patients showed slightly less maximum LV wall thicknesses (21 ± 5 mm vs. 22 ± 6 mm in male patients, $p = 0.03$), although the proportion of patients with extreme LV thickness (≥30 mm) was similar among the genders (Table 1). Female patients also had smaller left atrial and LV end-diastolic dimensions (Table 1).

OUTFLOW OBSTRUCTION AND MITRAL REGURGITATION. Female HCM patients more frequently showed LV outflow obstruction at rest, due to mitral valve systolic anterior motion (gradient ≥30 mm Hg, average 72 ± 31 mm Hg), compared with male patients (Table 1). At initial evaluation, female patients with obstruction were older (age 51 ± 23 vs. 37 ± 19 years, $p < 0.001$) and more symptomatic (NYHA class 1.9 ± 0.8 vs. 1.6 ± 0.7, $p < 0.001$) than male patients. The proportion of female patients with obstruction in NYHA functional classes III to IV was 24% (34 of 144), compared with only 11% of male patients (14 of 131; $p < 0.01$). Moderate-to-severe mitral regurgitation was also more common in female patients, usually related to the presence of outflow obstruction (16 [4%] vs. 11 [2%] for male patients, $p < 0.05$).

Triggers for echocardiographic diagnosis. Hypertrophic cardiomyopathy was diagnosed fortuitously and unrelated to cardiovascular symptoms or a family history of the disease in one-third of the study patients (Table 2). In these patients, HCM was initially suspected clinically by incidental recognition of a heart murmur or abnormal electrocardiogram during routine examinations, with diagnosis subsequently confirmed by echocardiography. Such HCM diagnoses were almost 50% less likely among female patients (23% vs. 41%

Table 1. Baseline Clinical Features of 969 HCM Patients According to Gender

Parameters	Overall	Male Patients	Female Patients	p Value
Number of (%) patients	969	576 (59%)	393 (41%)	
U.S.	605	354 (58%)	251 (42%)	0.24*
Italy	364	222 (61%)	142 (39%)	
Age at diagnosis (yrs)	42 ± 21	38 ± 18	47 ± 23	<0.001
Age at initial evaluation (yrs)	46 ± 20	42 ± 18	51 ± 22	<0.001
NYHA functional class at initial evaluation	1.6 ± 0.7	1.4 ± 0.6	1.8 ± 0.8	<0.001
I	521 (54%)	353 (61%)	168 (43%)	
II	346 (36%)	191 (33%)	155 (39%)	
III/IV	102 (10%)	32 (6%)	70 (18%)	
Chest pain	286 (29%)	150 (26%)	136 (35%)	0.005
Syncope	126 (13%)	57 (10%)	72 (18%)	<0.001
Coronary artery disease†	40 (4%)	26 (5%)	14 (4%)	0.21
Echocardiographic measurements				
LV outflow gradient ≥30 mm Hg	275 (28%)	131 (23%)	144 (37%)	<0.001
Mean outflow gradient (mm Hg)‡	61 ± 38	58 ± 37	62 ± 38	0.3
Max LV thickness (mm)	22 ± 6	22 ± 6	21 ± 5	0.03
≤15	96 (10%)	55 (10%)	41 (10%)	
16–19	262 (27%)	155 (27%)	107 (27%)	
20–24	344 (35%)	192 (33%)	152 (39%)	0.17§
25–29	145 (15%)	91 (16%)	54 (14%)	
≥30	122 (13%)	83 (14%)	39 (10%)	
Left atrium (mm)	42 ± 9	42 ± 9	41 ± 8	0.02
LVEDD (mm)	43 ± 7	45 ± 6	41 ± 7	<0.001

*Overall comparison between the U.S. and Italy; †hemodynamically significant atherosclerotic narrowing of ≥1 coronary artery documented by angiography; ‡among patients with resting LV outflow obstruction ≥30 mm Hg; §overall comparison among classes of LV thickness.

HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; Max = maximum; NYHA = New York Heart Association.

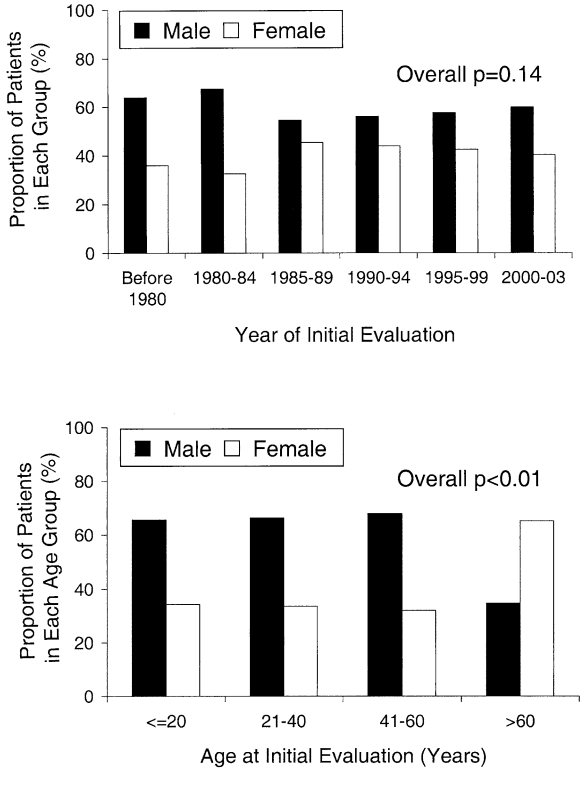

Figure 1. Distribution of 969 male and female patients with hypertrophic cardiomyopathy according to year of initial evaluation **(top panel)** and age at initial evaluation **(bottom panel)**.

in male patients; $p < 0.001$). Conversely, female patients were most commonly identified by virtue of new or worsening cardiac symptoms or acute cardiovascular events such as onset of atrial fibrillation, embolic stroke, or resuscitated cardiac arrest (Table 2). The genders were similar with respect to HCM diagnosis initially triggered by a family history of the disease (Table 2).

Outcome. Female gender was significantly associated with the combined end point of long-term symptomatic progression to NYHA functional classes III or IV or death from heart failure or stroke (Fig. 2, Table 3); this relationship was also evident when baseline clinical differences between the genders with respect to age, NYHA functional class, triggers for diagnosis, and presence of outflow obstruction were taken into consideration by multivariate analysis (independent relative hazard for female patients 1.5, $p < 0.001$; Table 4). Of note, risk for adverse outcome was highest among female patients >50 years old at initial evaluation, compared with female patients ≤50 years or with male patients (Fig. 3). In addition, female patients more often experienced nonfatal embolic stroke, despite a similar frequency of atrial fibrillation between the genders (Table 3).

Conversely, no significant differences were identified between the genders with regard to all-cause mortality, overall HCM-related deaths, and sudden cardiac death (Table 4, Fig. 2). In younger patients <40 years, a trend was identified suggesting increased risk of sudden cardiac death among female patients (annual incidence 1.6% vs. 0.9% in

Table 2. Circumstances Leading to Initial HCM Diagnosis According to Gender

	Overall (n = 969)	Male Patients (n = 576)	Female Patients (n = 393)	p Value
Routine medical examinations	324 (33%)	233 (41%)	91 (23%)	<0.001
Murmur	148 (15%)	99 (17%)	49 (12%)	
Abnormal ECG	176 (18%)	134 (24%)	42 (11%)	
Clinical manifestations	503 (52%)	257 (44%)	246 (63%)	<0.001
Symptoms	365 (38%)	185 (32%)	180 (46%)	<0.001
Dyspnea	135 (14%)	58 (10%)	77 (20%)	
Chest pain	116 (12%)	69 (12%)	47 (12%)	
Palpitations	76 (8%)	39 (7%)	37 (9%)	
Dizziness (presyncope)	19 (2%)	12 (2%)	7 (2%)	
Fatigue	19 (2%)	7 (1%)	12 (3%)	
Acute cardiovascular events	138 (14%)	72 (12%)	66 (17%)	<0.04
Atrial fibrillation	49 (5%)	28 (5%)	21 (5%)	
Stroke	8 (0.8%)	3 (0.4%)	5 (1%)	
Cardiac arrest (VF)	5 (0.5%)	1 (0.2%)	4 (1%)	
Syncope	58 (6%)	32 (6%)	26 (7%)	
Pulmonary edema	12 (1%)	4 (0.7%)	8 (2%)	
Acute myocardial infarction	5 (0.5%)	4 (0.7%)	1 (0.5%)	
Endocarditis	1 (0.2%)	0	1 (0.5%)	
Family history of HCM	142 (15%)	86 (15%)	56 (14%)	0.42

ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; VF = ventricular fibrillation.

male patients), although this comparison did not achieve statistical significance ($p = 0.07$). The proportion of patients who developed the end stage with systolic dysfunction (LV ejection fraction <50%) was also similar in the two genders (22 to 393, 6% in female patients and 29 to 576, 5%, in male patients; $p = 0.77$). Finally, U.S. and Italian patients did not differ with respect to the outcome end points by gender ($p > 0.1$).

Management. Treatment strategies did not different with respect to gender (Table 3). Specifically, the proportion of male patients and female patients who underwent surgical septal myectomy or alcohol septal ablation, received an ICD or dual-chamber pacemaker, or were treated pharmacologically with amiodarone or a beta-blocker did not differ significantly between the two groups (Table 3). Female patients were more often treated with disopyramide or verapamil ($p < 0.01$), probably related in part to their higher prevalence of outflow obstruction and congestive symptoms.

DISCUSSION

Under-representation and delayed diagnosis. Hypertrophic cardiomyopathy is a diverse cardiac disease, usually caused by mutant genes encoding proteins of the sarcomere, and transmitted as a Mendelian autosomal dominant trait (1,21). Therefore, the prevalence of HCM in the general population is expected to be equal among the two genders (21). In contrast, however, the present multicenter study documents a 3:2 predominance of male patients, consistent with most previous clinical reports showing a male majority ranging from 55% to 78% (2,3,7–10,24–30). Notably, the prevalence of male patients in our HCM population has not changed significantly over the last three decades, and was

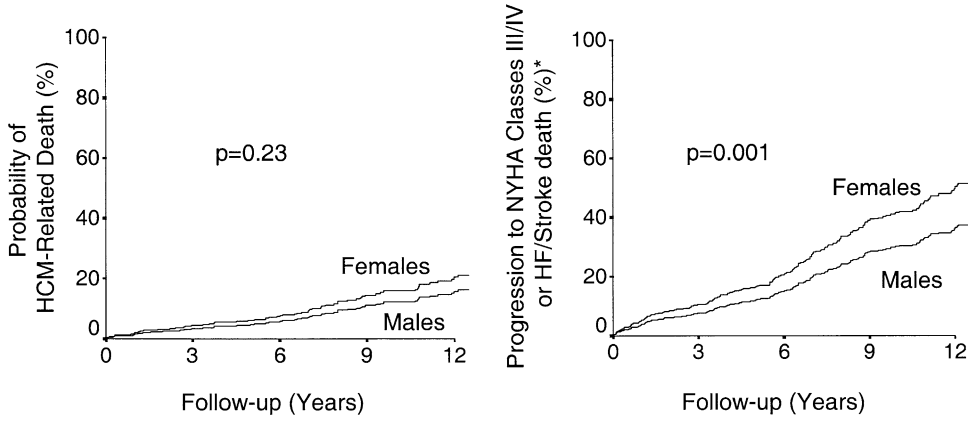

Figure 2. Relation of gender to overall hypertrophic cardiomyopathy (HCM)-related mortality **(left panel)** and progression to New York Heart Association (NYHA) functional classes III and IV, or heart failure (HF) or stroke death **(right panel)**. Hazard plot based on multivariate Cox regression analysis including age, NYHA functional class, and left ventricular outflow obstruction (gradient ≥30 mm Hg at rest) at initial evaluation. *Patients who were already in NYHA functional classes III to IV at first evaluation were excluded from this analysis.

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Table 3. Features at Final Evaluation and Clinical Outcome

Parameters	Overall	Male Patients	Female Patients	p Value
Age at final evaluation or death (yrs)	51 ± 20	48 ± 19	56 ± 22	<0.001
Follow-up (yrs)	6.2 ± 6.1	6.6 ± 6.5	5.5 ± 5.6	<0.01
On medical treatment	648 (76%)	365 (63%)	283 (72%)	<0.01
Beta-blockers	435 (45%)	251 (44%)	184 (47%)	0.17
Verapamil	318 (33%)	170 (30%)	148 (38%)	<0.01
Disopyramide	37 (4%)	14 (2%)	23 (6%)	<0.01
Amiodarone	142 (15%)	78 (14%)	64 (16%)	0.23
Major interventions for obstruction/ symptoms				
Alcohol septal ablation	21 (2%)	9 (2%)	12 (3%)	0.12
Surgical septal myectomy	59 (6%)	28 (5%)	31 (8%)	0.06
Mitral valve replacement	10 (1%)	5 (0.8%)	7 (2%)	0.24
Heart transplantation	8 (0.8%)	6 (1%)	2 (0.5%)	0.86
Pacemaker/ICD	81 (8%)	41 (7%)	40 (10%)	0.16
Final NYHA functional class	1.8 ± 0.8	1.7 ± 0.8	2.1 ± 0.9	<0.001
I	423 (44%)	299 (52%)	124 (32%)	
II	303 (31%)	172 (30%)	131 (33%)	
III/IV	243 (25%)	104 (18%)	138 (35%)	
Atrial fibrillation	204 (21%)	115 (20%)	89 (23%)	0.6
Paroxysmal	131 (13%)	74 (13%)	57 (15%)	
Chronic	73 (8%)	41 (7%)	32 (8%)	
Nonfatal stroke	20 (2%)	6 (1%)	14 (4%)	0.007
HCM-related death	110 (11%)	58 (10%)	52 (14%)	—
Sudden death	59 (6%)	33 (6%)	26 (7%)	—
Heart failure/stroke-related	51 (5%)	25 (4%)	26 (7%)	—
Non–HCM-related death	58 (6%)	22 (4%)	36 (9%)	—

HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

consistent in all age groups from childhood to middle age; only in those patients enrolled over 60 years of age was there an excess of female patients.

In addition to the apparent under-representation of women with HCM in this cohort, our data also suggest a delay in clinical identification. Indeed, women were older by an average of about nine years and significantly more symptomatic than men, both at the time of their initial HCM diagnosis and when first evaluated at our institutions. Among the subset of patients with LV outflow obstruction, who are potential candidates for invasive treatment options such as surgical septal myectomy or alcohol septal ablation (1,4,5), the delay in HCM diagnosis for women was even more striking (i.e., an average of 14 years). Finally, although a substantial proportion of male patients were identified with HCM fortuitously (by virtue of routine medical examinations unrelated to cardiac symptoms), in female patients this diagnosis more often required clinically obvious disease manifestations such as onset of exertional dyspnea and chest pain, or acute cardiovascular events including syncope, pulmonary edema, and cardiac arrest.

There are a number of possible explanations for the differences in prevalence of HCM by gender in our cohort.

Table 4. Relation Between Clinical Variables at Initial Evaluation and Outcome (Age-Adjusted Multivariate Cox Proportional Hazards Analysis)*

	Death From Any Cause		HCM-Related Death		Severe HF Symptoms† or HF/Stroke Death		Sudden Death	
Variables	Relative Risk (95% CI)	p Value	Relative Risk (95% CI)	p Value	Relative Risk (95% CI)	p Value	Relative Risk (95% CI)	p Value
Female gender	—	0.13	—	0.51	1.50 (1.11–2.00)	<0.001	—	0.97
Diagnosis by routine examinations‡	0.66 (0.45–0.97)	0.035	0.54 (0.34–0.87)	0.010	0.75 (0.54–1.05)	0.09	0.57 (0.35–0.95)	0.031
NYHA functional class II§	1.58 (1.08–2.30)	0.017	1.95 (1.20–3.16)	0.006	2.08 (1.51–2.87)	<0.001	1.94 (1.17–3.12)	0.094
NYHA functional classes III/IV§	1.70 (1.04–2.80)	0.032	2.48 (1.34–4.60)	0.004	n/a		n/a	
LV outflow obstruction (≥30 mm Hg at rest)	1.56 (1.10–2.22)	0.011	1.32 (1.02–2.19)	0.045	3.54 (2.64–4.75)	<0.001	1.84 (1.14–2.98)	0.012

*All models included age as a stratification factor (<20, 20–39, 40–60, >60 years); †progression to NYHA functional classes III/IV; ‡as compared with diagnosis raised by onset of HCM-related symptoms or cardiovascular events; §as compared with NYHA class I.

CI = confidence interval; HCM = hypertrophic cardiomyopathy; HF = heart failure; LV = left ventricular; n/a = not assessed (patients already in New York Heart Association [NYHA] classes III to IV at study entry were excluded from these analyses); — = variables removed from the final model.

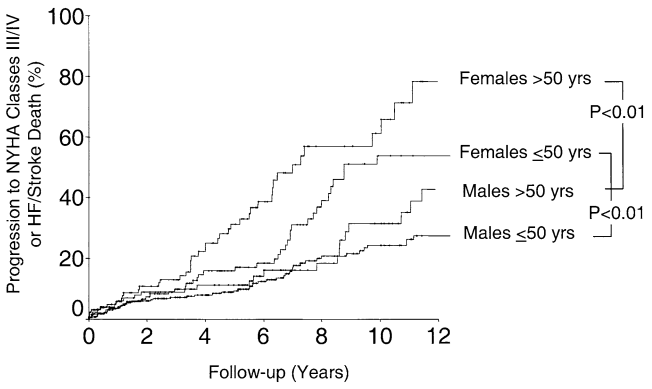

Figure 3. Cumulative risk of progression to New York Heart Association (NYHA) functional classes III and IV, or heart failure (HF) or stroke death related to age at initial evaluation and gender. Patients who were already in NYHA functional classes III to IV at initial evaluation were excluded from this analysis. Female patients >50 years versus female patients ≤50 years of age ($p < 0.005$); male patients >50 years versus male patients ≤50 years of age ($p = 0.02$).

The apparent under-representation of women may reflect failed diagnoses due to reduced patient awareness regarding cardiovascular risk (31–33), fewer indications for medical screening programs (34–37), and clinician bias (31–33). Lack of attention to early clinical signs in women has been previously suggested in cardiac conditions such as coronary artery disease and heart failure, and may relate to denial and greater focus on the health of others in the family (31–33). Moreover, the consistent reporting of male predominance in HCM cohorts (2,3,7–10,24–30), and the highly visible sudden deaths occurring largely in young male athletes with HCM (34), may well have promoted the misconception that this disease disproportionately and more severely affects young men (2). Of note, in this study the prevalence of sudden death among women with HCM was at least equal to that in men, both in the overall study group and among patients <40 years of age.

Besides these potentially important factors, delayed HCM diagnosis in women may be secondary to genetic and endocrine factors directly impacting phenotypic expression (21). For example, some investigators have even suggested that reduced penetrance and delayed disease onset may be more common in female patients with certain sarcomeric gene mutations (21). In addition, as in coronary artery disease, endocrine features associated with female gender may delay the development of the HCM phenotype or its clinical manifestations (38). Indeed, a protective effect of estrogens on development of secondary myocardial hypertrophy has been shown in animal models (39).

Gender and clinical outcome. Over an average follow-up of over six years, female patients with HCM had a 50% greater risk than male patients of progression to severe, disabling congestive symptoms or death from heart failure or embolic stroke. This finding was independent of age and functional class at initial evaluation and, therefore, was not solely attributable to delayed clinical diagnosis in women. Alternatively, the more progressive clinical course of HCM in our female patients may be explained in part by the greater prevalence of LV outflow obstruction compared with male patients, which in turn could be related to smaller LV cavity dimensions (25,40). Because outflow obstruction has been shown to be a powerful independent predictor of adverse outcome due to heart failure in HCM (10), the more frequent occurrence of obstruction in female patients likely contributed importantly to their more adverse long-term outcome. Other possibilities include an enhanced susceptibility of female patients with HCM to the consequences of atrial fibrillation (7), including heart failure, embolic stroke, and LV remodeling (25).

Finally, risk for heart failure-related clinical deterioration and death was greater among those female patients age 50 years or older (average age, 65 years), as compared with those <50 years, or with male patients, suggesting that postmenopausal endocrine changes may impact clinical course in HCM, as previously shown in coronary artery disease (41). However, we observed no differences in management strategies between the genders after the diagnosis of HCM with regard to pharmacologic or invasive treatments (1), such as the ICD (42) or surgical and percutaneous interventions aimed at relieving LV outflow obstruction (43). Thus, no potential biases in management strategies were identified for those patients already diagnosed with HCM.

The extent to which the two genders with HCM differ with regard to risk for disease progression cannot be totally ascribed to the known demographic and pathophysiologic variables, but suggests that other (as yet unresolved) mechanisms specifically related to the female gender may play an important role. Specifically, women may be prone to disease progression for a variety of physiologic factors related to age, including more limited response to treatment and increased comorbidity (44). Indeed, large epidemiologic studies of non-HCM populations with secondary forms of LV hypertrophy (including the Framingham study) have consistently reported an increased risk of death and cardiovascular events, or propensity for diastolic heart failure with preserved systolic function in female patients (14–17).

Potential treatment implications. That the diagnosis of HCM is less common and often delayed in female patients is potentially of clinical relevance, and underscores the importance for heightened attention to this disease in women. In female patients with LV outflow obstruction and heart failure symptoms, therapeutic options for pharmacologic, surgical, or percutaneous relief of the subaortic gradient may be delayed, which is likely to have an impact on the clinical course of the disease (1,4,6,43). Indeed, such a concern is consistent with the unfavorable long-term progression of disease demonstrated by our women with HCM, largely related to outflow obstruction (10). Moreover, women were exposed to a risk for sudden death that was at least equal to that of men, particularly when young. Thus, delayed or failed HCM diagnoses may potentially deprive

high-risk female patients (8) of the therapeutic options and protection offered by the ICD for primary prevention (42).

Conclusions. This study documents a variety of distinctions between the genders with regard to the clinical presentation and course of HCM. Women with HCM were underdiagnosed and older, with more advanced disease than men at initial evaluation. Furthermore, women showed greater likelihood of marked symptom progression or death due to heart failure or stroke, often associated with LV outflow obstruction. These gender-specific differences suggest that social, endocrine, or genetic factors may affect the diagnosis and clinical course, and underscore the importance of heightened suspicion for HCM in women. Such awareness may allow for timely implementation of treatment strategies capable of improving clinical course, including relief of obstruction and prevention of sudden death or stroke.

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