

# Gender and Age at Enrolment: the Predictor of Advanced Heart failure in Gene-negative Patients with Hypertrophic Cardiomyopathy

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## Research

**Keywords:** Hypertrophic cardiomyopathy, gene-negative, gender, age at enrolment, advanced heart failure

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## **Gender and Age at Enrolment: The Predictor of Advanced Heart failure in Gene-negative Patients with Hypertrophic Cardiomyopathy**

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### **Abstract**

**BACKGROUND:** Patients with hypertrophic cardiomyopathy (HCM) may develop concomitant advanced heart failure (HF). However, there is a paucity of data on the clinical outcomes of HCM patients without mutations who have advanced HF.

**Methods:** A total of 1529 unrelated patients with HCM were enrolled and followed up. All patients were genotyped by whole exome or panel sequencing. Patients without mutations were studied to assess the impact of family history, clinical findings and echocardiographic parameters on advanced HF.

**Results:** A total of 735 unrelated patients with HCM were included in the study. The mean follow up duration was  $3.2 \pm 2.3$  years. During follow-up, 97 patients had advanced HF. Multivariable analysis revealed that risk factors significantly associated with advanced HF were gender [adjusted hazard ratio (HR) 2.499, 95% confidence interval (CI) 1.531-4.081,  $P < 0.001$ ] and age at enrolment (adjusted HR 1.298, 95% CI 1.00-1.682,  $P = 0.049$ ) during the follow-up period.

**Conclusion:** Female and older at enrolment can increase risk of advanced HF in gene-negative patients with HCM. Early detection and treatment have an important role to play in management and prevention of disease-related complications for gene-negative patients.

**Keywords:** Hypertrophic cardiomyopathy; gene-negative; gender; age at enrolment; advanced heart failure

Hypertrophic cardiomyopathy (HCM) is a complex type of genetic heart disease that is defined by left ventricular hypertrophy unexplained by secondary causes[1].Over the past 20 years, a lot of evidence has supported the prevalence of HCM at about 1/500 USA[2], as well as in China[3].However, recent studies have shown that HCM is more common than previously estimated, with an estimated prevalence ranging from 1 in 500 to 1 in 200[4].

The demographics and epidemiology of HCM have changed, and there is increasing recognition of the dysfunction caused by exertion dyspnea, which has traditionally been considered a form of heart failure (HF)[5, 6].With the decrease in sudden cardiac death (SCD) caused by the use of implantable defibrillators in HCM, HF has become an increasingly prominent management problem. Exercising dyspnea with disease levels ranging from mild to severe (New York Heart Association Function Class III to IV) is often difficult to treat, leading to progressive disability. So, the early and accurate identification of risk factors for advanced HF have aroused widespread concern.

Studies have shown that many gene mutations cause HCM. So the current research mainly focuses on the effect of gene mutation on HF, including genetic status[7]and mutation dosage[8].At the same time, many studies have suggested that HCM patients with genetic mutations have worse symptoms and more severe adverse outcomes than those with negative mutations[9].Unfortunately, patients with negative mutations are ignored. Moreover, studies have found that the risk of poor prognosis remains in patients with negative genetic mutations[8].Therefore, it is urgent to study the prognostic factors of HCM patients without mutations and the influence of these risk factors.

In this study, we sought to analyze the correlation between the prognostic factors and the clinical phenotype in gene-negative patients with HCM, and evaluate the value of the factors in predicting the advanced HF, so as to provide a reference for the prognosis assessment of such patients.

## **METHODS**

### **STUDY POPULATION AND CLINICAL EVALUATION**

A total of 1529 unrelated patients with HCM were enrolled from 1999 to 2018 at Fuwai Hospital, Chinese Academy of Medical Sciences. Patients were diagnosed by a maximum left ventricular wall thickness  $\geq 15$  mm (or  $\geq 13$ -14 mm if having a HCM family history) measured

with 2-dimensional echocardiographic and/or cardiac magnetic resonance imaging, in the absence of other cardiac or systemic diseases capable of producing such magnitude of ventricular hypertrophy[10].Patients without mutations were included in the study. This study was approved by the Ethics Committee of Fuwai Hospital and the Affiliated Hospital of Qingdao University, and conformed to the principles of the Declaration of Helsinki. All participants gave written informed consent.

Clinical evaluation included sex, age at enrolment, family history of HCM, family history of SCD, syncope, left ventricular end-diastolic diameter (LVEDD), body surface area (BSA), left atrium (LA)diameter, maximal left ventricular wall thickness (LVWT), left ventricular ejection fraction (LVEF), systolic anterior movement (SAM), left ventricular outflow tract (LVOT) gradient and atrial fibrillation (AF).

#### **FOLLOW UP and OUTCOMES MEASUREMENT**

The patients were prospectively recruited and followed up by clinical visits or telephone consultation. The clinical outcomes measured in this study were advanced HF. We defined New York Heart Association class III or IV (NYHA III/IV) HF as advanced HF.

#### **STATISTICAL ANALYSIS**

Continuous variables, reported as means with mean  $\pm$  standard deviation (SD), were compared between groups with t-test or nonparametric tests, as appropriate. Multiple groups were compared using one-way ANOVA. Categorical variables, reported as number (%), were compared between groups with  $\chi^2$  or Fisher exact tests. Survival was modelled using Kaplan–Meier analysis and log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with univariable or multivariable Cox proportional hazard regression models. All probability values were 2-sided, and  $P < 0.05$  was considered significant. SPSS (V.23.0.0.0) was used for the analyses.

### **Results**

#### **Characteristics of Patients**

A total of 735(48.1%) unrelated patients with HCM were included in this study following the inclusion and exclusion criteria. The mean age at enrolment the studied patients was  $52.54 \pm 13.24$  years and 69.5% was male. The demographic and clinical characteristics of the studied patients were summarized in Table 1.

#### **Clinical Outcomes**

During the mean follow-up period of  $3.18 \pm 2.28$  years, there were 95 advanced HF. The univariate analysis showed that gender, age at enrolment, BSA and AF were related to advanced HF events. The multivariate Cox regression analysis and Kaplan–Meier analysis revealed that female was associated with a significantly higher risk of advanced HF than male (adjusted HR 2.499, 95% CI 1.531–4.081,  $P < 0.001$  Table 2, Figure 1). The analysis also showed that older at enrolment (adjusted HR 1.298, 95% CI 1.000–1.682,  $P = 0.049$ , Table 2 Figure 1).

## **DISCUSSION**

The presence of different phenotypes in any of the pathogenic mutations suggests that other factors besides genetic mutations may influence the development of HCM. And the 2014 guidelines of the European Society of Cardiology suggested that the cause of HCM in 25–30% of patients remains unknown[11]. In our study, we enrolled sarcomere gene mutation-negative HCM patients, and found that female and older at enrolment are associated with increased risk of advanced HF in HCM patients without mutations during the follow-up period.

HCM patients may have a high prevalence of HF. One of the studies, in a cohort of 1000 patients diagnosed with HCM, showed a HF incidence of nearly 50%, with symptoms ranging from mild to severe[12]. Another study, with a larger cohort of 3208 patients, showed that the prevalence of HF was 67%[13]. Thus, early and accurate identification of risk factors for advanced HF is of great value for the treatment and management of patients with HCM.

Some biomarkers have been related to the disease severity of HCM, However, due to lack of sensitivity and specificity, they cannot be a reliable clinical tool to guide treatment. For example, Brain natriuretic peptide (or N-terminal pro-brain natriuretic peptide) may be useful for nonobstructive HCM patients, but it is not a liable prognostic predictor for individuals with HCM[14]. In the past 15 years, genetic testing has played an important role in guiding the clinical management of patients with HCM. Genetic testing maybe offer excellent opportunities to identify individuals with mutations who will develop HCM before typical clinical manifestations arise. However, there is insufficient evidence that sarcomere gene mutations can predict the development of HF in patients with HCM, although mutation-positive patients are associated with a worse cardiovascular prognosis than mutation-negative patients[15].

During the past 20 years, a large number of studies have been conducted on HCM patients of different groups and races to determine whether the prognosis of women is worse than that of

men.[16-21]. Studies have found that patients with gene mutations have a worse prognosis than mutation-negative patients[8].After excluding the influence of genetic mutations on patients, we conducted research and found that women still can increase the risk of advanced HF during follow-up. This is consistent with previous studies<sup>[22]</sup>.This indicates that gender is an important determinant in HCM treatment, and women may need more aggressive diagnosis and treatment methods.

A major risk factor for HF and overall cardiovascular disease is age. About 1% of people over the age of 50 suffer from HF, which doubles every 10 years, making HF the leading cause of death for the elderly. [23].In the present study, HCM patients with sarcomere gene mutations are younger at enrolment[8]. It can be seen that gene mutations have an impact on the age at enrolment of patients with HCM. Thus, in the case of excluding this factor of gene mutation, our study found that older at enrolment was significantly increased the risk of advanced HF during follow-up. We warn that negative-mutation patients with HCM should still pay attention to the disease, and seek medical treatment in time after diagnosis and review them regularly to minimize the possibility of adverse events.

## CONCLUSION

Our study demonstrates that gender and age at enrolment are predictor of advanced HF events in gene-negative patients with HCM. This study may have implications for the management of HCM patients without gene mutations.

## List of abbreviations

hypertrophic cardiomyopathy	HCM
heart failure	HF
hazard ratio	HR
confidence interval	CI
sudden cardiac death	SCD
left ventricular end-diastolic diameter	LVEDD
Body Surface Area	BSA
left atrium	LA
left ventricular wall thickness	LVWT

left ventricular posterior wall	LVPW
left ventricular ejection fraction	LVEF
systolic anterior movement	SAM
left ventricular outflow tract	LVOT
atrial fibrillation	AF

### **Declarations**

Ethics approval and consent to participate: This study conformed to the principles of the Declaration of Helsinki. All participants gave written informed consent.

Consent for publication

Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have conflicts of interest.

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**Table 1** Baseline clinical and echocardiographic findings of gene-negative HCM patients

	Total	Patients without events (n=638)	Patients with events (n=97)	P-values
Male, n(%)	511(69.5)	464(72.7)	47(48.5)	<0.001
Age at enrolment, years	52.54±13.24	51.82±13.10	57.29±13.25	<0.001
Family history of HCM, n(%)	92(12.5)	79(12.4)	13(13.4)	0.869
Family history of SCD, n(%)	67(9.1)	56(8.8)	11(11.3)	0.447
Syncope, n(%)	68(9.3)	58(9.1)	10(10.3)	0.707
LVEDD, mm	45.42±6.19	45.37±5.80	45.70±8.34	0.713
BSA	1.92±0.25	1.93±0.26	1.86±0.21	0.012
LA diameter, mm	40.70±6.58	40.47±6.43	42.14±7.33	0.036
Maximal LVWT, mm	21.24±5.61	21.08±5.69	22.28±4.97	0.051
LVPW, mm	11.67±2.72	11.55±2.60	12.46±3.33	0.011
LVEF, %	67.03±8.12	67.40±7.59	64.55±10.71	0.013
SAM, n(%)	322(43.8)	286(44.8)	36(37.1)	0.187
LVOT gradient, mm Hg	43.25±43.42	42.75±41.89	46.54±52.47	0.498
AF, n(%)	84(11.4)	65(10.2)	19(19.6)	0.010

Values are n (%) or mean±SD.

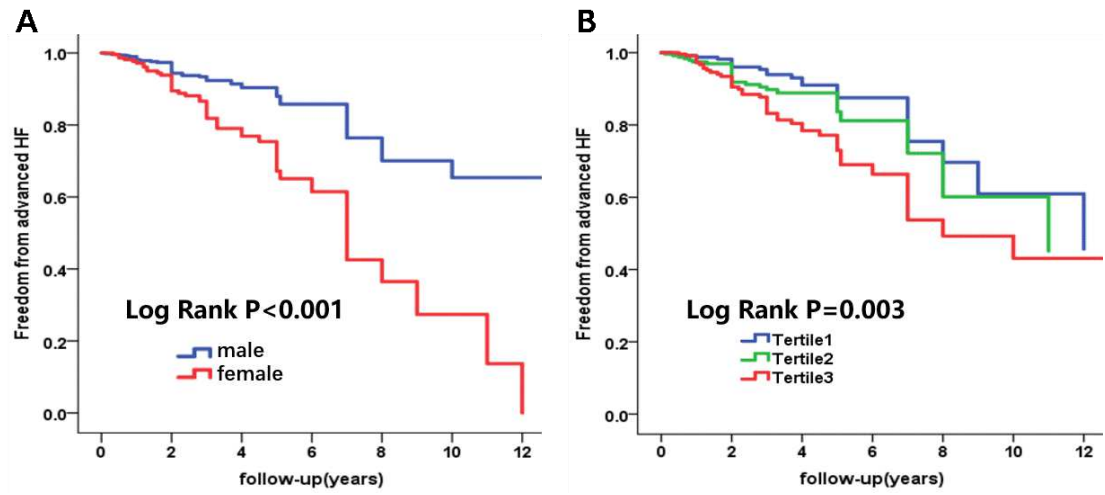
HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; LVEDD, left ventricular end-diastolic diameter; BSA, body surface area; LA, left atrium; LVWT, left ventricular wall thickness; LVPW, left ventricular posterior wall; LVEF, left ventricular ejection fraction; SAM, systolic anterior movement; LVOT, left ventricular outflow tract; AF, atrial fibrillation.

**Table 2** Univariable and multivariable Cox regression analysis of the association between clinical characteristics and outcomes in patients with HCM

Variants	Crude HR (95% CI)	Crude P-value	Adjusted* HR (95% CI)	Adjusted* P-value
Male	2.807(1.880-4.191)	<0.001	2.574(1.579-4.195)	<0.001
Age at enrolment	1.517(1.183-1.944)	0.001	1.298(1.00-1.682)	0.049
BSA	0.725(0.565-0.929)	0.010	1.019(0.761-1.366)	0.899
LA diameter	1.269(0.992-1.624)	0.058	-	-
LVEF	0.798(0.624-1.021)	0.072	-	-
AF	1.934(1.168-3.203)	0.010	0.988(0.553-1.766)	0.947

\*Models were adjusted for male, age at enrolment, BSA, AF (follow up time)

BSA, Body Surface Area; LA, Left atrium; LVEF, left ventricular ejection fraction; AF, atrial fibrillation.



**Figure 1** In follow-up time, survival curves for advanced HF events of genders(A), age at enrolment(B). The log rank test was used to calculate the P value

# Figures

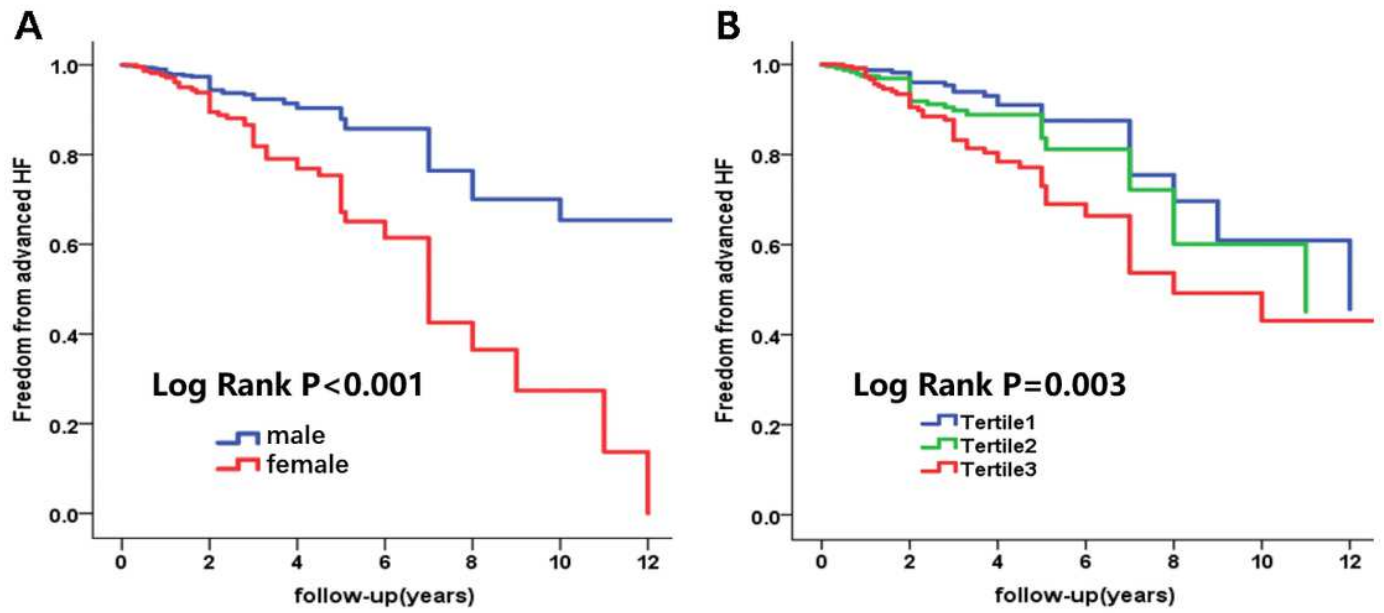


Figure 1

In follow-up time, survival curves for advanced HF events of genders(A), age at enrolment(B). The log rank test was used to calculate the P value