

Effects of sex on clinical outcomes of hypertrophic cardiomyopathy in Singapore

Tony YW Li ¹_{MBBS}, Selvie Yeo ², Nicholas JH Ngiam ³_{MBBS}, Chi-Hang Lee ^{1,2}_{MBBS}, Ting Ting Low ¹_{MBBS}, Yoke-Ching Lim ¹_{MBBS}, Lauren Kay Mance Evangelista ^{1,4}_{MD}, Edward CY Lee ¹_{MBBS}, Novi Yanti Sari ¹_{MBBS}, Tiong-Cheng Yeo ^{1,2}_{MBBS}, James WL Yip ^{1,2}_{MBBS}, Kian-Keong Poh ^{1,2}_{MBBS}, William KF Kong ^{1,2}_{MBChB}, Weiqin Lin ^{1,2}_{MBBS}, Ching-Hui Sia ^{*}_{1,2_{MBBS}, Raymond CC Wong ^{*}_{1,2_{MBBS}}}

ABSTRACT

Introduction: Despite the growing recognition that sex can affect the presentation and outcomes in hypertrophic cardiomyopathy (HCM), this relationship is understudied in Asians. Therefore, we aimed to explore sex differences in Asian patients with HCM.

Method: A total of 295 consecutive patients diagnosed with HCM were recruited from a tertiary cardiology centre from 2010 to 2017 over a mean of 3.9±2.7 years. We evaluated the effects of sex on the outcomes of HCM in Asian patients.

Results: HCM patients were more commonly men (72%). Women were older and had more comorbidities, including hypertension and atrial fibrillation. On transthoracic echocardiography, the indexed left ventricular end-systolic and end-diastolic volumes were similar, but more women had more-than-moderate mitral regurgitation and had a smaller left ventricular outflow tract (LVOT). Women more commonly had findings of obstructive physiology with significant LVOT obstruction, defined as >30 mmHg at rest. The use of implantable cardioverter defibrillators was similar across sexes. On multivariable analysis, women were found to be more likely to develop progressive heart failure requiring admission (hazard ratio [HR] 2.10, 95% confidence interval [CI] 1.05–4.71, *P*=0.021) but had a lower rate of all-cause mortality (HR 0.36, 95% CI 0.19–0.70, *P*=0.003).

Conclusion: Women diagnosed with HCM were older, had more comorbidities and were more likely to develop heart failure while men had a higher risk of all-cause mortality.

Ann Acad Med Singap 2023;52:348-55

Keywords: atrial fibrillation, cardiology, cardiomyopathy, heart failure, hypertrophic cardiomyopathy, sex

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common cause of inherited cardiomyopathy.¹ The phenotypic expression of HCM is highly diversified with varying extents of myocardial hypertrophy, which can affect different parts of the heart and result in varying extents of left ventricular outflow tract (LVOT) obstruction, diastolic dysfunction and arrhythmic potential. The large spectrum of phenotypic expression accounts for differences in clinical course and risk profile.²⁻⁶

Sex is known to be associated with differences in the presentation and outcomes in many cardiovascular conditions, including heart failure, valvular heart disease and coronary artery disease.⁷⁻⁹ There is increasing recognition that sex could have a similar impact in HCM where studies have pointed out that women tend to show poorer outcomes than men.¹⁰⁻¹⁵

Most studies on this matter involve Western populations. Studies on Asian populations are less common. In this study, we aimed to evaluate sex-specific differences in

¹ Department of Cardiology, National University Heart Centre, Singapore

² Yong Loo Lin School of Medicine, National University of Singapore, Singapore

³ Department of Medicine, National University Health System, Singapore

⁴ Department of Cardiology, University of the Philippines-Philippine General Hospital, Manila, Philippines

Correspondence: Dr Ching-Hui Sia, Department of Cardiology, National University Heart Centre, Singapore, 1E Kent Ridge Road, Tower Block Level 9, Singapore 119228.

Email: ching_hui_sia@nuhs.edu.sg

* Joint last authors

CLINICAL IMPACT

What is New

- Hypertrophic cardiomyopathy (HCM) is more common among men in Singapore.
- Women with HCM have a higher risk of progression to heart failure while men have a higher risk of all-cause mortality.
- Women tend to present later usually because of atypical symptoms (such as lack of chest pain) compared with men and delayed recognition of new symptoms.

Clinical Implications

- Measures for early detection of HCM and disease progression for women and a holistic approach to reduce risk for all-cause mortality for men may improve outcomes of patients with HCM.

the presentations and outcomes of HCM in an Asian cohort.

METHOD

This study comprised 295 consecutive patients diagnosed with HCM who were recruited at National University Heart Centre, Singapore from 2010 to 2017. The subjects were retrospectively identified from a comprehensive echocardiography database. We devised a search strategy for all subjects with reported left ventricular hypertrophy or HCM on the indication or diagnosis of transthoracic echocardiograms performed from 2010 to 2017. Subsequently, chart reviews were conducted to identify patients who were diagnosed with HCM, which yielded the final cohort of 295 subjects. Outcome data were collected for patients up to 31 December 2021, giving a study period from the index echocardiogram till last follow-up. Patients recruited either did not have hypertension or were well controlled. Patients who did not have a clear diagnosis of HCM (e.g. equivocal between hypertensive heart disease or HCM) were excluded. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (Reference number 2018/01329).

We collected baseline demographics, clinical data and echocardiographic parameters from the index echocardiogram. Outcome data were obtained by screening the Singapore electronic medical record. Echocardiographic data were interpreted and analysed according to the American Society of Echocardi-

graphy. The diagnosis of HCM was reached based on clinical and echocardiographic evaluation in accordance with consensus guidelines, where the presence of myocardial hypertrophy in the absence of local or systemic aetiologies with loading conditions would constitute HCM.¹⁶ All echocardiograms were re-evaluated by 2 independent cardiologists to determine the HCM subtype, and uncertain cases were adjudicated by an independent experienced echocardiologist. The patients were followed for a mean of 3.9 ± 2.7 years. Outcome data were collected until 31 December 2021 based on the review of the hospital medical records. Outcomes collected included first admission for heart failure as well as all-cause mortality. Mortality data in our hospital records are synchronised to the national death registry, such that we were able to capture all mortality events. However, we were unable to ascertain the cause of death if the death occurred outside our hospital.

Continuous variables were expressed as mean ($\pm$ standard deviation), while categorical variables were expressed as number (proportion). Binary logistic regression was used to establish the association between sex differences and HCM outcomes. All-cause mortality and progression heart failure were assessed using Cox regression analysis. *P* values were 2-sided and deemed significant if <0.05 . The statistical analysis was performed using SPSS Statistics version 27 (IBM Corp, Armonk, NY, US).

RESULTS

There was male predominance ($n=211$, 71.5%). Women were about 9 years older than men (66.6 ± 18.4 years versus 55.6 ± 15.1 years, $P<0.001$) at the time of diagnosis (Fig. 1), and formed most of those diagnosed above the age of 80.

In terms of comorbidities, women were more likely to have atrial fibrillation (25.0% vs 12.3%, $P=0.008$) and hypertension (56.0% vs 41.2%, $P=0.023$). The presence of other comorbidities, including hyperlipidaemia, diabetes mellitus, ischaemic heart disease, chronic kidney disease and peripheral vascular disease, was similar across the sexes. Men were more likely to be smokers than women (4.8% vs 26.1%, $P<0.001$) (Table 1).

On echocardiography, women were more likely to have significant LVOT gradient of >30 mmHg (28.6% vs 11.4%, $P<0.001$) as suggested by the echocardiographic finding of a smaller LVOT diameter (19.1 mm vs 21.5 mm, $P<0.001$). Women also had greater prevalence of more-than-moderate mitral regurgitation (11.9% vs 3.8%, $P=0.013$). While women had smaller left ventricular end-diastolic volumes (LVEDV), there was no significant difference after indexing for body

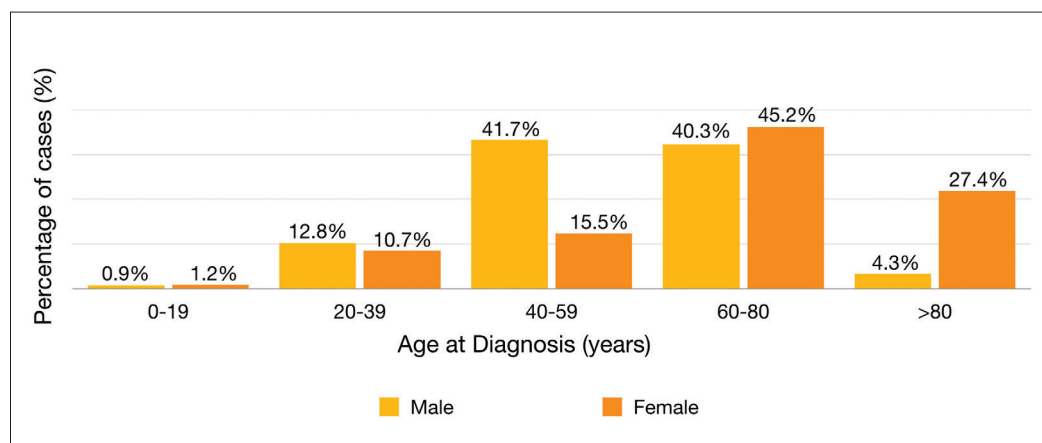


Fig. 1. Distribution of hypertrophic cardiomyopathy patients based on stratified age.

surface area. Women were more likely to have elevated cardiac filling pressures with a greater proportion with $E/e' > 14$ (63.1% vs 38.9%, $P < 0.001$) (Table 2). A total of 106 patients had a cardiac magnetic resonance imaging (cardiac MRI) done as part of their evaluation. Among these subjects, 85 had some extent of late gadolinium enhancement (LGE) detected on the cardiac MRI. However, we were unable to quantify the extent of LGE on these scans as quantification of LGE was not routinely performed in our centre during the study period.

At initial presentation, about half of the patients in both men and women's arms were asymptomatic. Most of these patients were screened because of an incidental abnormal electrocardiogram, and diagnosis was then confirmed by echocardiography and clinical review. For symptomatic patients, more women presented with dyspnoea (21.4% vs 9.5%, $P = 0.007$) while more men had chest pain (17.9% vs 30.3%, $P = 0.031$) (Table 3). There were 17 patients who already had implantable cardioverter defibrillators (ICDs) implanted prior to the index echocardiogram in this study.

In terms of long-term outcomes, women were more likely to progress to heart failure requiring admission (Fig. 2), but had a lower risk of all-cause mortality (Fig. 3). On multivariable Cox regression analysis, these associations persisted after correcting for age, hypertension, diabetes mellitus, left ventricular ejection function, atrial fibrillation and high-risk features such as a maximal wall thickness > 30 mm and a significant LVOT gradient of > 30 mmHg (hazard ratio [HR] 2.10, 95% confidence interval [CI] 1.05–4.71, $P = 0.021$; and HR 0.36, 95% CI 0.19–0.70, $P = 0.003$, respectively) (Table 3). The use of implantable cardioverter-defibrillators was similar across both sexes ($P = 0.848$).

Rates of arrhythmic events, namely, ventricular tachycardia/ventricular fibrillation (VT/VF) events either resuscitated or fatal, and appropriate ICD therapies were low and similar across both sexes.

We stratified the population by both sex and age for further analysis against a composite endpoint of stroke, progression to heart failure and all-cause mortality (Fig. 4). When stratified by age, there was no significant difference in outcomes in younger patients under the age of 50 years. However, women above 50 years experienced poorer overall outcomes ($P = 0.015$) than their male counterparts.

DISCUSSION

Our study found that in an Asian cohort, there were more male patients with HCM, while women were older at diagnosis and more commonly displayed an obstructive physiology. Women also had a higher risk of developing progressive heart failure requiring admission. On the other hand, men had a worse prognosis in terms of all-cause mortality.

Our findings that there is male predominance among HCM patients while women tended to be older at the point of diagnosis are consistent with other studies globally.^{11–14} However, it is unclear whether there is a significant genotypic or hormonal contribution to such findings. Otherwise, perhaps there are socioeconomic factors at play where a bias in screening or diagnostic strategies could have led to delayed or underdiagnosis in women. Some postulated there may be a genetic modifier that affects the degree and progression of cardiac hypertrophy, which could have contributed to the later onset of clinically manifest disease and thus later presentation in women. Our findings are consistent with literature where women are older and have higher rates

Table 1. Baseline characteristics and circumstances leading to diagnosis.

	Overall (n=295)	Men (n=211)	Women (n=84)	P value
Mean age at diagnosis ($\pm$ SD), years	58.7 ($\pm$ 16.8)	55.6 ($\pm$ 15.1)	66.6 ($\pm$ 18.4)	<0.001
Ethnicity, no. (%)				
Chinese	192 (65.1)	134 (53.5)	58 (69.0)	0.120
Malay	55 (18.6)	39 (18.5)	16 (19.0)	
Indian	36 (12.2)	30 (14.2)	6 (7.1)	
Others	121 (34.70)	78 (3.38)	4 (4.8)	
Body mass index, mean ($\pm$ SD), kg/m ²	25.3 ($\pm$ 4.5)	25.6 ($\pm$ 4.3)	24.4 ($\pm$ 4.9)	0.031
Systolic blood pressure, mean ($\pm$ SD), mmHg	127.2 ($\pm$ 20.8)	126.6 ($\pm$ 19.9)	128.5 ($\pm$ 22.9)	0.481
Smoking, no. (%)	59 (20)	55 (26.1)	4 (4.8)	<0.001
Past medical history				
Hypertension, no. (%)	134 (45.4)	87 (41.2)	47 (56.0)	0.023
Hyperlipidaemia, no. (%)	119 (40.3)	78 (37.0)	41 (48.8)	0.062
Diabetes mellitus, no. (%)	47 (15.9)	34 (16.1)	13 (15.5)	0.893
Ischaemic heart disease, no. (%)	82 (27.8)	58 (27.5)	24 (28.6)	0.851
Chronic kidney disease, no. (%)	3 (1.0)	2 (0.9)	1 (1.2)	0.852
Peripheral vascular disease, no. (%)	2 (0.7)	1 (0.5)	1 (1.2)	0.513
Atrial fibrillation, no. (%)	47 (15.9)	26 (12.3)	21 (25.0)	0.008
Reason for evaluation				
Asymptomatic, no. (%)	142 (48.1)	103 (48.8)	39 (46.4)	0.331
Symptomatic, no. (%)	153 (51.9)	108 (51.2)	45 (53.6)	
Clinical symptoms (if any), no. (%)				
Chest pain	79 (26.8)	64 (30.3)	15 (17.9)	0.031
Palpitations	42 (14.2)	27 (12.8)	15 (17.9)	0.264
Dyspnoea	38 (12.9)	20 (9.5)	18 (21.4)	0.007
Syncope	17 (5.8)	14 (6.6)	3 (3.6)	0.316
Family history, no. (%)				
Family history of HCM	18 (6.1)	13 (6.2)	5 (6.0)	0.946
Family history of SCD	3 (1.0)	1 (0.5)	2 (2.4)	0.185
Medication use, no. (%)				
Antiplatelet	90 (30.5)	67 (31.8)	23 (27.4)	0.462
Oral anticoagulation	58 (19.7)	33 (15.6)	25 (29.8)	0.006
Beta blocker	190 (64.4)	136 (64.5)	54 (64.3)	0.978
ACE inhibitor/ARB	82 (27.8)	56 (26.5)	26 (31.0)	0.460
CCB	58 (19.7)	34 (16.1)	24 (28.6)	0.016
Diuretics	49 (16.6)	28 (13.3)	21 (25.0)	0.016

ACE: angiotensin converting enzyme; ARB: aldosterone receptor blocker; CCB: calcium channel blocker; HCM: hypertrophic cardiomyopathy; SCD: sudden cardiac death; SD: standard deviation
P values in bold are statistically significant.

Table 2. Echocardiographic data.

	Overall (n=295)	Men (n=211)	Women (n=84)	P value
LVEF, mean ($\pm$ SD)	64.8 ($\pm$ 11.6)	64.7 ($\pm$ 10.7)	64.8 ($\pm$ 13.7)	0.984
LVEF <50%, no. (%)	20 (6.8)	12 (5.7)	8 (9.4)	0.242
LVEDV, mean ($\pm$ SD), mL	93.4 ($\pm$ 34.3)	96.4 ($\pm$ 34.8)	86.1 ($\pm$ 32.0)	0.021
LVEDVi, mean ($\pm$ SD), mL/m ²	53.70 ($\pm$ 18.66)	55.22 ($\pm$ 19.66)	53.10 ($\pm$ 18.28)	0.378
LVESV, mean ($\pm$ SD), mL	30.0 ($\pm$ 18.2)	30.5 ($\pm$ 19.1)	28.6 ($\pm$ 15.8)	0.404
LVESVi, mean ($\pm$ SD), mL/m ²	17.20 ($\pm$ 9.95)	18.25 ($\pm$ 10.02)	16.79 ($\pm$ 9.92)	0.258
E/e', mean ($\pm$ SD)	15.57 ($\pm$ 8.41)	14.51 ($\pm$ 7.56)	18.24 ($\pm$ 9.79)	0.001
E/e' >14, no. (%)	135 (45.8)	82 (38.9)	53 (63.1)	<0.001
LA diameter, mean ($\pm$ SD), mm	43.2 ($\pm$ 9.8)	43.1 ($\pm$ 8.5)	43.4 ($\pm$ 12.5)	0.851
LVMI, mean ($\pm$ SD), g/m ²	138.5 ($\pm$ 46.9)	139.3 ($\pm$ 47.0)	136.4 ($\pm$ 47.0)	0.637
Maximum wall thickness, mean ($\pm$ SD), mm	20.4 ($\pm$ 4.6)	20.9 ($\pm$ 4.6)	19.4 ($\pm$ 4.4)	0.010
Maximum wall thickness >30 mm, no. (%)	8 (2.7)	7 (3.3)	1 (1.2)	0.010
LVOT gradient $\geq$ 30 mmHg, no. (%)	48 (16.3)	24 (11.4)	24 (28.6)	<0.001
More than moderate MR, no. (%)	18 (6.1)	8 (3.8)	10 (11.9)	0.013
Pattern of hypertrophy, no. (%)				
Localised basal hypertrophy	53 (20.0)	36 (17.1)	17 (20.2)	0.342
Reverse curvature septal hypertrophy, no (%)	44 (14.9)	17 (8.1)	9 (10.7)	
Apical	106 (35.9)	75 (35.5)	31 (36.9)	
Concentric	87 (29.5)	61 (28.9)	26 (31.0)	
Mid cavity	1 (0.3)	1 (0.5)	0 (0)	
Others	4 (1.4)	3 (1.4)	1 (1.2)	
Presence of LGE on CMR imaging	85 (28.8)	66 (31.3)	19 (22.6)	0.140

CMR: cardiovascular magnetic resonance; LA: left atrium; LGE: late gadolinium enhancement; LVEDV: left ventricular end-diastolic volume; LVEDVi: indexed left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end systolic volume; LVESVi: indexed left ventricular systolic volume; LVMI: left ventricular mass index; LVOT: left ventricular outflow tract, MR: mitral regurgitation; SD: standard deviation
P values in bold are statistically significant.

Table 3. Eventual outcomes.

Variable	Overall (n=295)	Men (n=211)	Women (n=84)	P value
ICD implant, no. (%)	44 (14.9)	32 (15.2)	12 (14.3)	0.848
Resuscitated VT/VF or appropriate ICD therapy, no. (%)	5 (1.7)	5 (2.4)	0	<0.001
Stroke, no. (%)	36 (12.2)	20 (9.5)	16 (19.0)	0.026
Myocardial infarction, no. (%)	39 (13.2)	27 (12.8)	12 (14.3)	0.733
Heart failure, no. (%)	33 (11.2)	14 (6.6)	19 (22.6)	<0.001
Death (all-cause), no. (%)	65 (22.0)	44 (20.9)	21 (25)	0.439
Follow-up duration, mean ($\pm$ SD), years	3.92 ($\pm$ 2.72)	3.91 ($\pm$ 2.73)	3.92 ($\pm$ 2.71)	0.982

ICD: implantable cardioverter defibrillator; VT/VF: ventricular tachycardia/ventricular fibrillation; SD: standard deviation
P values in bold are statistically significant.

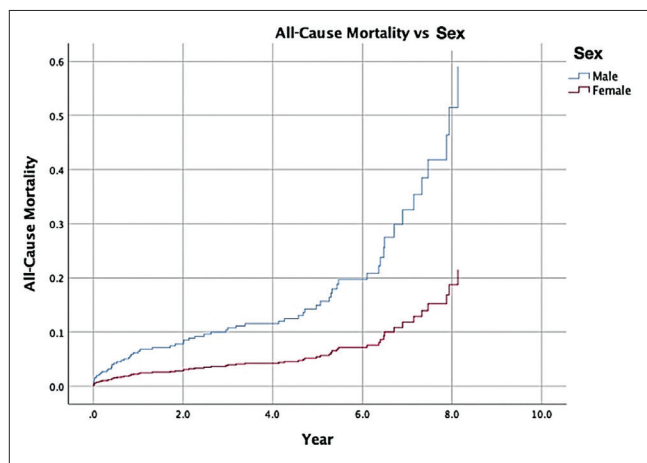


Fig. 2. Cox regression curves for all-cause mortality.
Hazard ratio 0.36, 95% confidence interval 0.19–0.70, $P=0.003$

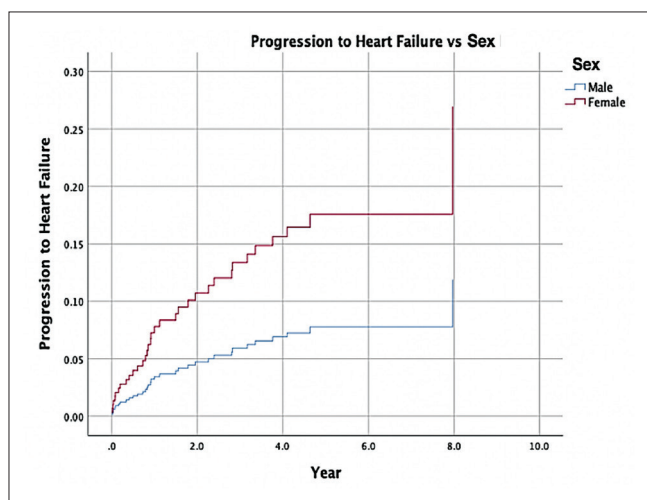


Fig. 3. Cox regression curves for heart failure.
Hazard ratio 2.10, 95% confidence interval 1.05–4.71, $P=0.021$

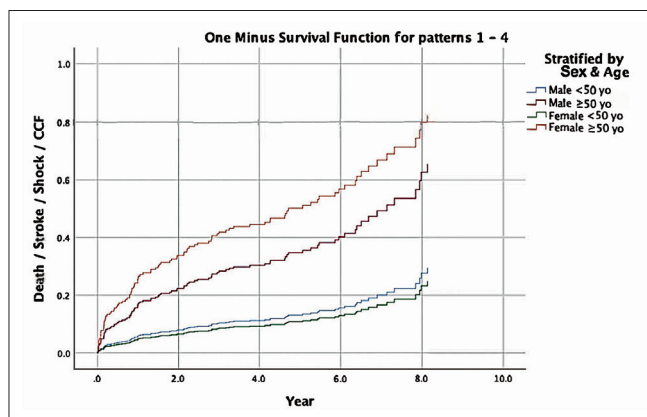


Fig. 4. Progression of hypertrophic cardiomyopathy patients to stroke, congestive heart failure and death as stratified by age and sex.
CCF: congestive cardiac failure; yo: years old

of obstructive physiology. Studies have alluded to the role of oestrogen in modulating myocardial hypertrophy in animal models while others have shown that there are differences in gene expression and therefore phenotypic expression between sexes.^{17–20}

Beyond biochemical and physiologic differences between the sexes, there could also be psychosocial differences where women approach their own health and seek medical attention in a manner different from men. Studies have shown that women are often less aware of their risk of developing cardiovascular disease. Sometimes, their physicians are similarly biased and could less frequently explore such conditions with them.^{21,22} It is well described that women tend to present later often because of atypical symptoms or delayed recognition and response to new symptoms. Taking ischaemic heart disease for example, women with chest pain have been shown to be more delayed in seeking medical attention, leading to delayed diagnosis and intervention.²³ The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients study showed that women with eventual ST-elevation myocardial infarction were likely to present without chest pain.²⁴ This is also seen in our cohort where more men presented with chest pain than women (30.3% vs 17.9%, $P=0.031$).

In terms of eventual outcomes, our study concurs with literature that women with HCM have a higher risk of progression to heart failure. Some have postulated that the development of heart failure in HCM progresses along 3 major pathways, namely, LV systolic dysfunction, LVOT obstruction, and the absence of obstruction with preserved systolic function.²⁵ First, in terms of systolic function, we found that there was no significant difference in systolic function across the sexes. With regard to the second mechanism, several studies have shown that despite similar degrees of hypertrophy, women were more likely to demonstrate obstructive physiology.^{12,13,26,27} We made a similar observation in our experience where women were more likely to have significant obstructive disease with a significant LVOT gradient at rest. However, even after accounting for obstructive physiology in the multivariable analysis, women were still more likely to develop heart failure. This leads us to postulate that heart failure in women would have occurred mostly via the third pathway with diastolic dysfunction. This is supported by the finding where women were more likely to have elevated filling pressures with a higher E/e' and were also more likely to have had prior atrial fibrillation. All of these are risk factors for progressive diastolic dysfunction and would

be in keeping with other heart failure cohorts where females were at higher risk of developing heart failure with preserved ejection fraction (HFpEF).²⁸

Another interesting finding is that the risk of progression to heart failure really starts to diverge at older ages. We noticed that when stratified by younger age, there was a large divergence in outcomes in women compared with men above the age of 50 years. One hypothesis is that the female hormonal profile represents a point of difference that leads to this great divergence in outcomes. Postmenopausal endocrine changes in women could also have an important role in the difference of presentations and outcomes. Studies have shown that oestrogen deficiency is associated with impaired ventricular relaxation, myocardial hypertrophy and fibrosis.^{29,30} Oestrogen deficiency postmenopause could have contributed to the greater risk of progression to heart failure. Beyond HCM and even within HFpEF, women have also been shown to have greater age-dependent changes in diastolic ventricular function and arterial stiffness, and therefore have a greater risk of progression to heart failure. Nevertheless, further studies focusing on postmenopausal changes and outcomes in women are needed to support this hypothesis.

While women have a higher risk of progressing to heart failure, it was actually men who had a higher risk of all-cause mortality. Unfortunately, as this was a retrospective study, the specific cause of death was often unavailable and we were unable to adjudicate whether this higher rate of mortality was due to cardiovascular causes or related to HCM. This could be studied in future prospective studies.

Limitations

A limitation is that only all-cause mortality was reported, as the specific cause of death was often unavailable. This means that we were unable to adjudicate the rates of cardiovascular mortality, including the risk of sudden cardiac death in the study. Furthermore, genetic testing for HCM was uncommon in our institution and thus this information was not available in our cohort. Finally, as a retrospective single-centre study, our findings are subject to its inherent limitations and we can only establish relation, not causality.

CONCLUSION

Women diagnosed with HCM tended to be older, had more comorbidities and were at higher risk of developing heart failure, while men had a high risk of all-cause mortality.

Funding

CHS was supported by the National University of Singapore Yong Loo Lin School of Medicine's Junior Academic Fellowship Scheme.

Conflicts of interest

The authors report no conflict of interest for this study.

REFERENCES

1. Cirino AL, Harris S, Lakdawala NK, et al. Role of Genetic Testing in Inherited Cardiovascular Disease: A Review. *JAMA Cardiol* 2017;2:1153-60.
2. Semsarian C, Ingles J, Maron MS, et al. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2015;65:1249-54.
3. Maron BJ. Clinical Course and Management of Hypertrophic Cardiomyopathy. *N Engl J Med* 2018;379:655-68.
4. Sabater-Molina M, Pérez-Sánchez I, Hernández Del Rincón JP, et al. Genetics of hypertrophic cardiomyopathy: A review of current state. *Clin Genet* 2018;93:3-14.
5. Tjahjardi C, Butcher SC, Zegkos T, et al. Differences in Characteristics and Outcomes Between Patients With Hypertrophic Cardiomyopathy From Asian and European Centers. *J Am Heart Assoc* 2022;11:e023313.
6. Sia CH, Ho JSY, Kong WKF, et al. Apical hypertrophic cardiomyopathy complicated by apical aneurysm. *J Nucl Cardiol* 2021;28:756-9.
7. Mendirichaga R, Jacobs AK. Sex Differences in Ischemic Heart Disease-the Paradox Persists. *JAMA Cardiol* 2020;5:754-6.
8. Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. *Eur Heart J* 2019;40:3859-68c.
9. Dweck MR, Kwiecinski J. Emerging Sex Differences in Aortic Stenosis. *JACC Cardiovasc Imaging* 2019;12:106-8.
10. Butters A, Lakdawala NK, Ingles J. Sex Differences in Hypertrophic Cardiomyopathy: Interaction With Genetics and Environment. *Curr Heart Fail Rep* 2021;18:264-73.
11. Siontis KC, Ommen SR, Geske JB. Sex, Survival, and Cardiomyopathy: Differences Between Men and Women With Hypertrophic Cardiomyopathy. *J Am Heart Assoc* 2019;8:e014448.
12. Geske JB, Ong KC, Siontis KC, et al. Women with hypertrophic cardiomyopathy have worse survival. *Eur Heart J* 2017;38:3434-40.
13. Olivetto I, Maron Martin S, Adabag AS, et al. Gender-Related Differences in the Clinical Presentation and Outcome of Hypertrophic Cardiomyopathy. *J Am Coll Cardiol* 2005;46:480-7.
14. Trongtorsak A, Polpichai N, Thangjui S, et al. Gender-Related Differences in Hypertrophic Cardiomyopathy: A Systematic Review and Meta-Analysis. *Pulse (Basel)* 2021;9:38-46.
15. Lu DY, Pozios I, Haileselassie B, et al. Clinical Outcomes in Patients With Nonobstructive, Labile, and Obstructive Hypertrophic Cardiomyopathy. *J Am Heart Assoc* 2018;7:e006657.
16. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. *Circulation* 2020;142:e558-e631.
17. Lind JM, Chiu C, Ingles J, et al. Sex hormone receptor gene variation associated with phenotype in male hypertrophic cardiomyopathy patients. *J Mol Cell Cardiol* 2008;45:217-22.

18. Arain FA, Kuniyoshi FH, Abdalrhim AD, et al. Sex/gender medicine. The biological basis for personalized care in cardiovascular medicine. *Circ J* 2009;73:1774-82.
19. Maass AH, Ikeda K, Oberdorf-Maass S, et al. Hypertrophy, Fibrosis, and Sudden Cardiac Death in Response to Pathological Stimuli in Mice With Mutations in Cardiac Troponin T. *Circulation* 2004;110:2102-9.
20. Yang QL, Zuo L, Ma ZL, et al. Gender- and age-related differences in distinct phenotypes of hypertrophic cardiomyopathy-associated mutation MYBPC3-E334K. *Heart Vessels* 2021;36:1525-35.
21. Bairey Merz CN, Andersen H, Sprague E, et al. Knowledge, Attitudes, and Beliefs Regarding Cardiovascular Disease in Women: The Women's Heart Alliance. *J Am Coll Cardiol* 2017;70:123-32.
22. Daugherty SL, Blair IV, Havranek EP, et al. Implicit Gender Bias and the Use of Cardiovascular Tests Among Cardiologists. *J Am Heart Assoc* 2017;6:e006872.
23. van Oosterhout REM, de Boer AR, Maas AHEM, et al. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *J Am Heart Assoc* 2020;9:e014733.
24. Lichtman JH, Leifheit EC, Safdar B, et al. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction. *Circulation* 2018;137:781-90.
25. Maron MS, Olivetto I, Zenovich AG, et al. Hypertrophic Cardiomyopathy Is Predominantly a Disease of Left Ventricular Outflow Tract Obstruction. *Circulation* 2006;114:2232-9.
26. Dimitrow PP, Czarnecka D, Strojny JA, et al. Impact of gender on the left ventricular cavity size and contractility in patients with hypertrophic cardiomyopathy. *Int J Cardiol* 2001;77:43-8.
27. Rowin EJ, Maron MS, Wells S, et al. Impact of Sex on Clinical Course and Survival in the Contemporary Treatment Era for Hypertrophic Cardiomyopathy. *J Am Heart Assoc* 2019;8:e012041.
28. Scantlebury DC, Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? *Curr Opin Cardiol* 2011;26:562-8.
29. Li S, Gupta AA. The Role of Estrogen in Cardiac Metabolism and Diastolic Function. *Methodist DeBakey Cardiovasc J* 2017;13:4-8.
30. Knowlton AA, Lee AR. Estrogen and the cardiovascular system. *Pharmacol Ther* 2012;135:54-70.