

Age and Sex Differences in the Risk of Sudden Cardiac Death in Patients with Hypertrophic Cardiomyopathy: A Multi-Centre Cohort Study

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Objective: There is a significant difference in prognosis among patients with hypertrophic cardiomyopathy (HCM) across different age groups and gender groups. This study aims to explore the risk of sudden cardiac death (SCD) in various age groups and genders.

Methods: A cohort of 2781 patients with HCM, initially evaluated between 1996 and 2023, were followed for a median of 4.54 years. The patients were divided into three age groups: youth group (aged ≤ 40 years), middle-aged group (aged between 40 and 60 years), and elderly group (aged ≥ 60 years). The outcome event was (SCD). Kaplan-Meier survival curves and Cox regression analysis were employed to compare outcomes across different age groups for both genders. Additionally, restricted cubic splines (RCS) were utilized to evaluate the potential relationship between age and prognosis within different gender categories.

Results: A total of 128 patients (4.6%) experienced SCD. In the whole population, significant age differences were observed in the Kaplan-Meier survival curves for SCD (log-rank $P < 0.0001$). Significant age differences in SCD were also noted in both genders (log-rank $P < 0.0001$). In multivariate Cox regression analysis, age was an independent predictor of SCD in the whole population [HR: 0.983; 95% CI: 0.972–0.994; $P = 0.003$] and female patients [HR: 0.963; 95% CI: 0.947–0.98; $P < 0.001$]. However, it was not significant in male patients [HR: 0.995; 95% CI: 0.98–1.01; $P = 0.538$].

Conclusion: In patients with HCM, age was an independent predictor of SCD both the whole population and female patients. Compared to young patients, the risk of SCD is reduced by 71.4% in middle-aged patients and by 43.5% in elderly patients across the whole population. Among male patients, the risk of SCD decreases by 68.5% in middle-aged patients and by 10.7% in elderly patients. In female patients, the risk of SCD is reduced by 77.8% in middle-aged patients and by 75.3% in elderly patients.

Keywords: hypertrophic cardiomyopathy, sudden cardiac death, restricted cubic splines

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic heart disease known for its unpredictable nature and recognised risk for sudden cardiac death (SCD).¹ It is the leading cause of SCD among adolescents and young athletes.^{2–4} However, as the disease progresses and cardiac remodelling worsens, adult HCM patients also have an increased risk of SCD.⁴ Moreover, the incidence of HCM in elderly patients is increasing, which is attributed to increased awareness among physicians and advancements in imaging techniques.¹ Recent evidence suggests that implantable cardioverter-defibrillators (ICDs) are effective in preventing SCD in high-risk HCM patients.^{5,6} Nonetheless, the natural history of HCM and the risk of adverse events in elderly patients have not been fully resolved.

Sex differences in the clinical presentation of HCM have received increasing attention.⁷ A series of studies have indicated that female HCM patients have a greater risk of cardiovascular mortality and all-cause mortality, yet no significant association has been found between female sex and the risk of SCD.^{7–12} Notably, current HCM management guidelines have yet to provide specific commentary on sex differences in prognosis.^{3,13} Additionally, SCD has always been a topic of great concern for HCM patients. Therefore, this study aims to investigate the differences in SCD among HCM patients of various ages and sexes.

Methods

Study Population

This observational cohort study included 2781 patients diagnosed with HCM, all of whom were hospitalised across 13 tertiary hospitals from 1996 to 2023. Patients with cardiac or systemic conditions that could result in comparable degrees of hypertrophy, such as Fabry disease, Noonan syndrome, cardiac amyloidosis, and amyloid cardiomyopathy, were excluded from the study (Figure 1). Given the large time span of data collection, we have segmented the patient data by year and conducted baseline comparison analysis according to the different stages of the release of relevant guidelines. The results show that there are indeed significant differences among the data of different time periods (Supplement Table 1). But among the three groups of patients, there was no significant difference in the KM survival curves between males and females (Supplement Figure 1). However, there were significant differences in SCD across different age groups from 1996 to 2014 (Supplement Figure 2a), while no significant differences were observed between the age groups from 2015–2019 and from 2020–2023 (Supplement Figure 2 b-c). This may also reflect from a certain perspective that with the continuous progress in the management of HCM and the improvement of medical standards, the SCD rate of patients with HCM has indeed been significantly reduced.

Diagnostic Criteria and Definitions

The diagnosis of HCM is based on a maximal end-diastolic wall thickness of ≥ 15 mm anywhere in the left ventricle, in the absence of another cause of hypertrophy in adults. This measurement can be obtained via various imaging techniques,

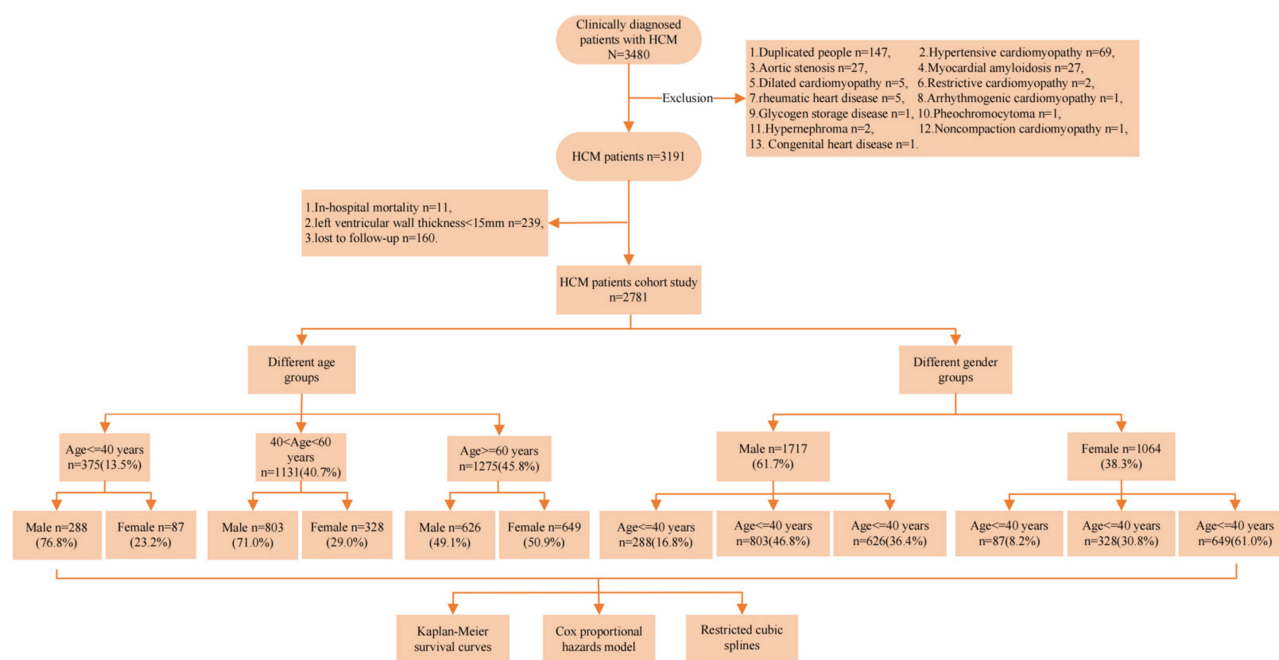


Figure 1 Patient flow diagram.

including echocardiography and cardiac magnetic resonance imaging (CMR).³ More limited hypertrophy (13–14 mm) can also be diagnostic when present in family members of a patient with HCM or in conjunction with a positive genetic test that identifies a pathogenic or likely pathogenic variant, typically found in a sarcomere gene.³

The patients were categorised into three age groups: the youth group (aged ≤ 40 years), the middle-aged group (aged between 40 and 60 years), and the elderly group (aged ≥ 60 years).

Follow-up and Endpoints

The follow-up period of this study began in October 2011 and ended in April 2024. The primary endpoint of the study was SCD, defined as an unexpected death occurring either in the absence of symptoms or within one hour of symptom onset in patients who had previously exhibited a relatively stable or uneventful clinical course.¹⁴ Data regarding the occurrence of SCD were meticulously collected through a combination of methods, which included reviewing medical records from outpatient clinic visits and hospitalisations, conducting telephone interviews with patients or their families, and verifying survival status through national police records. Patients who could not be contacted within six months following discharge were classified as lost to follow-up.

Statistical Analysis

In this study, continuous variables are presented as the means $\pm$ standard deviations (SDs) for normally distributed data or as the medians with interquartile ranges (IQRs) for nonnormally distributed data. The differences between groups for continuous variables were assessed via the unpaired Student's *t* test for normally distributed data and the Wilcoxon rank test for nonnormally distributed data. Categorical variables are expressed as proportions, with group differences evaluated via the Pearson chi-square test.

To identify factors independently associated with mortality, Cox proportional hazards modelling was employed. Hazard ratios (HRs), along with 95% confidence intervals (CIs) and P values, were reported to support the analysis. In the multivariate Cox regression analysis, factors were adjusted on the basis of a significance level of $P \leq 0.05$, as determined by univariate analysis.

In the multivariate model adjustment, the variables adjusted for the whole population are age, hyperlipemia, atrial fibrillation (AF), atrioventricular block (AVB), intraventricular conduction block (IVCD), pulmonary hypertension (PH), apical HCM (AHCM), hypertrophic obstructive cardiomyopathy (HOCM), modified shock index (MSI), left ventricular diameter (LVD), left atrial diameter (LAD), left ventricular ejection fraction (LVEF), left ventricular posterior wall thickness (LVPW), left ventricular outflow tract gradient (LVOTG), N - terminal pro - B - type natriuretic peptide Log (NT-pro-BNP), uric acid (UA), alkaline phosphatase (ALP), creatinine, triglyceride - glucose index (TyG), creatinine kinase-myocardial band (CK-MB) etc, while for the male cohort, they are age, ventricular tachycardia (VT), AF, IVCD, familial HCM (FHCM), alcohol septal ablation (ASA) or septal myectomy (SM), AHCM, QRS, LVD, LAD, LVEF, LVPW, Log (NT-pro-BNP), albumin, TSH, ALP, random blood glucose, TyG, CK-MB etc, and for the female cohort, they are age, PH, LVD, LVEF, LVPW, LVOTG, Log (NT-pro-BNP), UA, ALP, creatinine, LDL-C, lactic dehydrogenase (LDH) etc.

All the statistical analyses were conducted via R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria), with a significance threshold set at P values ≤ 0.05 considered statistically significant.

Results

Baseline Clinical Characteristics

The study included a total of 2781 patients with HCM, with a median follow-up period of 4.54 years (IQR: 2.13–7.99 years). The study population consisted of 375 patients in the youth group (13.5%), 1131 patients in the middle-aged group (40.7%), and 1275 patients in the elderly group (45.8%), of whom 1717 were men (61.7%) and 1064 were women (38.3%). A total of 128 patients (4.6%) experienced SCD, with 41 patients (10.9%) in the youth group, 34 patients (3%) in the middle-aged group, and 53 patients (4.2%) in the elderly group.

Table I Baseline Demographic and Clinical Characteristics of the Whole Population in Different Age Groups and Gender Groups

	Overall N=2781	Age≤40 Years n=375	40 <Age<60years n=1131	Age≥60 Years n=1275	P Value	Male n=1717	Female n=1064	P Value
Age, years (mean (SD))	57.00 ±15.39	30.37 ±9.40	50.93 ±5.15	70.22 ±7.14	<0.001	54.27±14.94	61.42±15.07	<0.001
Female, n (%)	1064 (38.3)	87 (23.2)	328 (29.0)	649 (50.9)	<0.001			
NYHA class III–IV, n (%)	925 (33.3)	131 (34.9)	437 (38.7)	357 (28.0)	<0.001	542 (31.6)	383 (36.0)	0.018
Course of disease, month (median [IQR])	12.00 [0.13–60.00]	18.00 [1.00–60.00]	24.00 [0.66–72.00]	7.50 [0.10–60.00]	<0.001	12.00 [0.23–72.00]	12.00 [0.10–60.00]	0.135
Syncope, n (%)	321 (11.5)	61 (16.3)	146 (12.9)	114 (8.9)	<0.001	199 (11.6)	122 (11.5)	0.969
Family history of HCM, n (%)	191 (6.9)	64 (17.1)	84 (7.4)	43 (3.4)	<0.001	118 (6.9)	73 (6.9)	1
Family history of SCD, n (%)	36 (1.3)	11 (2.9)	17 (1.5)	8 (0.6)	0.002	24 (1.4)	12 (1.1)	0.66
Stroke, n (%)	345 (12.4)	14 (3.7)	85 (7.5)	246 (19.3)	<0.001	185 (10.8)	160 (15.0)	0.001
Ventricular arrhythmia, n (%)	402 (14.5)	38 (10.1)	182 (16.1)	182 (14.3)	0.017	261 (15.2)	141 (13.3)	0.172
VT, n (%)	236 (8.5)	19 (5.1)	110 (9.7)	107 (8.4)	0.019	152 (8.9)	84 (7.9)	0.417
NSVT, n (%)	141 (5.2)	6 (1.7)	74 (6.8)	61 (4.8)	0.001	95 (5.5)	46 (4.3)	0.185
AF, n (%)	495 (17.8)	29 (7.7)	159 (14.1)	307 (24.1)	<0.001	259 (15.1)	236 (22.2)	<0.001
LBBB, n (%)	123 (4.4)	32 (8.5)	64 (5.7)	27 (2.1)	<0.001	69 (4.0)	54 (5.1)	0.222
RBBB, n (%)	147 (5.3)	23 (6.1)	62 (5.5)	62 (4.9)	0.583	102 (5.9)	45 (4.2)	0.061
AVB, n (%)	113 (4.1)	18 (4.8)	35 (3.1)	60 (4.7)	0.101	76 (4.4)	37 (3.5)	0.257
CAD, n (%)	558 (20.1)	33 (8.8)	205 (18.1)	320 (25.1)	<0.001	353 (20.6)	205 (19.3)	0.436
ICD, n (%)	58 (2.1)	9 (2.4)	30 (2.7)	19 (1.5)	0.124	36 (2.1)	22 (2.1)	1
ASA&SM, n (%)	464 (16.7)	128 (34.1)	249 (22.0)	87 (6.8)	<0.001	308 (17.9)	156 (14.7)	0.028
ESC % 5-y SCD risk score					<0.001			0.002
Low risk (<4%), n	2372 (85.3)	232 (61.9)	926 (81.9)	1214 (95.2)		1435 (83.6)	937 (88.1)	
Intermediate risk (4–6%), n	294 (10.6)	96 (25.6)	145 (12.8)	53 (4.2)		197 (11.5)	97 (9.1)	
High risk (>6%), n	115 (4.1)	47 (12.5)	60 (5.3)	8 (0.6)		85 (5.0)	30 (2.8)	
TRI (mean (SD))	21.18 ±12.44	6.52 ±3.33	16.01 ±5.21	30.08 ±11.99	<0.001	19.20±11.67	24.35±12.97	<0.001
SI (mean (SD))	0.62 ±0.19	0.67 ±0.19	0.62 ±0.18	0.60 ±0.19	<0.001	0.61±0.19	0.62±0.19	0.331
MSI (mean (SD))	0.84 ±0.24	0.91 ±0.28	0.82 ±0.24	0.83 ±0.24	<0.001	0.83±0.25	0.85±0.24	0.047

Age SI (mean (SD))	34.78 ±14.11	19.81 ±7.26	31.22 ±9.05	42.35 ±14.56	<0.001	32.99 ±13.47	37.67±14.65	<0.001
<i>Electrocardiogram</i>								
QRS, ms (mean (SD))	106.45 ±26.84	113.23 ±31.56	106.56 ±25.35	104.18 ±26.25	<0.001	107.41±26.20	104.82±27.84	0.022
QT, ms (mean (SD))	416.96 ±51.55	416.66 ±53.28	418.29 ±48.55	415.78 ±53.75	0.536	414.04±48.80	421.86±55.55	<0.001
QTc, ms (mean (SD))	454.11 ±48.27	466.55 ±52.99	451.59 ±47.93	452.56 ±46.42	<0.001	450.86±48.59	459.55±47.26	<0.001
PR, ms (mean (SD))	169.18 ±37.02	165.99 ±28.77	166.67 ±34.53	172.79 ±41.43	<0.001	169.56±34.42	168.54±41.08	0.53
<i>Echocardiogram</i>								
LVD, mm (mean (SD))	43.81 ±6.61	43.03 ±7.57	44.47 ±6.70	43.45 ±6.15	<0.001	44.83±6.71	42.16±6.09	<0.001
RVD, mm (mean (SD))	20.05 ±3.33	19.39 ±3.65	20.22 ±3.28	20.09 ±3.25	<0.001	20.39±3.37	19.49±3.17	<0.001
LAD, mm (mean (SD))	40.45 ±7.31	38.99 ±8.02	40.37 ±7.08	40.94 ±7.25	<0.001	40.52±7.27	40.32±7.39	0.486
RA, n (%)	206 (7.9)	11 (3.1)	62 (5.8)	133 (11.1)	<0.001	128 (7.9)	78 (7.8)	1
LVEF, % (mean (SD))	66.37 ±9.82	67.09 ±9.71	66.34 ±10.19	66.19 ±9.51	0.328	66.30±9.94	66.50±9.62	0.611
IVS, mm (mean (SD))	18.21 ±4.96	19.94 ±6.36	18.32 ±5.14	17.60 ±4.14	<0.001	18.26±5.16	18.13±4.63	0.513
Maximal LV wall Thickness, mm (mean (SD))	19.70 ±4.49	21.77 ±5.96	20.01 ±4.57	18.81 ±3.59	<0.001	19.90±4.69	19.36±4.13	0.002
LVPW, mm	11.98 ±3.05	12.39 ±3.79	12.02 ±3.06	11.83 ±2.78	0.01	12.08±3.02	11.82±3.09	0.047
AHCM, n (%)	290 (10.4)	24 (6.4)	121 (10.7)	145 (11.4)	0.02	214 (12.5)	76 (7.1)	<0.001
HOCM, n (%)	1259 (45.3)	219 (58.4)	549 (48.5)	491 (38.5)	<0.001	705 (41.1)	554 (52.1)	<0.001
Pulmonary hypertension, n (%)	226 (8.8)	18 (5.2)	61 (5.9)	147 (12.4)	<0.001	106 (6.2)	120 (11.3)	<0.001
<i>Cardiac magnetic resonance</i>								
CMR-LGE, n (%)	451 (49.2)	101 (69.7)	240 (61.5)	110 (28.8)	<0.001	312 (18.2)	139 (13.1)	<0.001
<i>Laboratory examination</i>								
AST/ALT, (mean (SD))	1.31 ±1.27	1.16 ±0.76	1.14 ±1.04	1.50 ±1.52	<0.001	1.17±0.96	1.53±1.63	<0.001
TG/HDL-C, (mean (SD))	1.64 ±1.85	1.88 ±3.31	1.82 ±1.71	1.41 ±1.24	<0.001	1.79±2.15	1.40±1.15	<0.001
TyG, (mean (SD))	8.78 ±0.64	8.66 ±0.61	8.82 ±0.62	8.77 ±0.66	0.001	8.79±0.63	8.75±0.65	0.192
Log (NT-pro-BNP), (mean (SD))	3.10 ±0.54	3.08 ±0.53	3.02 ±0.52	3.17 ±0.55	<0.001	3.01±0.52	3.24±0.53	<0.001

(Continued)

Table 1 (Continued).

	Overall N=2781	Age≤40 Years n=375	40 <Age<60years n=1131	Age≥60 Years n=1275	P Value	Male n=1717	Female n=1064	P Value
Creatinine, (mean (SD))	87.95 ±68.80	88.23 ±111.25	86.23 ±62.79	89.44 ±56.36	0.555	95.19±80.49	76.03±40.44	<0.001
Medication								
Betablocker, n (%)	2037 (73.4)	287 (76.9)	859 (76.0)	891 (70.0)	0.001	1248 (72.7)	789 (74.2)	0.42
Ca ²⁺ antagonist, n (%)	612 (22.0)	87 (23.3)	291 (25.8)	234 (18.4)	<0.001	404 (23.5)	208 (19.5)	0.016
End point								
SCD, n (%)	128 (4.6)	41 (10.9)	34 (3.0)	53 (4.2)	<0.001	85 (5.0)	43 (4.0)	0.308

Abbreviations: NYHA, New York Heart Association; VT, ventricular tachycardia; NSVT, non-sustained ventricular tachycardia; AF, atrial fibrillation; LBBB, left bundle branch block; RBBB, right bundle branch block; AVB, atrioventricular block; CAD, coronary artery disease; ICD, implantable cardioverter defibrillator; ASA, alcohol septal ablation; SM, septal myectomy; TRI, thrombolytic risk index; SI, shock index; MSI, modified shock index; LVD, left ventricular diameter; RVD, right ventricular diameter; LAD, left atrial diameter; RA, right atrial; LVEF, left ventricular ejection fraction; IVS, interventricular septum; LVPW, left ventricular posterior wall thickness; AHCM, apical HCM; HOCM, obstructive HCM; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TG, triglyceride; HDL-C, high - density lipoprotein cholesterol; TyG, triglyceride - glucose index; NT-pro-BNP, N - terminal pro - B - type natriuretic peptide.

The baseline demographic, clinical, and biochemical characteristics across different age groups and sexes are detailed in [Table 1](#). Compared with younger patients, there is a gradual decline in the proportion of individuals with a history of syncope, as well as a decrease in the incidence of a family history of SCD. As age progresses, the prevalence of stroke, coronary artery disease (CAD), and AF steadily increases, whereas the proportion of patients classified as intermediate risk or high risk for 5-year SCD decreases. Additionally, the maximal thickness of the left ventricular wall gradually decreases. The proportion of patients with ICD implantation is relatively low, with only 58 patients (2.1%) undergoing ICD implantation. It is notable that the proportion of ICD implantation is relatively higher in the young (2.4%) and middle-aged groups (2.7%) than in the elderly group (1.5%). However, there is no significant difference in gender distribution between men (2.1%) and women (2.1%). In CMR, there were a total of 451 patients showing late gadolinium enhancement (LGE). It is notable that the proportion of LGE was significantly higher in the young (69.7%) and middle-aged groups (61.5%) than in the elderly group (28.8%), and the proportion of male patients (18.2%) was also higher than that of female patients (13.1%).

[Table 2](#) outlines the baseline demographic, clinical, and biochemical characteristics of the males and females among the different age groups. In the youth group, a greater proportion of women exhibited concomitant PH, and their levels of Log (NT-proBNP) were elevated. Conversely, men had a higher TyG index. In the middle-aged group, men had a greater incidence of CAD and a relatively greater incidence of AHCM, along with elevated TyG index and creatinine levels. Additionally, more women presented with left bundle branch block (LBBB). In the elderly group, women were older on average (71.13 years vs 69.27 years), and a greater proportion of them were classified as New York Heart Association (NYHA) class 3–4, with elevated log (NT-proBNP) levels. In terms of ICD implantation and LGE, no significant differences were observed between men and women of different age groups.

Outcomes of SCD Across Different Age Groups and Sexes

[Table 3](#) presents the incidence of SCD across different age groups. The data revealed that the incidence of SCD was highest in the young group at 10.9%, whereas the middle-aged group presented the lowest incidence at 3%. The elderly group fell in between these two groups, with an incidence of 4.2%. Furthermore, the incidence of SCD among elderly male patients was greater than that among their female counterparts (5.3% vs 3.1%). The Kaplan–Meier survival curve indicated a significant difference in SCD between men and women in the youth group (log-rank $P = 0.036$); however, no significant difference was observed between sexes in either the middle-aged group or the elderly group (log-rank $P = 0.92$; log-rank $P = 0.054$) ([Figure 2](#)).

Role of Age in the Prediction of SCD Across the Whole Population and in Both Sexes

The Kaplan–Meier analysis revealed significant differences in SCD across the age groups within the whole population and among both sexes (log-rank $P < 0.0001$, [Figure 3A–C](#)). Furthermore, the multivariable Cox regression analysis indicated that age was an independent predictor for SCD in the whole population [HR: 0.983; 95% CI: 0.972–0.994; $P = 0.003$] and in females [HR: 0.963; 95% CI: 0.947–0.98; $P < 0.001$]. However, in male patients, age was not significantly associated with SCD [HR: 0.995; 95% CI: 0.98–1.01; $P = 0.538$] ([Table 4](#)).

Role of Different Age Groups in Predicting SCD Across the Whole Population and in Both Sexes

In the whole population, the risk of SCD in the middle-aged group was significantly lower (71.4%) than that in the young group [HR: 0.286; 95% CI: 0.18–0.455; $P < 0.001$], whereas the risk in the elderly group was 43.5% lower [HR: 0.565; 95% CI: 0.368–0.867; $P = 0.009$]. For male patients, the risk of SCD in the middle-aged group decreased by 68.5% [HR: 0.315; 95% CI: 0.176–0.563; $P < 0.001$], whereas the risk in the elderly group was reduced by only 10.7% [HR: 0.893; 95% CI: 0.495–1.614; $P = 0.709$], although this reduction was not statistically significant. In contrast, among female patients, the risk of SCD in the middle-aged group was reduced by 77.8% [HR: 0.222; 95% CI: 0.093–0.526; $P = 0.001$], and the risk in the elderly group decreased by 75.3% [HR: 0.247; 95% CI: 0.122–0.5; $P < 0.001$] ([Table 4](#)).

Table 2 Baseline Demographic and Clinical Characteristics of Different Genders in Different Age Groups

	Overall N=2781	Age≤40 years		P value	40<Age<60 years		P value	Age≥60 years		P value
		Male n=288	Female n=87		Male n=803	Female n=328		Male n=626	Female n=649	
Age, years (mean (SD))	57.00 ±15.39	30.89 ±9.15	28.67 ±10.08	0.053	50.95 ±5.14	50.88 ±5.18	0.838	69.27 ±7.02	71.13 ±7.15	<0.001
Follow-up time, years (median [IQR])	4.54 [2.13–7.99]	6.57 [2.96–10.89]	5.62 [2.85–9.91]	0.165	5.63 [2.54–10.17]	5.11 [2.22–8.24]	0.003	3.50 [1.86–5.90]	3.51 [1.83–5.87]	0.968
NYHA class III–IV, n (%)	925 (33.3)	96 (33.3)	35 (40.2)	0.292	299 (37.2)	138 (42.1)	0.147	147 (23.5)	210 (32.4)	0.001
Course of disease, month (median [IQR])	12.00 [0.13–60.00]	24.00 [1.00–60.00]	12.00 [1.00–60.00]	0.798	24.00 [0.54–72.00]	24.00 [0.69–72.00]	0.796	6.48 [0.10–72.00]	8.00 [0.10–60.00]	0.602
Syncope, n (%)	321 (11.5)	44 (15.3)	17 (19.5)	0.436	105 (13.1)	41 (12.5)	0.869	50 (8.0)	64 (9.9)	0.283
HCM family history, n (%)	191 (6.9)	49 (17.0)	15 (17.2)	1	53 (6.6)	31 (9.5)	0.125	16 (2.6)	27 (4.2)	0.152
SCD family history, n (%)	36 (1.3)	9 (3.1)	2 (2.3)	0.97	11 (1.4)	6 (1.8)	0.759	4 (0.6)	4 (0.6)	1
Stroke, n (%)	345 (12.4)	9 (3.1)	5 (5.7)	0.419	63 (7.8)	22 (6.7)	0.593	113 (18.1)	133 (20.5)	0.301
Ventricular arrhythmia, n (%)	402 (14.5)	32 (11.1)	6 (6.9)	0.348	122 (15.2)	60 (18.3)	0.231	107 (17.1)	75 (11.6)	0.006
VT, n (%)	236 (8.5)	14 (4.9)	5 (5.7)	0.959	74 (9.2)	36 (11.0)	0.426	64 (10.2)	43 (6.6)	0.027
NSVT, n, n (%)	141 (5.1)	4 (1.4)	2 (2.3)	0.916	50 (6.2)	24 (7.3)	0.589	41 (6.5)	20 (3.1)	0.006
AF, n (%)	495 (17.8)	20 (6.9)	9 (10.3)	0.417	107 (13.3)	52 (15.9)	0.31	132 (21.1)	175 (27.0)	0.017
LBBB, n (%)	123 (4.4)	20 (6.9)	12 (13.8)	0.074	35 (4.4)	29 (8.8)	0.005	14 (2.2)	13 (2.0)	0.925
RBBB, n (%)	147 (5.3)	18 (6.2)	5 (5.7)	1	46 (5.7)	16 (4.9)	0.67	38 (6.1)	24 (3.7)	0.066
IVCD, n (%)	88 (3.2)	13 (4.5)	7 (8.0)	0.311	37 (4.6)	13 (4.0)	0.75	11 (1.8)	7 (1.1)	0.43
AVB, n (%)	113 (4.1)	15 (5.2)	3 (3.4)	0.699	28 (3.5)	7 (2.1)	0.316	33 (5.3)	27 (4.2)	0.421
CAD, n (%)	558 (20.1)	21 (7.3)	12 (13.8)	0.097	170 (21.2)	35 (10.7)	<0.001	162 (25.9)	158 (24.3)	0.571
ICD, n (%)	58 (2.1)	7 (2.4)	2 (2.3)	1	18 (2.2)	12 (3.7)	0.254	11 (1.8)	8 (1.2)	0.588
ASA or SM, n (%)	464 (16.7)	98 (34.0)	30 (34.5)	1	168 (20.9)	81 (24.7)	0.19	42 (6.7)	45 (6.9)	0.962
ESC % 5-y SCD risk score				0.117			0.393			0.325
Low risk (<4%), n	2372 (85.3)	186 (64.6)	46 (52.9)		656 (81.7)	270 (82.3)		593 (94.7)	621 (95.7)	
Intermediate risk (4%–6%), n	294 (10.6)	70 (24.3)	26 (29.9)		100 (12.5)	45 (13.7)		27 (4.3)	26 (4.0)	
High risk (>6%), n	115 (4.1)	32 (11.1)	15 (17.2)		47 (5.9)	13 (4.0)		6 (1.0)	2 (0.3)	

TRI (mean (SD))	21.19 ±12.44	6.56 ±3.20	6.36 ±3.75	0.62	15.86 ±5.25	16.47 ±5.38	0.078	29.37 ±11.96	30.76 ±11.98	0.039
SI (mean (SD))	0.62 ±0.19	0.66 ±0.19	0.72 ±0.18	0.017	0.61 ±0.18	0.63 ±0.18	0.023	0.60 ±0.19	0.60 ±0.20	0.911
MSI (mean (SD))	0.84 ±0.24	0.90 ±0.28	0.96 ±0.25	0.083	0.81 ±0.24	0.85 ±0.23	0.011	0.82 ±0.23	0.83 ±0.24	0.433
Age -SI (mean (SD))	34.79 ±14.11	19.79 ±6.98	19.89 ±8.16	0.907	30.87 ±8.95	32.15 ±9.36	0.032	41.82 ±14.44	42.85 ±14.63	0.21
<i>Electrocardiogram</i>										
QRS (mean (SD))	106.10 ±27.14	111.88 ±29.76	116.75 ±36.66	0.207	106.44 ±26.61	105.90 ±26.56	0.758	105.90 ±26.02	101.97 ±25.65	0.007
QT (mean (SD))	416.04 ±51.78	413.35 ±53.36	421.70 ±52.00	0.199	413.70 ±46.39	426.73 ±52.89	<0.001	412.80 ±51.04	417.08 ±56.65	0.158
QTC (mean (SD))	453.66 ±48.76	463.31 ±52.23	475.69 ±66.92	0.071	447.28 ±46.79	458.42 ±49.50	<0.001	448.88 ±48.38	456.50 ±44.66	0.004
PR (mean (SD))	168.98 ±37.89	165.62 ±28.65	169.20 ±37.47	0.345	167.33 ±34.08	164.26 ±37.21	0.18	172.52 ±39.33	171.45 ±44.07	0.649
<i>Echocardiogram</i>										
LVD (mean (SD))	43.79 ±6.63	43.57 ±7.61	40.49 ±6.84	0.001	45.29 ±6.55	42.34 ±6.49	<0.001	44.58 ±6.56	42.44 ±5.77	<0.001
RVD (mean (SD))	20.07 ±3.36	19.53 ±3.55	18.66 ±3.95	0.049	20.49 ±3.28	19.60 ±3.11	<0.001	20.58 ±3.51	19.70 ±3.10	<0.001
LAD (mean (SD))	40.48 ±7.34	39.00 ±7.71	38.51 ±8.62	0.611	40.76 ±7.01	39.51 ±7.10	0.007	40.90 ±7.37	41.13 ±7.33	0.584
RAD enlargement, n (%)	206 (7.4)	6 (2.1)	5 (5.7)	0.158	50 (6.2)	12 (3.7)	0.115	72 (11.5)	61 (9.4)	0.256
LVEF (mean (SD))	66.37 ±9.80	67.10 ±9.86	66.43 ±9.09	0.57	66.42 ±10.07	66.20 ±10.63	0.751	65.79 ±9.71	66.61 ±9.19	0.123
IVS (mean (SD))	18.22 ±4.87	19.80 ±6.11	20.22 ±6.65	0.586	18.23 ±5.18	18.52 ±4.70	0.386	17.62 ±4.16	17.68 ±4.01	0.808
Maximal LV thickness (mean (SD))	19.70 ±4.49	21.65 ±6.02	22.17 ±5.78	0.477	20.06 ±4.71	19.88 ±4.22	0.565	18.90 ±3.58	18.72 ±3.60	0.376
LVPW (mean (SD))	11.97 ±3.02	12.22 ±3.38	12.60 ±4.56	0.397	12.05 ±3.04	11.79 ±2.98	0.189	11.93 ±2.74	11.79 ±2.84	0.374
AHCM, n (%)	290 (10.4)	20 (6.9)	4 (4.6)	0.593	105 (13.1)	16 (4.9)	<0.001	89 (14.2)	56 (8.6)	0.002
PH, n, n (%)	226 (8.1)	9 (3.1)	9 (10.3)	0.013	37 (4.6)	24 (7.3)	0.092	60 (9.6)	87 (13.4)	0.041
<i>Cardiac magnetic resonance</i>										
CMR-LGE, n (%)	451 (16.2)	75 (26.0)	26 (29.9)	0.568	175 (21.8)	65 (19.8)	0.511	62 (9.9)	48 (7.4)	0.135
<i>Laboratory examination</i>										
AST/ALT (mean (SD))	1.31 ±1.25	1.07 ±0.66	1.45 ±0.92	<0.001	1.10 ±1.11	1.30 ±0.75	0.002	1.34 ±0.79	1.64 ±1.93	<0.001
TG/HDL-C (mean (SD))	1.61 ±1.74	1.99 ±3.37	1.15 ±0.61	0.022	1.89 ±1.79	1.46 ±1.20	<0.001	1.41 ±1.23	1.41 ±1.22	0.939

(Continued)

Table 2 (Continued).

	Overall N=2781	Age≤40 years		P value	40<Age<60 years		P value	Age≥60 years		P value
		Male n=288	Female n=87		Male n=803	Female n=328		Male n=626	Female n=649	
TyG (mean (SD))	8.78 ±0.66	8.71 ±0.67	8.39 ±0.52	<0.001	8.84 ±0.65	8.71 ±0.58	0.002	8.75 ±0.65	8.84 ±0.70	0.016
Log (NT-pro-BNP) (mean (SD))	3.10 ±0.55	3.00 ±0.50	3.36 ±0.54	<0.001	3.00 ±0.53	3.12 ±0.53	0.001	3.09 ±0.55	3.24 ±0.55	<0.001
Creatinine, (mean (SD))	87.29 ±65.98	93.41 ±118.91	72.23 ±38.38	0.103	91.58 ±67.69	71.22 ±33.76	<0.001	96.72 ±62.87	80.30 ±42.76	<0.001
Medication										
Betablocker, n (%)	2037 (73.2)	217 (75.3)	70 (80.5)	0.4	603 (75.1)	256 (78.0)	0.328	428 (68.4)	463 (71.3)	0.274
Ca ²⁺ antagonist, n (%)	612 (22.0)	67 (23.3)	20 (23.0)	1	218 (27.1)	73 (22.3)	0.103	119 (19.0)	115 (17.7)	0.601
End point										
SCD, n (%)	128 (4.6)	27 (9.4)	14 (16.1)	0.118	25 (3.1)	9 (2.7)	0.89	33 (5.3)	20 (3.1)	0.069

Note: abbreviation see [Table 1](#).

Table 3 Proportion of SCD in Patients According to Age and Gender Groups

Whole Population	Overall N=2781	Age≤40 n=375	40<Age<60 n=1131	Age≥60 n=1275	P value
SCD	128 (4.6)	41 (10.9)	34 (3.0)	53 (4.2)	<0.001
Men (N=1717, 61.7%)	Overall N=1717	Age≤40 n=288	40<Age<60 n=803	Age≥60 n=626	
SCD	85 (5.0)	27 (9.4)	25 (3.1)	33 (5.3)	<0.001
Women (N=1064, 38.3%)	Overall N=1064	Age≤40 n=87	40<Age<60 n=328	Age≥60 n=649	
SCD	43 (4.0)	14 (16.1)	9 (2.7)	20 (3.1)	<0.001

RCS Analysis and Threshold Analysis in Predicting SCD

As illustrated in Figure 4a–c, the fully adjusted RCS analysis revealed that age was significantly associated with SCD in the whole population, with all demonstrating a nonlinear relationship (P -overall<0.001, P for nonlinearity<0.001). When stratified by sex, the results indicated that age remained significantly associated with SCD among male (P <0.001, P for

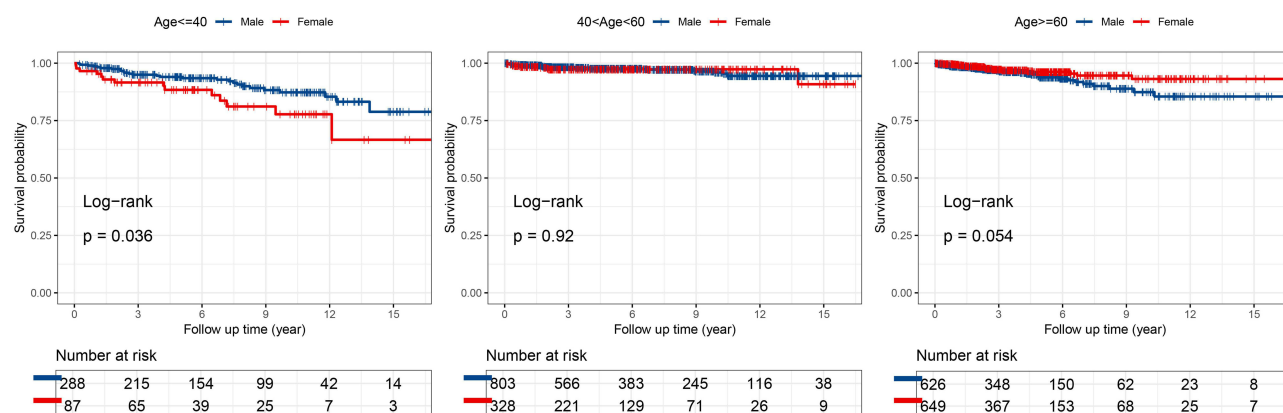


Figure 2 Kaplan-Meier survival curves for SCD stratified by different genders across different age groups. (A) SCD in Age≤40 years group of male and female patients, (B) SCD in 40<Age<60 years group of male and female patients, (C) SCD in Age≥60 years group of male and female patients.

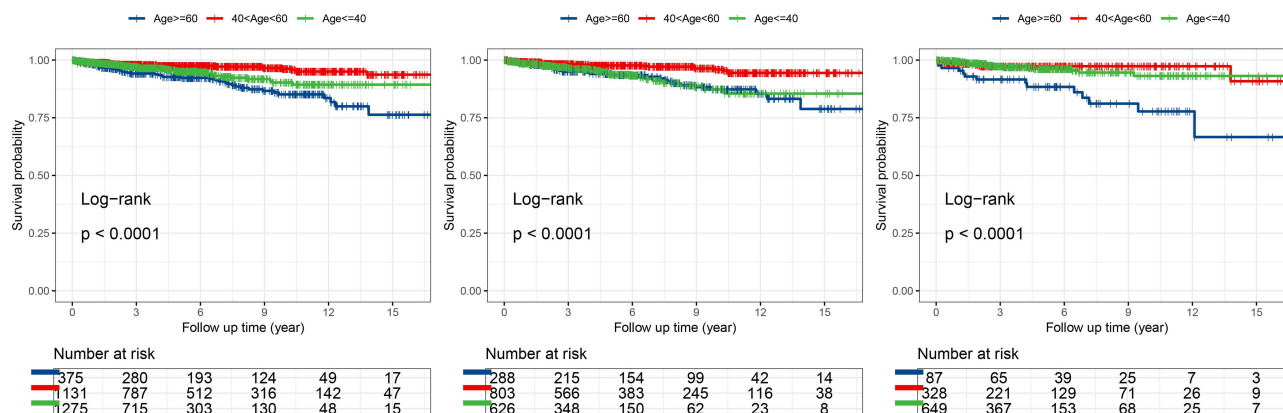


Figure 3 Kaplan-Meier survival curves for SCD stratified by different age groups in the whole population and different genders. (A) SCD in the whole population of different age groups, (B) SCD in male HCM patients of different age groups, (C) SCD in female HCM patients of different age groups.

Table 4 Association of Age and SCD via Cox Regression Analysis

	Univariable Cox Regression Analysis			Multivariable Cox Regression Analysis		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Whole population (N=2781)						
Age	0.983	0.972–0.994	0.003	0.983	0.972–0.994	0.003
Age≤40	Reference			Reference		
40<Age<60	0.294	0.186–0.385	<0.001	0.286	0.18–0.455	<0.001
Age≥60	0.582	0.463–0.882	0.011	0.565	0.368–0.867	0.009
Men (N=1717, 61.7%)						
Age	0.995	0.98–1.01	0.538	—	—	—
Age≤40	Reference			Reference		
40<Age<60	0.35	0.203–0.547	<0.001	0.315	0.176–0.563	<0.001
Age≥60	0.919	0.603–1.544	0.75	0.893	0.495–1.614	0.709
Women (N=1064, 38.3%)						
Age	0.965	0.949–0.982	<0.001	0.963	0.947–0.98	<0.001
Age≤40	Reference			Reference		
40<Age<60	0.184	0.08–0.128	<0.001	0.222	0.093–0.526	0.001
Age≥60	0.255	0.425–0.509	<0.001	0.247	0.122–0.5	<0.001

nonlinearity <0.001) and female patients ($P<0.001$, P for nonlinearity= 0.008), indicating that a nonlinear relationship was maintained.

Discussion

The study indicated that age was an independent predictor of SCD in both the whole population and among female patients. Compared with that of younger patients, the risk of SCD was reduced by 71.4% in middle-aged patients and by 43.5% in elderly patients across the entire population. In male patients, the risk of SCD decreased by 68.5% in middle-aged individuals and by 10.7% in elderly individuals. In contrast, female patients experienced a more significant reduction in risk, with a 77.8% decrease in middle-aged patients and a 75.3% decrease in elderly patients.

SCD is one of the most serious and devastating outcomes that patients with HCM may experience.¹⁵ Research has indicated that the risk of SCD is generally highest during adolescence and young adulthood rather than in later

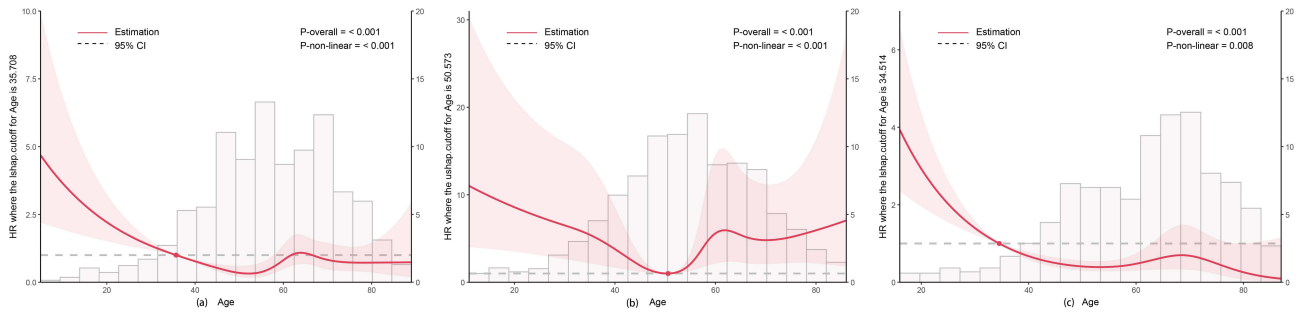


Figure 4 Restricted cubic spline modelling and threshold analysis of age effects on SCD in the whole population and across different genders. (a) SCD in the whole population, (b) SCD in male HCM patients, (c) SCD in female HCM patients.

adulthood.^{16,17} The incidence of adverse events in young HCM patients (7–29 years old) was $\approx$ 2-fold greater than that in middle-aged patients (30–59 years old). However, following major treatment interventions, the annual mortality rate for HCM remains nearly the same in both groups (0.5%).^{18,19} This elevated risk in younger populations is partly due to the active and dynamic physiological changes occurring during growth, as well as the potentially more aggressive disease phenotypes that may manifest during these years.^{17,20,21} During childhood and adolescence, certain risk factors for SCD, such as severe left ventricular hypertrophy, left ventricular outflow tract obstruction (LVOTO), and arrhythmias, can be more pronounced.^{22–25} Additionally, young individuals may be more likely to engage in physical activities that could trigger arrhythmic events in.²⁶

In the present study, 375 young patients (12.8%) were included in the whole population. The prevalence of SCD was 3.6 times greater in the middle-aged group (10.9% vs 3%) and 2.6 times greater in the elderly group (10.9% vs 4.2%). Notably, the youth group represented the highest proportion of individuals at high risk of 5-year SCD. Additionally, the incidence of SCD among young female patients was greater than that among their male counterparts (16.1% vs 9.4%). Research has indicated that the incidence of unexplained SCD in female patients under the age of 40 years is greater than that in males, particularly within the 35 to 44 years age range.²⁷ In the present study, the proportion of female patients who experienced SCD was significantly greater than that of male patients, suggesting that younger female patients may be more susceptible to SCD. This observation may be related to the fact that the female patients in this study tended to be younger than their male counterparts (28 vs 30 years).

Furthermore, the number of young female patients was considerably lower than that of young male patients, which highlights the issue of insufficient early diagnosis among females. This finding is consistent with prior conclusions that female patients are generally diagnosed at an older age.^{7,8,28,29} However, it is important to note that the data are not entirely consistent with the previous research, in which young female patients had a greater risk of SCD than young male patients did. Therefore, further research is needed to validate these findings. Although the risk of SCD among young female patients is significantly greater than that among young male patients, female sex is not an independent risk factor for SCD.

In adult cardiovascular practice, the subgroup of HCM patients aged 30 to 59 years (middle-aged) is the most frequently assessed group and is associated with a higher incidence of adverse complications.¹⁹ For middle-aged HCM patients, prognosis is influenced by a variety of factors, including the age at diagnosis, genetic mutations, and sex.^{10,30,31} Notably, those diagnosed at a younger age (under 40 years) tend to experience poorer outcomes than their counterparts diagnosed at an older age (over 60 years).³⁰ Research indicates that the cumulative incidence of overall composite outcomes by age 60 years for patients diagnosed before age 40 years is 77%, whereas for patients diagnosed at age 60 years or older, it is 32% by age 70 years.³⁰ Additionally, mortality rates for young HCM patients (aged 20 to 29) are four times higher than those of the general US population.³⁰

In this study, middle-aged patients constituted 40.7% of the overall population, with a notable predominance of males in this age group. While ventricular arrhythmia was more prevalent among these patients, the incidence of SCD was the lowest, at just 3%. In the present study, it is important to highlight that this demographic group represents the primary group receiving ICD treatment, accounting for 2.7% of the population. When the middle-aged group was compared with the youth group, the risk of SCD in the middle-aged group was reduced by 71.4%. Further analysis by sex revealed that the risk of SCD was decreased by 68.5% in males and 77.8% in females in the middle-aged group. Consequently, middle-aged patients had a lower risk of SCD than their younger counterparts did. Previous research supports these findings, demonstrating that the 5-year and 10-year survival rates for patients aged 30 to 59 years under contemporary treatment strategies are 98% and 94%, respectively, which are not significantly different from the all-cause mortality rates of the general population.¹⁹

In elderly HCM patients, the overall prognosis is relatively favourable, with a low risk of HCM-related mortality.^{1,32} Most deaths in this population are attributed to causes unrelated to HCM.³² Heart failure and AF are the most common adverse events among HCM patients; however, these conditions typically emerge several years after the initial diagnosis.^{10,30} While HF is more prevalent among elderly HCM patients, their prognosis is comparable to that of younger individuals.³³ Notably, female patients with HCM generally experience poorer cardiovascular outcomes than their male counterparts do, with elderly women being particularly susceptible to HF and cardiovascular mortality.³¹ Even

in the presence of conventional risk factors, the risk of SCD remains low in elderly HCM patients.¹ As a result, proactive implantation of an ICD for preventive measures is generally not recommended.^{1,34}

In this study, the incidence of SCD among elderly patients was found to be 4.2%, with men exhibiting a greater likelihood of experiencing SCD than women (5.3% vs 3.1%). Across each category of 5-year SCD risk, men consistently demonstrated a greater risk than women; however, the differences between the sexes were not statistically significant. Overall, the risk of SCD among elderly patients was reduced by 43.5%, with a decrease of 10.7% observed in males and a notable 75.3% in females. This finding indicates that elderly patients, compared with their younger counterparts, have a lower risk of SCD and that this difference is even more noticeable in women. Additionally, elderly HCM patients often present with a greater burden of cardiovascular comorbidities, which are closely associated with a poorer prognosis for HCM patients. These comorbidities included AF,³⁵ CAD,³⁶ and PH,³⁷ all of which were more common in this age group in the present study.

Furthermore, quantitative CMR-LGE can provide important prognostic information for SCD in patients with HCM.³⁸ The larger the LGE range, the higher the risk of patients developing ventricular arrhythmias and SCD,³⁹ for every 10% increase in LGE, the risk of SCD increases by approximately 1.56 times (HR: 1.56 per 10% LGE).⁴⁰ For HCM patients over 60 years old, the association between the range of LGE and the risk of SCD is not significant.⁴¹ This indicates that in elderly patients, LGE may play a limited role in the risk stratification of SCD. In the present study, the detection rate of LGE was higher in the young and middle-aged groups than in the elderly group, which might partly explain the higher rate of SCD in the young group. However, this study failed to achieve quantitative analysis of LGE.

According to the current guidelines, ICD is one of the effective strategies for preventing SCD.⁴² The implantation of ICD has changed the natural course of HCM, enabling many patients to achieve normal or near-normal lifespan.^{43,44} In young patients, ICD is equally effective and can prevent potentially fatal arrhythmias.⁴⁵ Through risk stratification, the decision-making for ICD implantation has become more precise. In the present study, a total of 58 patients received ICD implantation. Among them, the proportion of patients in the young group and the middle-aged group was relatively high, which might be related to the higher proportion of high-risk patients in these two age groups. Among all age groups, the gender differences are not significant.

The prognosis of young HCM patients is influenced by several factors, including age, genetic mutations, family history, and sex.^{3,30} Young individuals have a greater risk of SCD, and female patients have a worse prognosis.^{7,10} Therefore, individualised risk assessment and long-term monitoring are crucial for improving the prognosis of these patients. In contrast, middle-aged patients generally have a better overall prognosis, with lower mortality rates related to HCM. For this group, the primary causes of death were often non-HCM-related diseases.^{1,30} HF and AF are the main adverse events, and female patients have poorer cardiovascular outcomes.³⁰ The prognosis of asymptomatic patients is significantly better than that of symptomatic patients.⁴⁶ For patients over the age of 60, HCM-related mortality is low, with an annual mortality rate of approximately 0.64%.¹ The leading causes of death in this age group include embolic stroke, HF, postoperative complications, and SCD due to arrhythmias.

Based on the present research findings, young patients have a higher risk of experiencing SCD, and a larger proportion of them show LGE. Therefore, early clinical management of young patients is of crucial importance. Moreover, further research is still needed to clarify the gender differences between male and female patients with HCM in order to formulate evidence-based guidelines for gender-specific management of HCM. However, this study acknowledges the potential confounding factors, as the time span of the cohort is long and the proportion of patients undergoing CMR examination is relatively low. Future research should include larger and more comprehensive cohorts to better assess the risk of SCD in HCM patients.

Study Limitations

There are several limitations to this study. First, given that the study's results are derived from a Chinese cohort, it is important to conduct further research to evaluate the applicability of these findings to other populations. Second, the fact that the patients in the study were drawn from different hospitals over a substantial time span introduces data heterogeneity. This variability can affect the consistency and reliability of the findings, as differences in medical practices, patient demographics, and temporal healthcare advancements can lead to variations in outcomes.

Understanding and accounting for these factors is crucial for accurately interpreting the study's conclusions and assessing their broader relevance. Third, LGE is indeed recognised as an important prognostic marker for HCM, as it can indicate myocardial fibrosis and is associated with adverse cardiac events. However, the small sample size of patients who underwent CMRI imaging limits the statistical power and the ability to draw strong conclusions about the relationship between LGE and clinical outcomes within our cohort. Finally, the absence of genetic testing in our cohort limits the ability to explore the role of genetic factors in the prognosis of patients with HCM and different sexes.

Conclusion

In patients with HCM, age was an independent predictor of SCD across the entire population. Compared with that of young patients, the risk of SCD was reduced by 71.4% in middle-aged patients and by 43.5% in elderly patients. Specifically, among male patients, the risk of SCD decreased by 68.5% in middle-aged individuals and by 10.7% in elderly individuals. In contrast, female patients experienced a more significant reduction, with the risk of SCD declining by 77.8% in middle-aged patients and by 75.3% in elderly patients.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Statement

Ethical approval was obtained from the Research Ethics Committees of Sichuan Provincial People's Hospital (No. 2022424), and the study protocol was approved by the Institutional Review Board. Given the nature of the anonymized data and the low-risk profile of the research, ethical guidelines do not require informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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