Journal of the American Heart Association

ORIGINAL RESEARCH

Clinical Characteristics and Outcomes in Patients With Apical and Nonapical Hypertrophic Cardiomyopathy

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BACKGROUND: Apical hypertrophic cardiomyopathy (ApHCM) is a variant of hypertrophic cardiomyopathy, with distinct clinical characteristics and outcomes. We aimed to clarify the natural history of patients with ApHCM and identify the risk of end-stage heart failure incidence.

METHODS AND RESULTS: This retrospective study was conducted on patients with hypertrophic cardiomyopathy in China between January 2009 and February 2024. Patients were stratified into ApHCM and non-ApHCM groups. The primary outcome was a composite of major adverse cardiovascular events, including all-cause deaths, heart failure hospitalization, sudden cardiac death, and ventricular tachycardia. The secondary outcome was the incidence of end-stage heart failure, defined as left ventricular ejection fraction <50%. Kaplan-Meier and univariable and multivariable Cox proportional analyses were applied. Adjustment variables were included for important baseline characteristics, comorbidities, and medication use. Of 5653 patients enrolled with hypertrophic cardiomyopathy, 584 (10.3%) had ApHCM and 5069 (89.7%) had non-ApHCM. During the median follow-up period of 4.6 years (1.6–8.0 years), major adverse cardiovascular events occurred in 32.2% (n=1808), with a lower incidence in patients with ApHCM than non-ApHCM (20.4% versus 33.3%, $P<0.001$). Non-ApHCM was an independent predictor of major adverse cardiovascular events (hazard ratio [HR], 1.65 [95% CI, 1.36–1.99]; $P<0.001$). In the serial cohort, patients with ApHCM exhibited a lower incidence of end-stage heart failure than those with non-ApHCM (12.4% versus 2.7%, $P<0.001$). Non-ApHCM was associated with a higher risk of end-stage heart failure development (HR, 2.31 [95% CI, 1.28–4.15]; $P<0.001$). In subgroup and sensitivity analysis, the results were consistent for our main and secondary outcomes.

CONCLUSIONS: ApHCM is relatively common in hypertrophic cardiomyopathy and shows lower rates of all-cause mortality and heart failure hospitalizations than non-ApHCM.

Key Words: apical ■ echocardiography ■ end-stage heart failure ■ hypertrophic cardiomyopathy ■ prognosis

Hypertrophic cardiomyopathy (HCM) is the most commonly inherited cardiomyopathy, characterized by unexplained left ventricular hypertrophy, with a prevalence rate of approximately 1 in 500 individuals in the general populace.[1–3] The clinical course is variable, ranging from asymptomatic disease to heart failure (HF) symptoms, stroke, and sudden cardiac death (SCD).[4,5] Apical hypertrophic cardiomyopathy (ApHCM) is a distinct subtype of HCM, characterized by hypertrophy in the left ventricular apex.[6–8] ApHCM is characterized by ethnic differences, a higher prevalence in athletes, a lower prevalence of sarcomeric gene mutations, and characteristic structural features such as apical scar and aneurysm formation.[9] Despite

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This article was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 11.

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CLINICAL PERSPECTIVE

What Is New?

- Patients with apical hypertrophic cardiomyopathy tend to have a lower risk of developing end-stage heart failure and a favorable prognosis, but a similar risk of sudden cardiac death and ventricular arrhythmias when compared with those with nonapical hypertrophic cardiomyopathy.

What Are the Clinical Implications?

- This finding emphasizes the importance of routine, comprehensive evaluations for nonapical hypertrophic cardiomyopathy to identify those at the highest risk for adverse events, and screening and surveillance guidelines for sudden cardiac death and ventricular arrhythmias should not differentiate between hypertrophic cardiomyopathy subtypes.

Nonstandard Abbreviations and Acronyms

ApHCM	apical hypertrophic cardiomyopathy
ES-HF	end-stage heart failure
HCM	hypertrophic cardiomyopathy
MACE	major adverse cardiovascular event
SCD	sudden cardiac death
SGLT-2	sodium-glucose cotransporter-2

acknowledging this morphological variation, many aspects of ApHCM have not been adequately studied.

HF is the main adverse outcome of HCM, which is associated with poor prognosis and quality of life.[10–13] A subset of patients with HCM may even develop left ventricular remodeling and end-stage HF (ES-HF), characterized by systolic dysfunction, usually defined as left ventricular ejection fraction (LVEF) <50%.[14,15] Although there are not enough data from large cohorts on the natural history of the disease, previous studies indicated a distinct risk profile of this phenotype and different prognosis compared with non-ApHCM.[5,16,17] Understanding these differences is essential for tailoring appropriate management strategies and improving patient outcomes in HCM.[18]

Thus, in a large cohort of patients with HCM, we aimed to compare the phenotypic characteristics and natural history of ApHCM with non-ApHCM. Additionally, we aim to assess ES-HF incidence in these 2 phenotypes of HCM.

METHODS

Study Design

This was an observational study of patients diagnosed with HCM who underwent comprehensive clinical and echocardiographic evaluation at the First Affiliated Hospital of Wenzhou Medical University from January 2009 to February 2024. We searched electronic medical records for the Wenzhou Heart cohort with >1 million consecutive transthoracic echocardiogram reports using the keywords hypertrophic cardiomyopathy.[19–21] We screened all patients with HCM but excluded those with incomplete transthoracic echocardiogram or poor image, missing baseline echocardiography data, no clinical or echocardiography follow-up data, and a follow-up time of <30 days. We collected baseline information from the electronic medical records, including demographic features, medical history, medications at discharge, echocardiographic evaluations, and follow-up data. We also reviewed the available data to check HCM diagnosis, HCM type, and clinical outcomes, and the identification was done manually. We obtained baseline information from the electronic medical records, such as demographic features, medical history, medication at discharge, echocardiographic evaluation, and follow-up data.

The study was conducted in compliance with the Declaration of Helsinki. The research protocol was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University. Informed consent was waived by the committee. To access the data supporting the findings, please contact the corresponding author at zhouxiaodong@wmu.edu.cn.

Study Definitions

HCM was diagnosed when left ventricular wall thickness was ≥15 mm (or ≥13 mm in patients with a family history of HCM), in the absence of any other causes of hypertrophy, such as uncontrolled hypertension, cardiac valve disease, and phenocopies based on guideline recommendations using echocardiography or cardiac magnetic resonance imaging.[22,23] ApHCM is characterized by the presence of hypertrophy, which can either exclusively involve the left ventricular apex (pure ApHCM) or be located at both the apex and the interventricular septum, with the apex being the thickest segment (mixed ApHCM).[24] The definition of ES-HF involved the measurement of LVEF, which should be <50%, by using 2-dimensional echocardiography.[14,15]

Outcomes

The primary end point was a combination of major adverse cardiovascular events (MACEs), including all-cause mortality, hospitalization due to HF, SCD, and ventricular tachyarrhythmia (VT). All-cause mortality

included deaths from any cause during the follow-up period. SCD was defined as the nonviolent, nontraumatic, and unexpected fatality in previously stable individuals caused by a cardiac event. Hospitalization due to HF was defined as any admission for ≥24 hours with a primary diagnosis of HF and worsening symptoms of HF (≥1) or objective evidence of worsening of HF (≥2 physical examination findings or 1 physical examination and 1 finding indicating worsening of HF) from the following: laboratory test, invasive test, or augmentation of therapy.[25] VT is defined as ≥3 consecutive beats, a QRS duration ≥120 ms and a heart rate ≥100 bpm, encompassing both sustained and non-sustained forms. It would be better to describe analytically the mode of recording (eg, electrocardiograph, Holter, reveal, implanted cardioverter-defibrillator). The second end point was the incidence of ES-HF, which refers to the advanced stage of HF characterized by systolic dysfunction, defined as LVEF <50%.[5,26] Follow-up data were collected from medical records of inpatients and outpatients. The follow-up period was between HCM diagnosis and the final clinical follow-up or death, whichever came first. Medical reports were obtained and assessed by physicians for each reported event.

Statistical Analysis

Continuous variables that follow normal distribution were presented as mean±SD, whereas nonnormally distributed continuous variables were presented as median with interquartile range (IQR). The number and percentage of patients were used to present categorical variables. To compare groups, we applied the Student *t* test for continuous variables with equal variances, Welch correction for continuous variables with unequal variances, and the χ^2 test for categorical variables. For sample-size calculation, we used the documented prevalence of MACEs in patients with HCM in the literature, which ranged from 30% to 40%. To detect an increase in the incidence of MACEs from 20% to 40% with a type I error probability of 0.05, we estimated that 282 patients were required to provide 90% power. Univariate and multivariate Cox regression analyses were conducted to identify independent predictors of the combined outcome among both subjects with ApHCM and non-ApHCM. Adjustment variables were included for age, sex, body mass index, smoker, alcohol use, hypertension, diabetes, ischemic stroke, atrial fibrillation, chronic kidney disease, New York Heart Association class III and IV, SGLT-2 (sodium-glucose cotransporter-2) inhibitors, mineralocorticoid receptor antagonist, diuretic, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor, β-blocker, and calcium channel blocker. Hazard ratios (HRs) and their corresponding 95% CIs were calculated. We used the Kaplan-Meier method to compute event-free survival curves and compared the differences between the curves using the log-rank test. We conducted multiple sensitivity analyses to assess the reliability of our findings. To minimize the effect of lead-time bias (people with longer survival may have a greater possibility for events), we left-truncated the follow-up period at 1 or 3 years and conducted time-to-event analyses again. Additionally, we also conducted competing risk regression using the Fine-Gray model to estimate subdistribution hazard ratios (SHRs) for all-cause mortality. A 2-tailed significance level of $P<0.05$ was considered statistically significant. All statistical analyses were performed using the 26.0 version of IBM SPSS software for Macintosh.

RESULTS

Baseline Characteristics

Our study identified 6674 patients with confirmed ApHCM based on the evaluation of echocardiographic images and electronic medical records. After excluding 1021 patients according to the inclusion and exclusion criteria, we included 5653 patients in the baseline model (Figure 1). At baseline, the average age of the patients was 60.1±14.6 years, with 72.2% men and a male:female ratio of 2.6:1, whereas 11.7% had diabetes and 52.8% had hypertension. Five hundred eighty-four patients (10.3%) had ApHCM, and 5069 (89.7%) had non-ApHCM. Detailed baseline characteristics of the total study population, stratified by ApHCM and non-ApHCM, are shown in Table 1. Patients with ApHCM were more likely to be men than those with non-ApHCM (75.9% versus 71.8%, $P<0.001$). Hypertension, diabetes, chronic kidney disease, and ES-HF at baseline were more prevalent in patients with non-ApHCM compared with ApHCM (all $P<0.001$).

In terms of echocardiographic parameters, patients with non-ApHCM had a smaller left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and left atrial diameter, along with higher LVEF (all $P<0.001$). The use of diuretics, mineralocorticoid receptor antagonists, and renin-angiotensin-aldosterone system inhibitors and calcium channel blockers in the ApHCM group was lower compared with the non-ApHCM group.

CUMULATIVE INCIDENCE OF MACEs STRATIFIED BY ApHCM AND NON-ApHCM

At a median follow-up of 4.6 (IQR, 1.8–8.0) years, 1808 patients (32.0%) developed MACEs, including 355 all-cause deaths, 1577 HF hospitalization, 155

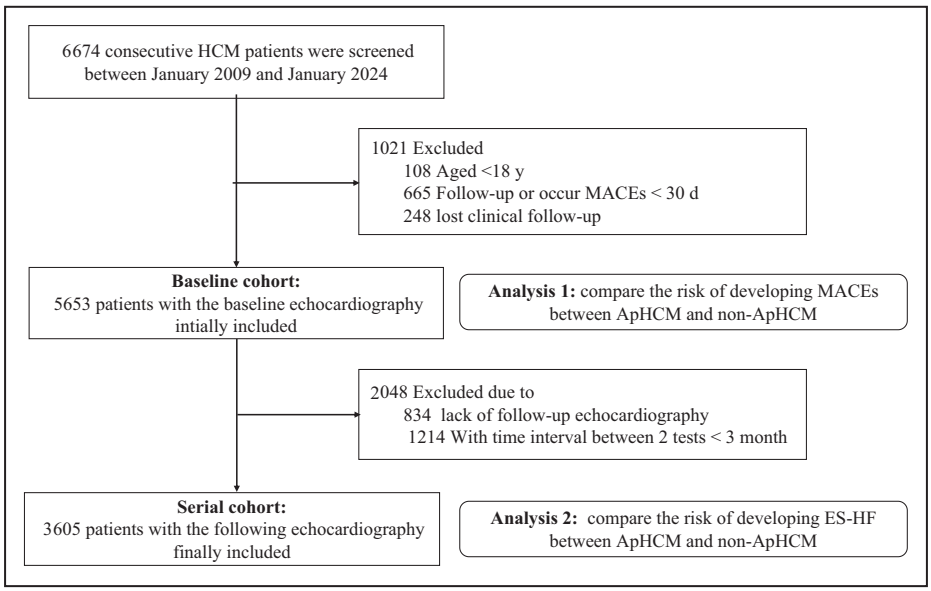

Figure 1. Flow diagram.
ApHCM indicates apical hypertrophic cardiomyopathy; ES-HF, end-stage heart failure; HCM, hypertrophic cardiomyopathy; and MACEs, major adverse cardiac events.

SCD, and 196 VT (Table 2). Compared with patients with ApHCM, patients with non-ApHCM had a higher incidence of MACEs (20.4% versus 33.3%, *P*<0.001), all-cause deaths (6.7% versus 2.0%, *P*<0.001), and HF hospitalization (29.1% versus 17.3%, *P*<0.001). Kaplan-Meier survival analysis illustrated a significant difference in the cumulative event-free survival rate for MACEs (*P*<0.001), all-cause death (*P*<0.001), HF hospitalization (*P*<0.001), SCD (*P*=0.001), and VT (*P*=0.002) between these 2 groups (Figures 2 and 3). In Cox proportional hazard analysis, ApHCM was associated with a lower risk of MACEs (HR, 1.65 [95% CI, 1.36–1.99], *P*<0.001).

Incidence of ES-HF Between Patients With ApHCM and Non-ApHCM

In our serial echo cohort, 3605 patients were enrolled for analysis. Two hundred forty-nine (7.7%) patients with HCM experienced a decline in LVEF and developed ES-HF. Detailed baseline characteristics and echocardiographic evaluation stratified by ES-HF and non–ES-HF are shown in Table 3. Patients with ApHCM have a lower risk of incident ES-HF than those with non-ApHCM (4.3% versus 10.7%, *P*<0.001). Cumulative incidence function curves using Fine-Gray competing risks analysis demonstrated a significant association between ApHCM and ES-HF development compared with non-ApHCM (*P*<0.001), as shown in Figure 4. Cox proportional hazards regression analysis showed a strong association between non-ApHCM and developing ES-HF (HR, 2.31 [95% CI, 1.28–4.15]; *P*<0.001) (Table 4).

Subgroup and Sensitivity Analysis

In addition, we conducted several subgroup analyses to further explore the relationship between ApHCM and adverse outcomes (Figure 5). When comparing subgroups stratified by age <60 years, hypertension, diabetes, chronic kidney disease, and New York Heart Association class III and IV, the results indicated that ApHCM remained significantly associated with the lower risk of MACEs in different subgroups (all *P*<0.001). In a landmark analysis, we only considered individuals who had been event free for at least 1 or 3 years after their initial echocardiography. Non-ApHCM in both >1 year (HR, 1.74 [95% CI, 1.41–2.14]; *P*<0.001) and >3 years (HR, 1.69 [95% CI, 1.34–2.13]; *P*<0.001) remained significantly associated with the risk of MACEs. In subgroup and sensitivity analyses, non-ApHCM remained significantly associated with the risk of incident ES-HF (Figure 5). In competing risk regression with all-cause death as the competing risk, the HRs showed similar results for ES-HF. During the follow-up period, there were a total of 225 coronary events observed. Of these, 28 events were potentially correlated with ES-HF, whereas the remaining 162 events occurred in patients who did not experience ES-HF, and 35 patients experienced coronary events after developing ES-HF. Given the impact of coronary events on reduced LVEF, we conducted a competing risk regression analysis with coronary events and all-cause death as the competing risks. Non-ApHCM exhibited a significant association with the risk of incident ES-HF (SHR, 2.00 [95% CI, 1.10–3.67]; *P*=0.022). We also redefined the follow-up period where patients were censored at their last follow-up if they did

Table 1. Baseline Characteristics and Echocardiographic Evaluation of the Baseline Cohort Stratified by ApHCM and Non-ApHCM

Variables	Total N=5653 (100%)	Non-ApHCM N=5069 (89.7%)	ApHCM N=584 (10.3%)	*P* value
Demographic data				
Age, y	60.1±14.6	60.4±14.7	57.6±13.8	<0.001
Men, n (%)	4082 (72.2%)	3639 (71.8%)	443 (75.9%)	0.038
BMI, kg/m^2	24.6±3.3	24.6±3.4	24.7±2.7	0.744
Smoker, n (%)	1295 (22.9%)	1189 (23.5%)	106 (18.2%)	0.004
Alcohol use, n (%)	1068 (18.9%)	974 (19.2%)	94 (16.1%)	0.068
Comorbidities, n (%)				
Hypertension	2985 (52.8%)	2748 (54.2%)	237 (40.6%)	<0.001
Diabetes	659 (11.7%)	612 (12.1%)	47 (8.0%)	0.004
Atrial fibrillation	526 (9.3%)	481 (9.5%)	45 (7.7%)	0.160
Ischemic stroke	134 (2.4%)	120 (2.4%)	14 (2.4%)	0.964
CKD	645 (11.4%)	611 (12.1%)	34 (5.8%)	<0.001
NYHA class III–IV	817 (14.5%)	768 (15.2%)	49 (8.4%)	<0.001
Clinical parameters				
Troponin I, ng/mL	0.04 (0.01–0.12)	0.04 (0.01–0.13)	0.02 (0.01–0.06)	<0.001
NT-proBNP, ng/L	341 (113–977)	339 (111–1002)	371 (129–832)	0.957
eGFR, mL/min×1.73 m^2	83.4 (60.0–100.1)	82.9 (57.7–99.8)	89.1 (72.3–102.1)	<0.001
hs-CRP, mg/L	5.0 (1.9–18.1)	5.0 (2.1–19.6)	3.0 (0.9–7.4)	<0.001
Medicine treatment, n (%)				
SGLT-2 inhibitors	74 (1.3%)	70 (1.4%)	4 (0.7%)	0.161
MRA	1188 (21.0%)	1113 (22.0%)	75 (12.8%)	<0.001
Diuretic	1848 (32.7%)	1754 (34.6%)	94 (16.1%)	<0.001
β-Blocker	3356 (59.4%)	3001 (59.2%)	355 (60.8%)	0.460
ACEI/ARB/ARNI	3038 (53.7%)	2782 (54.9%)	256 (43.8%)	<0.001
Calcium channel blocker	2698 (47.7%)	2514 (49.6%)	184 (31.5%)	<0.001
Echocardiographic evaluation				
LVEF, %	63.5±8.5	63.2±8.6	65.9±7.0	<0.001
ES-HF, n (%)	686 (12.1%)	661 (13.0%)	25 (4.3%)	<0.001
LVEDD, mm	48.1±6.6	48.1±6.8	48.6±5.6	0.046
LVESD, mm	31.4±6.0	31.4±6.1	30.8±5.0	0.005
LAD, mm	44.7±6.4	44.8±6.4	44.1±5.9	0.006
LV-MWT, mm	16 (15–18)	16 (15–18)	12.0 (11–16)	<0.001
LV posterior wall thickness	12.3±2.4	12.5±2.4	11.1±1.7	<0.001
LV outflow obstruction >30 mm Hg, n (%)	651 (11.5%)	618 (12.1%)	33 (5.6%)	<0.001
LV apical aneurysms, n (%)	25 (0.4%)	20 (0.4%)	5 (0.9%)	0.111
PASP, mm Hg	33.5±9.8	33.6±10.0	32.8±7.9	0.034
E/e′ ratio	12.7±5.1	12.8±5.2	11.7±4.1	0.006
E/A ratio	0.9±0.6	0.8±0.5	1.0±1.1	0.046

ACEI indicates angiotensin-converting enzyme inhibitor; ApHCM, apical hypertrophic cardiomyopathy; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CKD, chronic kidney disease; E/e′ ratio: ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annulus velocity (e′); E/A ratio: ratio of peak early diastolic mitral inflow velocity (E) to peak late diastolic mitral inflow velocity (A); eGFR, estimated glomerular filtration rate; ES-HF, end-stage heart failure; hs-CRP, high-sensitivity C-reactive protein; LAD, left atrial diameter; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; MWT, maximum wall thickness; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; and SGLT-2, sodium-glucose cotransporter-2.

not experience the event of interest, such as ES-HF, their last clinical follow-up for mortality, or at the time of myocardial infarction if it occurred, whichever came first.

Non-ApHCM continued to show a significant association with the risk of incident ES-HF (HR, 2.18 [95% CI, 1.18–4.01]; *P*=0.013). We performed a sensitivity analysis

Table 2. Clinical Outcomes in the Entire Cohort Stratified by ApHCM and Non-ApHCM

Variables	Total N=5653	Non-ApHCM N=5069	ApHCM N=584	*P* value
Follow-up period, y	4.6 (1.6–8.0)	4.4 (1.5–7.9)	6.3 (2.6–9.5)	<0.001
MACEs	1808 (32.0%)	1689 (33.3%)	119 (20.4%)	<0.001
All-cause deaths	355 (6.3%)	341 (6.7%)	14 (2.4%)	<0.001
HF hospitalization	1577 (27.9%)	1476 (29.1%)	101 (17.3%)	<0.001
SCD	155 (2.7%)	140 (2.8%)	15 (2.6%)	0.786
VT	196 (3.5%)	175 (3.5%)	21 (3.6%)	0.858

ApHCM indicates apical hypertrophic cardiomyopathy; HF, heart failure; MACEs, major adverse cardiac events; SCD, sudden cardiac death; and VT, ventricular tachyarrhythmia.

to assess the stability of the association when the LVEF cutoff was set at ejection fraction <40%. Non-ApHCM had a significant association with the risk of incident ES-HF (HR, 1.86 [95% CI, 1.14–3.04]; *P*=0.013). When excluding patients with left ventricular outflow obstruction >30 mm Hg, we found that non-ApHCM was associated with an increased risk of incident MACEs (HR, 1.59 [95% CI, 1.31–1.94]; *P*<0.001) and ES-HF development (HR, 2.22 [95% CI, 1.23–4.01]; *P*=0.008).

DISCUSSION

In this large contemporary cohort of patients with HCM in China, we compared the prevalence, clinical characteristics, and outcomes of ApHCM and non-ApHCM, analyzed the risk factors for development of ES-HF, and made the following observations: (1) ApHCM is a relatively common disease variant, accounting for 10.3% of the HCM population, and is characterized by distinct demographic and clinical traits. (2) Patients with ApHCM tend to have a lower risk of developing ES-HF and a favorable prognosis when compared with those with non-ApHCM. (3) The risk of SCD and ventricular arrhythmias was similar in the 2 groups.

Prevalence and Clinical Characteristics

The incidence of ApHCM in our data set was 10.3% of the HCM population. Previous studies have shown that ApHCM may occur more frequently in individuals of Asian descent, with incidence rates of 21% in China, 30% in Japan, and 38% in Korea.[27–29] Although they found that the proportion of men in consecutive patients with HCM can vary widely, ranging from 53% to 78%, this male predominance was more pronounced in Asian patients with ApHCM. Our finding showed that 72.2% of the enrolled patients were men. ES-HF was one of the most common complications associated with poor prognosis.[15,30,31] We found that ES-HF prevalence in patients with HCM was 14.5% at baseline, whereas in those with HCM but without ES-HF, ApHCM had a lower prevalence of HF than patients with non-ApHCM.

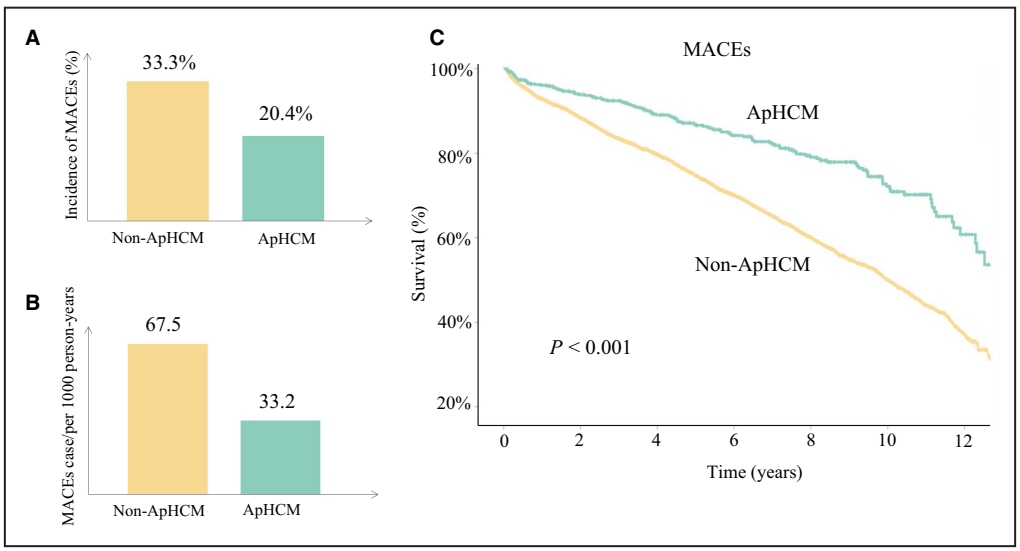

Figure 2. Incidence of clinical outcomes stratified by ApHCM and non-ApHCM.
A, Incidence rate of MACEs. **B**, Incidence rate of MACEs per 1000 person-years. **C**, Kaplan-Meier curve. ApHCM indicates apical hypertrophic cardiomyopathy; and MACEs, major adverse cardiac events.

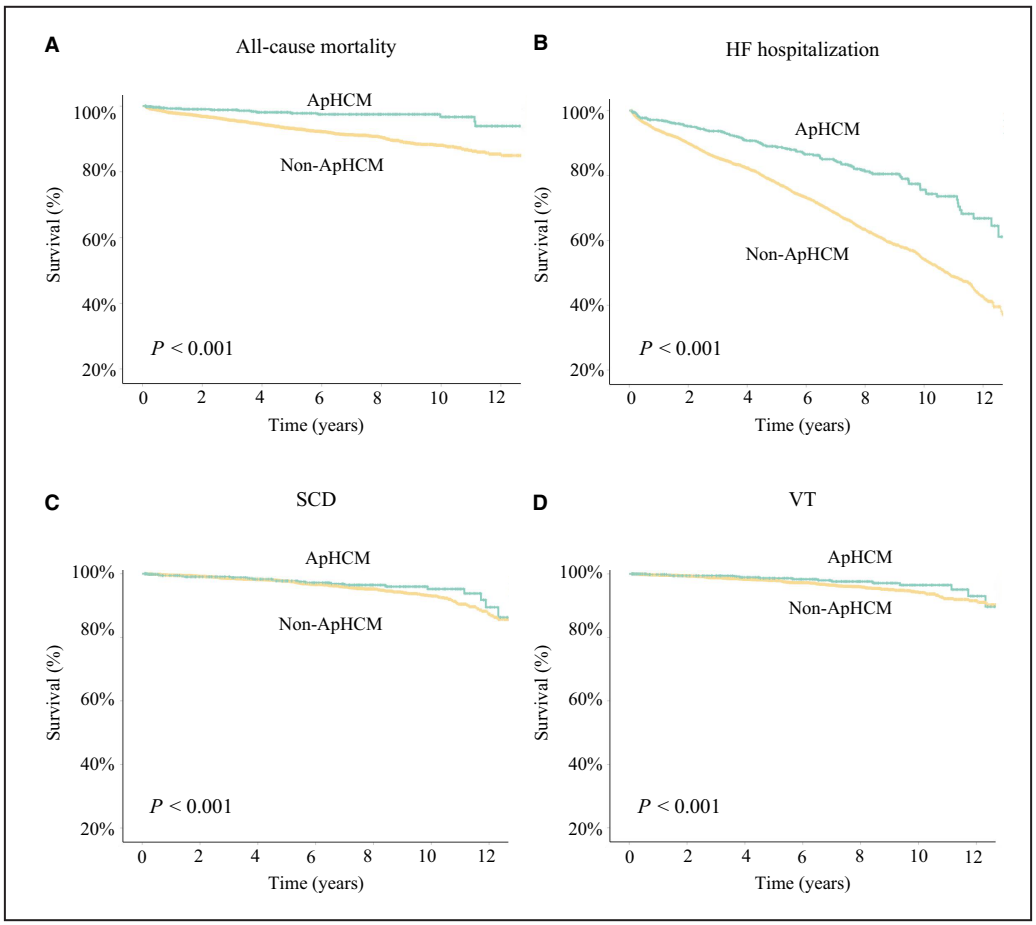

Figure 3. Kaplan-Meier event-free survival curves stratified by ApHCM and non-ApHCM.
A, All-cause death. **B**, HF hospitalization. **C**, SCD. **D**, VT. ApHCM indicates apical hypertrophic cardiomyopathy; HF, heart failure; SCD, sudden cardiac death; and VT, ventricular tachycardia.

Clinical Outcomes

We found that patients with ApHCM have a significantly lower rate of mortality related to all-cause, cardiovascular, and HF compared with patients with non-ApHCM. These findings are consistent with most previous studies, indicating a favorable long-term prognosis for this subgroup.[32–34] Notably, not all research supports the idea of a harmless clinical outcome for the ApHCM phenotype.[29,32] Moon et al discovered that all-cause mortality was higher in 454 patients with ApHCM who were older, had a history of arterial hypertension and diabetes, and showed certain echocardiographic risk markers, which were linked to a worse prognosis.[29] A meta-analysis showed that patients with ApHCM had a lower annual mortality rate (0.81%–1.55%) compared with patients with non-ApHCM.[35] Ma et al conducted a study on 2268 patients with HCM from 13 tertiary hospitals to examine the clinical prognosis for patients with ApHCM and non-ApHCM using propensity score matching.[36] Their findings indicate the patients with ApHCM, both before and after matching, had a better prognosis compared with patients with non-ApHCM. The study revealed lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and sudden SCD rates in patients with ApHCM than in patients with non-ApHCM. However, when multivariate Cox regression models were applied, ApHCM was no longer statistically significant for cardiovascular mortality, cardiac transplantation, and SCD. In line with this study, our findings indicated that the incidence of VT and SCD in ApHCM was not significantly higher than in patients with non-ApHCM. Currently, the information available on ventricular arrhythmias in ApHCM is conflicting in previous studies.[35,37,38] Zadok et al assessed the risk of SCD in patients with ApHCM using the HCM Risk-SCD 5-year prediction model.[37] The study revealed a lower incidence of malignant ventricular arrhythmias and SCD in patients with ApHCM compared with the nonobstructive non-ApHCM subgroup.[37] Conversely, Steinberg et al found that patients with ApHCM had a higher risk of sustained VT than patients with non-ApHCM.[38]

Patients With ApHCM Have a Lower Risk of Developing ES-HF Than Patients With Non-ApHCM

Another interesting finding of our study was the lower incidence of ES-HF in patients with ApHCM in our serial

Table 3. Baseline Characteristics and Echocardiographic Evaluation of the Serial Cohort Stratified by ES-HF and Non–ES-HF

Variables	Total N=3605	Non–ES-HF N=3329	ES-HF N=276	*P* value
Demographic data				
Age, y	60.5±14.3	60.1±14.0	64.5±14.6	<0.001
Men, n (%)	2560 (71.0%)	2347 (70.5%)	213 (77.0.2%)	0.019
BMI, kg/m^2	24.5±3.3	24.6±3.3	24.2±3.6	0.072
Smoker, n (%)	892 (24.7%)	801 (24.1%)	91 (33.0%)	<0.001
Alcohol use, n (%)	721 (20.0%)	647 (19.4%)	74 (26.8%)	0.003
Comorbidities, n (%)				
Hypertension	1932 (53.6%)	1771 (53.2%)	161 (58.3%)	0.100
Diabetes	378 (10.5%)	351 (10.5%)	27 (9.8%)	0.692
Atrial fibrillation	443 (12.3%)	371 (11.1%)	72 (26.1%)	<0.001
Ischemic stroke	84 (2.3%)	77 (2.3%)	7 (2.5%)	0.813
CKD	401 (11.1%)	347 (10.4%)	54 (19.6%)	<0.001
NYHA class III–IV	550 (15.3%)	473 (14.2%)	77 (27.9%)	<0.001
Clinical parameters				
Troponin I	0.03 (0.01–0.11)	0.03 (0.01–0.09)	0.06 (0.03–0.30)	<0.001
NT-proBNP	326 (110–912)	314 (105–866)	458 (164–1509)	<0.001
eGFR	82.9 (59.2–99.2)	84.2 (61.4–99.6)	60.2 (25.7–85.4)	<0.001
hs-CRP	5.0 (1.7–16.6)	5.0 (1.6–16.1)	6.5 (3.0–28.2)	<0.001
Medicine treatment, n (%)				
SGLT-2 inhibitors	45 (1.2%)	42 (1.3%)	3 (1.1%)	1.000
MRA	791 (21.9%)	693 (20.8%)	98 (35.5%)	<0.001
Diuretic	1274 (35.3%)	1114 (33.5%)	160 (58.0%)	<0.001
β-Blocker	2311 (64.1%)	2130 (64.0%)	181 (65.6%)	0.595
ACEI/ARB/ARNI	2073 (57.5%)	1886 (56.7%)	187 (67.8%)	<0.001
Calcium channel blocker	1731 (48.0%)	1587 (47.7%)	144 (52.2%)	0.150
Echocardiographic evaluation				
ApHCM, n (%)	368 (10.2%)	356 (10.7%)	12 (4.3%)	<0.001
Non-ApHCM, n (%)	3237 (89.8%)	2973 (89.3%)	264 (95.7%)	<0.001
LVEF, %	65.0±6.3	65.3±6.2	60.9±6.2	<0.001
LVEDD, mm	47.7±6.3	47.5±6.1	50.9±7.1	<0.001
LVESD, mm	30.7±5.0	30.4±4.8	34.2±5.8	<0.001
LAD, mm	44.8±6.4	44.7±6.3	46.3±6.9	<0.001
LV-MWT, mm	16.0 (15.0–18.0)	16.0 (15.0–18.0)	15.0 (15.0–17.0)	0.729
LV posterior wall thickness	12.3±2.3	12.2±2.3	13.1±2.2	<0.001
LV apical aneurysms	10 (0.3%)	6 (0.2%)	4 (1.4%)	<0.001
PASP, mm Hg	33.6±9.7	33.6±9.6	34.4±10.3	0.223
E/e′ ratio	13.1±5.2	13.0±5.2	15.8±5.0	0.143
E/A ratio	0.9±0.7	0.9±0.7	0.7±0.5	0.405
Following echo evaluation				
LVEF, %	63.3±8.0	65.1±5.2	42.5±5.6	<0.001
LVEDD, mm	48.0±6.3	47.7±5.8	54.8±8.0	<0.001
LVESD, mm	31.5±5.6	30.6±4.4	42.2±7.7	<0.001
LAD, mm	45.9±6.6	45.7±6.6	48.4±7.0	<0.001
LV-MWT, mm	15.0 (12.0–17.0)	15.0 (12.0–17.0)	13.0 (12.0–15.0)	<0.001
LV posterior wall thickness	11.8±1.9	11.8±1.9	12.1±2.1	0.016

(*Continued*)

Table 3. Continued

Variables	Total N=3605	Non–ES-HF N=3329	ES-HF N=276	*P* value
LV outflow obstruction >30 mm Hg, n (%)	495 (13.7%)	466 (13.9%)	29 (10.5%)	0.105
LV apical aneurysms	22 (0.6%)	8 (0.2%)	12 (4.3%)	<0.001
PASP, mm Hg	35.4±10.7	35.1±10.4	38.9±13.4	<0.001
E/e′ ratio	12.9±5.2	12.8±5.2	17.4±6.8	0.001
E/A ratio	0.9±0.5	0.9±0.5	1.2±0.9	0.066

ACEI indicates angiotensin-converting enzyme inhibitor; ApHCM, apical hypertrophic cardiomyopathy; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CKD, chronic kidney disease; E/e′ ratio: ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annulus velocity (e′); E/A ratio: ratio of peak early diastolic mitral inflow velocity (E) to peak late diastolic mitral inflow velocity (A); eGFR, estimated glomerular filtration rate; ES-HF, end-stage heart failure; hs-CRP, high-sensitivity C-reactive protein; LAD, left atrial diameter; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; MWT, maximum wall thickness; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; and SGLT-2, sodium-glucose cotransporter-2.

echo cohort. ES-HF is linked to poor prognosis, related to myocardial fibrosis, SCD, and refractory HF.[39–41] A small subset of patients with HCM, roughly 2% to 5% with an incidence rate of 0.5 to 1.0 patients per 100 patient-years, may experience disease progression to ES-HF. We noted that 8.1% of patients with non-ApHCM and 3.2% with ApHCM experienced an LVEF decline and developed ES-HF during the ≈4-year follow-up period. On multivariable analysis, non-ApHCM was significantly associated with a 2.3-fold risk of the future development of ES-HF. These observations suggest that a diagnosis of non-ApHCM may be a predictor of disease progression in patients with HCM. This result should be interpreted cautiously, because current risk stratification algorithms do not consider different phenotypical patterns such as ApHCM, which may be important for accurate risk stratification.

Clinical Implication

Building on the findings from the cohort of patients with HCM in China, several implications for clinical practice can be drawn to enhance patient care and treatment strategies. First, the distinct demographic and clinical traits associated with ApHCM outlined in the study underscore the need for tailored diagnostic protocols to accurately identify this variant. Second, given the finding that patients with ApHCM generally have a lower risk of developing ES-HF and tend to have a more favorable prognosis than those with non-ApHCM, less closed echocardiographic reexaminations are needed. Third, the similar risk of SCD and ventricular arrhythmias between ApHCM and non-ApHCM groups suggests that screening and surveillance guidelines for these complications should not differentiate between HCM subtypes. Future studies on genetic markers,

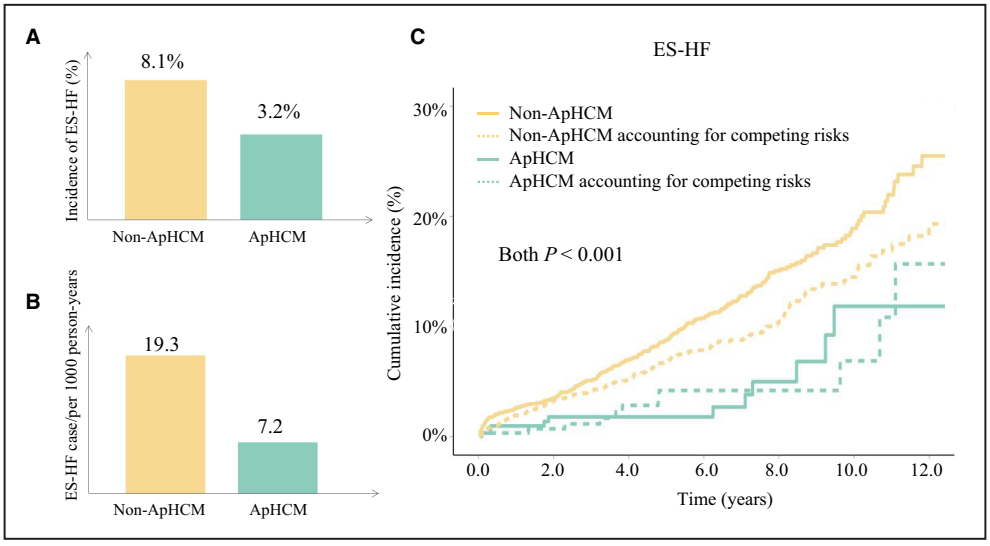

Figure 4. Incidence of clinical outcomes stratified by ApHCM and non-ApHCM.
A, Incidence rate of ES-HF. **B**, Incidence rate of ES-HF per 1000 person-years. **C**, Cumulative incidence curve using Fine-Gray competing risks analysis. ApHCM indicates apical hypertrophic cardiomyopathy; and ES-HF, end-stage heart failure.

Table 4. Subgroup Analysis and Competing Risk Regression for Incident ES-HF

Variable	Non-ApHCM	ApHCM	Multivariable analysis		Competing risk analysis	
			Adjusted HR (95% CI)	*P* value	SHR (95% CI)	*P* value
All	264/3237 (8.2)	12/368 (3.3)	2.31 (1.28–4.15)	0.005	2.20 (1.24–3.89)	0.007
Age						
<60 y	85/1407 (6.0)	6/197 (3.0)	1.35 (0.58–3.15)	0.491	1.33 (0.54–3.27)	0.530
≥60 y	179/1830 (9.8)	6/171 (3.5)	3.17 (1.37–7.36)	0.007	2.84 (1.32–6.10)	0.007
Sex						
Women	57/954 (6.0)	6/91 (6.6)	0.83 (0.35–1.97)	0.678	0.78 (0.31–1.97)	0.597
Men	207/2283 (9.1)	6/277 (2.2)	3.75 (1.65–8.52)	0.002	3.59 (1.66–7.76)	0.001
Hypertension						
No	108/1452 (7.4)	7/221 (3.2)	2.30 (1.06–5.03)	0.036	2.18 (1.00–4.76)	0.050
Yes	156/1785 (8.7)	5/147 (3.4)	2.08 (0.85–5.10)	0.110	2.04 (0.85–4.86)	0.108
Diabetes						
No	237/2882 (8.2)	12/345 (3.5)	2.20 (1.22–3.96)	0.009	2.10 (1.18–3.73)	0.011
Yes	27/355 (7.6)	0/23 (0.0)	-	-	-	-
CKD						
No	211/2854 (7.4)	11/350 (3.1)	2.18 (1.18–4.01)	0.013	2.11 (1.14–3.92)	0.018
Yes	53/383 (13.8)	1/18 (5.6)	-	-	-	-
NYHA III–IV						
No	190/2721 (7.0)	9/334 (2.7)	2.16 (1.10–4.25)	0.025	2.15 (1.09–4.25)	0.027
Yes	74/516 (14.3)	3/34 (8.8)	2.84 (0.69–11.75)	0.149	2.07 (0.70–6.10)	0.189
Follow-up						
>1 y	193/2547 (7.6)	9/306 (2.9)	2.42 (1.22–4.78)	0.011	2.27 (1.18–4.37)	0.014
>3 y	141/1789 (7.9)	7/213 (3.3)	2.43 (1.11–5.33)	0.026	2.24 (1.06–4.72)	0.034

Adjusted for age, sex, BMI, smoker, alcohol use, hypertension, diabetes, ischemic stroke, atrial fibrillation, CKD, NYHA class III–IV, SGLT-2 inhibitor, MRA, diuretic, ACEI/ARB/ARNI, β-blocker, and calcium channel blocker. ACEI indicates angiotensin-converting enzyme inhibitor; ApHCM, apical hypertrophic cardiomyopathy; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CKD, chronic kidney disease; ES-HF, end-stage heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT-2, sodium-glucose cotransporter-2; and SHR, subdistribution hazard ratios.

molecular mechanisms, and treatment response differences between the subtypes may uncover additional insights to further refine patient management.

Study Limitations

Although our HCM cohort is substantial, it is important to acknowledge that the current study has some limitations. First, the analysis of this study was limited by its single-center observational nature. Patients were not followed up at specific intervals but were guided by their cardiologists and their tendencies. Second, genetic testing and late gadolinium enhancement on cardiac magnetic resonance imaging can expand the spectrum of the HCM disease and identify HCM phenocopies with varying natural histories. Because these tests are unavailable to most patients, we could not determine any correlation between HCM phenotype and genotype. However, our study was primarily focused on the clinical and imaging aspects of HCM. Further research in this area may be necessary to provide more insight into the genetic components of HCM. Third, the use of echocardiography contrast enhancement or magnetic resonance imaging was not routinely done, leading to an underestimation of the prevalence of apical aneurysms. Fourth, in our study, patients with non-ApHCM are more likely to have comorbid conditions such as hypertension and chronic kidney disease, compared with the ApHCM group. Although we performed multivariate Cox regression analysis to minimize the impact, several unmeasured potential confounding factors are still present and likely contribute toward a higher rate of MACEs in patients with ApHCM. Fifth, we reviewed all available data (ECG, Holter, reveal, implantable cardioverter-defibrillator) to check for the occurrence of VT. However, the recording of VT is often event-driven, which may lead to an underestimation of the event incidence in some patients, because asymptomatic VT is not recorded. Last, this cohort included a Chinese population, so results may not be generalizable to other ethnic groups.

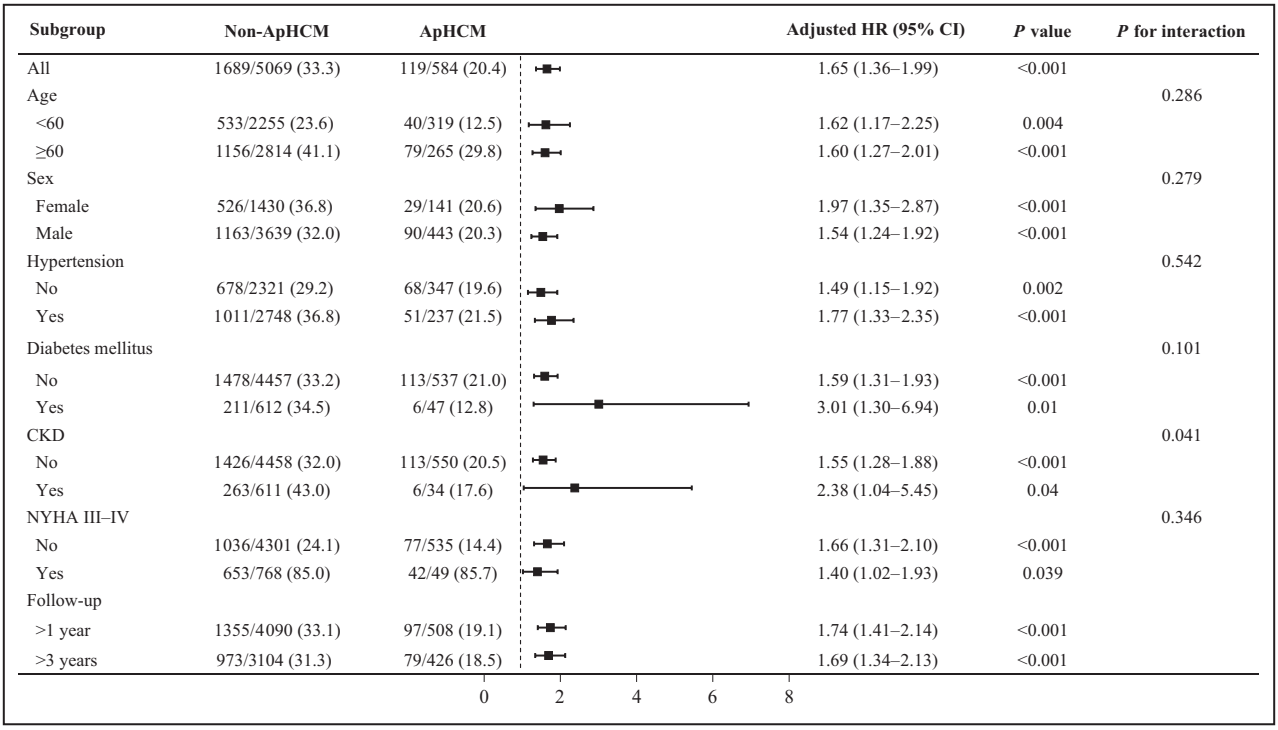

Figure 5. Subgroup and sensitivity analysis of the association between ApHCM/non-ApHCM and incident ES-HF.
Adjusted for age, sex, BMI, smoker, alcohol use, hypertension, diabetes, ischemic stroke, atrial fibrillation, CKD, NYHA class III–IV, SGLT-2 inhibitors, MRA, diuretic, ACEI/ARB/ARNI, β-blocker, and calcium channel blocker. ACEI indicates angiotensin-converting enzyme inhibitor; ApHCM, apical hypertrophic cardiomyopathy; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CKD, chronic kidney disease; ES-HF, end-stage heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; and SGLT-2, sodium-glucose cotransporter-2.

CONCLUSIONS

ApHCM is distinct from non-ApHCM in terms of its features and exhibited a relatively favorable prognosis with a lower rate of all-cause deaths, HF hospitalization, SCD, and VT. Moreover, patients with ApHCM patients have a lower incidence of ES-HF when compared with non-ApHCM. This may be the reason why most patients with ApHCM experience a milder course of the disease than those with non-ApHCM.

ARTICLE INFORMATION

Received May 20, 2024; accepted August 15, 2024.

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Sources of Funding

This study was supported by the Wenzhou Science and Technology Bureau Project (Y20220081, 2022Y0726, Y20210036).

Disclosures

None.

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