Prognosis for patients with apical hypertrophic cardiomyopathy: A multicenter cohort study based on propensity score matching

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ABSTRACT

Background: Apical hypertrophic cardiomyopathy (AHCM) is a subtype of HCM, and few studies on the prognosis in AHCM are available.

Aims: This study aimed to explore the clinical prognosis for AHCM and non-AHCM patients through clinical data based on propensity score matching (PSM) in a large cohort of Chinese HCM patients.

Methods: The cohort study included 2268 HCM patients, 226 AHCM and 2042 non-AHCM patients from 13 tertiary hospitals, who were treated between 1996 and 2021. Fifteen demographic and clinical variables of 226 AHCM patients and 2042 non-AHCM patients were matched using 1:2 PSM. A Cox proportional hazard regression model was constructed to assess the effect of AHCM on mortality.

Results: During a median follow-up of 5.1 (2.4–8.4) years, 353 (15.6%) of the 2268 HCM patients died, of whom 205 died due to cardiovascular mortality/cardiac transplantation and 94 experienced sudden cardiac death (SCD). In the matched cohort, the ACHM patients had lower rates of all-cause mortality ($P = 0.003$), cardiovascular mortality/cardiac transplantation ($P = 0.03$), and SCD ($P = 0.02$) than the non-AHCM patients. Furthermore, the Cox proportional hazard regression model showed that AHCM was an independent prognostic predictor of all-cause HCM mortality ($P = 0.004$) and a univariable prognostic predictor of cardiovascular mortality/cardiac transplantation ($P = 0.03$) and for SCD ($P = 0.03$). However, AHCM was not significant in multivariable Cox regression models in relation to cardiovascular mortality/cardiac transplantation and SCD.

Conclusion: AHCM had a favorable prognosis both before and after matching, with lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD than non-AHCM.

Key words: apical hypertrophic cardiomyopathy, all-cause mortality, cardiovascular mortality/cardiac transplantation, propensity score matching, sudden cardiac death

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiomyopathy and usually manifests as thickening of the left ventricular wall without secondary causes and left ventricular dilatation [1]. Notably, apical hypertrophic cardiomyopathy (AHCM) is a specific type of primary HCM that was first reported in Japan by Sakamoto et al. in 1976 [2]. Myocardial hypertrophy in AHCM is mainly limited to the apex of the left ventricular papillary muscle, usually without left ventricular outflow tract (LVOT) dynamic obstruction and an LVOT gradient [3–4]. Moreover, AHCM is the most common HCM in East Asian populations, accounting for 25% of all

WHAT'S NEW?

Propensity score matching can address the imbalance of confounders in observational studies. This study aimed to explore the clinical prognosis in apical hypertrophic cardiomyopathy (AHCM) and non-AHCM patients through clinical data based on propensity score matching. We showed that AHCM had a favorable prognosis both before and after matching, with lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and sudden cardiac death than non-AHCM.

the cases of HCM in the Asian population and 1%–10% of the HCM cases in non-Asian populations [5].

HCM patients may experience palpitations, shortness of breath, chest tightness, and chest pain, as well as symptoms of cardiac dysfunction [1]. Nevertheless, AHCM patients may be more likely to have fewer clinical signs or symptoms [3]. The typical clinical features of AHCM are giant negative T waves (GNTs) on electrocardiogram (ECG) and "spade-like" changes on echocardiography [2, 3]. Many studies have confirmed the favorable prognosis in AHCM [5–9]. However, recent studies have questioned this [4, 10], as fatal arrhythmias and even sudden cardiac death (SCD) have also been reported in AHCM patients [11–14].

Propensity score matching is a statistical technique introduced in 1983 and provides a method for effectively adjusting for confounding variables that are known and measured in observational data [15]. Studies on AHCM prognosis are not completely consistent, and there are few studies on the prognostic value of AHCM in HCM patients. Therefore, this study aimed to evaluate AHCM prognosis as well as the effect of AHCM on HCM mortality based on propensity score matching.

METHODS

Study population

We conducted a multicenter cohort study on 2268 HCM patients, 226 with AHCM and 2042 with non-AHCM, who were hospitalized at 13 tertiary hospitals from 1996 to 2021. In addition, we performed propensity score matching for AHCM and non-AHCM with a 1:2 ratio. Ultimately, 226 AHCM patients and 452 non-AHCM patients were enrolled after matching. Patients with cardiac or systemic disease capable of producing similar magnitudes of hypertrophy, such as cardiac amyloidosis, Fabry disease, Noonan syndrome, and amyloidosis cardiomyopathy etc., were excluded.

Diagnostic criteria and definitions

HCM is defined as a wall thickness of left ventricular myocardium ≥15 mm in one or more left segments. It can be measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging [CMR], or computed tomography [CT]), rather than explained by loading conditions alone [16, 17]. Patients with familial HCM or a family history of SCD in first-degree relatives with a smaller degree of wall thickness (13–14) can be diagnosed with HCM [16].

The diagnostic criteria for AHCM include a left ventricular apex (below the insertion of papillary muscles) ≥15 mm as shown by a two-dimensional echocardiogram or CMR. However, since the apex is the thinnest part of the left ventricle, a lower threshold (13–14 mm) can be used to diagnose AHCM when clinical manifestations and other imaging features (electrocardiography, family history, genotyping, CMR imaging, echocardiography, *etc.*) favor AHCM diagnosis [16–18].

Follow-up and endpoint

The follow-up began in October 2011, and the last follow-up was completed in August 2022. The primary endpoint of the study was all-cause mortality, and the secondary endpoints were cardiovascular mortality/cardiac transplantation and SCD. Cardiovascular mortality was defined as stroke, cerebral infarction, heart failure (HF), and appropriate implantable cardioverter-defibrillator (ICD) discharges. SCD was an unexpected death that occurred in the absence of or within 1 hour from symptom onset in patients who had previously experienced a relatively stable or uneventful course [19]. Ventricular arrhythmias were defined as frequent ventricular premature beats and ventricular tachycardia detected by a 24-hour Holter electrocardiogram. Non-sustained ventricular tachycardia was also indicated by a 24-hour Holter electrocardiogram. Data on the occurrence of all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD during follow-up were collected by reviewing medical records (outpatient center attendance and hospitalization), performing telephone interviews, and reviewing survival status records through the National Police Stations. Patients who were lost within 6 months of discharge were regarded as lost to follow-up. The study conformed to the principles of the Declaration of Helsinki and was approved by the Ethics Commission of Sichuan Provincial People's Hospital.

Statistical analysis

Continuous variables were described as medians with interquartile ranges (IQR), and differences between the two groups were analyzed by the Mann–Whitney U test. The Shapiro–Wilk test was used to define the normal distribution. Categorical variables were expressed as proportions, and differences between groups were analyzed by the Pearson χ^2 test. A logit model was performed based on 28 baseline variables, and variables with a $P \leq 0.15$ were then entered into propensity score matching (e.g., age,

sex, syncope, family history of SCD, ventricular arrhythmias, QRS duration, QTc duration, QT duration, PR duration, right bundle branch block [RBBB], left ventricular [LV] diameter, left atrial [LA] diameter, left ventricular ejection fraction [LVEF], Log N-terminal pro-B-type natriuretic peptide [NT-proBNP], creatinine). Propensity score matching was performed using a 1:2 ratio in R using the MatchIt package with nearest-neighbor matching to adjust for potential confounding in the comparison between the AHCM and non-AHCM groups. Cumulative survival estimates were calculated according to the Kaplan–Meier method, and differences were assessed by the log-rank test. A stepwise variable selection procedure for Cox's proportional hazard model was performed to identify the factors independently associated with mortality by R packages My.stepwise. Hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values were provided. The survival curve was obtained based on the R packages survival. Analysis was performed with R Version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria), with *P*-values <0.05 considered statistically significant.

RESULTS

Baseline characteristics

Table 1 summarizes the baseline clinical characteristics of the unmatched and matched cohorts. In the unmatched cohort, a total of 2268 patients met the initial inclusion criteria, of whom 1435 (63.3%) were males and 833 females (36.7%), with a median age of 56 (46–66) years. Compared to the non-AHCM patients, the AHCM patients had a more infrequent history of syncope and familial HCM, lower incidence of ventricular arrhythmias and ventricular tachycardia, shorter QRS and QTc duration, smaller LA diameter, smaller interventricular septum (IVS) thickness and maximal LV wall thickness, and a lower circulating Log (NT-proBNP) level. The matched cohort analysis showed that 24 baseline variables were not significantly different between the two groups except for IVS thickness, maximal LV wall thickness, beta-blockers, and Ca^{2+} antagonists.

Follow-up results of the unmatched cohort

Before matching, the median follow-up time was 5.1 (2.4–8.4) years. Meanwhile, there were 18 (8.0%) patients and 335 (16.4%) patients in all-cause mortality in the AHCM group and non-AHCM group, respectively. Nine (4.0%) cardiovascular deaths occurred in the AHCM group, and 196 (9.6%) occurred in the non-AHCM group. SCD occurred in 3 (1.3%)ACHM patients and 91 (4.5%) patients with non-AHCM. The Kaplan-Meier curves for the unmatched cohort of AHCM and non-AHCM patients are shown in Figure 1. There were significant differences between AHCM and non-AHCM in relation to all-cause mortality (*P* <0.001), cardiovascular mortality/cardiac transplantation (*P* <0.001), and SCD (*P* = 0.009).

Outcome of propensity score matching analysis

Primary endpoint: All-cause mortality

The Kaplan–Meier curves for all-cause mortality in the AHCM and non-AHCM patients after matching are shown in Figure 2A. Notably, all-cause mortality was lower in AHCM patients (*P* = 0.003). The Cox proportional hazard model for all-cause mortality in the unmatched and matched cohorts is shown in Table 2. According to the Cox proportional hazard regression model, AHCM (HR, 0.461; 95% CI, 0.271–0.784; *P* = 0.004), age (HR, 1.040; 95% CI, 1.022–1.059; *P* <0.001), LVEF (HR, 0.976; 95% CI, 0.953–0.999; *P* = 0.04), and Log (NT-proBNP) (HR, 7.181; 95% CI, 3.767–13.687; *P* <0.001) were independent prognostic predictors of all-cause mortality in the matched cohort.

Secondary endpoint: Cardiovascular mortality/ /cardiac transplantation and SCD

The Kaplan–Meier curves for cardiovascular mortality/ /cardiac transplantation after matching are shown in Figure 2B. The AHCM patients had lower cardiovascular mortality/cardiac transplantation (*P* = 0.03) than the non-AHCM patients. Meanwhile, Cox regression analysis showed that AHCM was a univariable predictor of cardiovascular mortality/cardiac transplantation (HR, 0.448; 95% CI, 0.214–0.935; *P* = 0.03), which was not confirmed after adjusting for other clinical predictors in the multivariable analysis (HR, 0.506; 95% CI, 0.239–1.069; *P* = 0.07). In the matched cohort (Table 3), male sex (HR, 0.485; 95% CI, 0.260–0.904; *P* = 0.02), ventricular arrhythmias (HR, 2.318; 95% CI, 1.064–5.052; *P* = 0.03), QTc duration (HR, 1.007; 95% CI, 1.002–1.013; *P* = 0.01), and Log (NT-proBNP) (HR, 10.114; 95% CI, 4.085–25.045; *P* <0.001) were independent prognostic predictors of cardiovascular mortality/cardiac transplantation.

Likewise, after matching, the AHCM patients had a lower rate of SCD (*P* = 0.020) (Figure 2C). The Cox proportional hazard regression model is shown in Table 4. Left bundle branch block (HR, 8.654; 95% CI, 1.665–44.993; *P* = 0.01), diastolic blood pressure (HR, 0.955; 95% CI, 0.920–0.992; *P* = 0.02), LV diameter (HR, 1.067; 95% CI, 1.014–1.123; *P* = 0.01), Log (NT-proBNP) (HR, 5.142; 95% CI, 1.030–25.670; *P* = 0.046), IVS thickness (HR, 1.126; 95% CI, 1.035–1.226; *P* = 0.006), and Ca^{2+} antagonists (HR, 0.313; 95% CI, 0.102–0.962; *P* = 0.04) were independent prognostic predictors of SCD. AHCM was a univariable predictor (HR, 0.262; 95% CI, 0.077–0.885; *P* = 0.03) but not significant in multivariable Cox regression models for SCD.

Subgroup analysis

To better investigate the effect of AHCM on HCM mortality, we generated forest plots showing the differences in the subgroups. In the all-cause mortality group (Figure 3A), AHCM was a protective predictor in the subgroups of males, with New York Heart Association (NYHA) class I–II, age ≤60 years, LV diameter ≤50 mm, LVEF >55%, and Log

Table 1. Baseline characteristics of the unmatched and the propensity score matched cohort

Variables	Unmatched cohort (n = 2268)				Matched cohort (n = 678)		
	Non-AHCM (n = 2042)	AHCM (n = 226)	*P*-value	%missing	Non-AHCM (n = 452)	AHCM (n = 226)	*P*-value
Follow-up time, year, median (Q1–Q3)	4.9 (2.4–8.3)	7.1 (3.8–10.0)	<0.001	0	5.3 (2.7–8.7)	7.0 (2.8–10.0)	0.02
Age, years, median (Q1–Q3)	55 (45–65)	59 (48–66)	0.097	0	56 (47–67)	57 (49–66)	0.63
Sex, male, n (%)	1262 (61.8)	173 (76.5)	0.001	0	338 (74.8)	173 (76.5)	0.68
NYHA I-II class, n (%)	1242 (60.9)	140 (61.9)	0.80	0	300 (66.4)	140 (61.9)	0.29
DBP, mm Hg, median (Q1–Q3)	75 (68–82)	80 (70–80)	0.11	0.04	79 (70–86)	80 (70–80)	0.53
Syncope, n (%)	283 (13.9)	18 (8.0)	0.02	0	36 (8.0)	18 (8.0)	1.000
FHCM, n (%)	186 (9.1)	7 (3.1)	0.003	0	23 (5.1)	7 (3.1)	0.32
Family history of SCD, n (%)	33 (1.6)	2 (0.9)	0.57	0	5 (1.1)	2 (0.9)	1.000
Electrocardiograph							
QRS, ms, median (Q1–Q3)	100 (88–119)	96 (83–108)	<0.001	12.52	95 (84–107)	98 (84–107)	0.37
QT, ms, median (Q1–Q3)	420 (389–450)	426 (390–449)	0.47	12.92	418 (389–440)	420 (398–445)	0.09
QTc, ms, median (Q1–Q3)	449 (427–478)	443 (418–469)	0.01	13.89	447 (422–460)	447 (424–464)	0.65
PR, ms, median (Q1–Q3)	164 (150–190)	162 (151–184)	0.47	20.28	169 (149–178)	166 (151–180)	0.86
Atrial fibrillation, n (%)	370 (18.1)	38 (16.8)	0.69	0	60 (13.3)	38 (16.8)	0.26
LBBB, n (%)	68 (3.3)	4 (1.8)	0.29	0	6 (1.3)	4 (1.8)	0.91
RBBB, n (%)	103 (5.0)	10 (4.4)	0.81	0	19 (4.2)	10 (4.4)	1.000
Ventricular arrhythmias, n (%)	368 (18.0)	25 (11.1)	0.01	0	43 (9.5)	25 (11.1)	0.62
VT, n (%)	216 (10.6)	13 (5.8)	0.03	0	25 (5.5)	13 (5.8)	1.000
NSVT, n (%)	140 (7.0)	10 (4.8)	0.28	3.22	12 (2.7)	10 (4.4)	0.32
Echocardiography							
LV diameter, mm, median (Q1–Q3)	43 (40–47)	47 (44–51)	<0.001	8.11	46 (43–49)	47 (44–50)	0.09
LA diameter, mm, median (Q1–Q3)	39 (35–44)	37 (34–42)	<0.001	7.41	38 (34–42)	38 (34–41)	0.998
RA, n (%)	121 (6.6)	13 (6.6)	1.000	10.89	20 (4.4)	13 (5.8)	0.57
RV diameter, mm, median (Q1–Q3)	20 (18-22)	21 (19-22)	<0.001	12.83	20 (18–22)	20 (19–22)	0.06
LVEF, %, median (Q1–Q3)	68 (62–73)	66 (61–71)	0.71	9.08	66 (63–72)	66 (63–70)	0.54
IVS, mm, median (Q1–Q3)	19 (15–22)	12 (10–15)	<0.001	6.70	17 (14–19)	13 (10–17)	<0.001
Maximal wall thickness, mm, median (Q1–Q3)	19 (17–23)	16 (14–20)	<0.001	5.56	18 (16–20)	17 (14–20)	<0.001
LVOT obstruction, n (%)	975 (47.7)	30 (13.3)	<0.001	0	168 (37.2)	30 (13.3)	<0.001
Laboratory investigations							
Log (NT-proBNP), fmol/l, median (Q1–Q3)	3.1 (2.8–3.4)	2.9 (2.7–3.1)	<0.001	28.09	3.1 (2.8–3.1)	3.0 (2.8–3.1)	0.43
Creatinine, µmol/l, median (Q1–Q3)	76.9 (64.6–91.2)	77.9 (69.3–91.0)	0.37	5.91	79.3 (66.7–88.7)	79.5 (70.8–89.4)	0.45
Medicine at baseline							
Beta-blocker, n (%)	1578 (77.5)	188 (83.6)	0.04	0.26	342 (75.7)	189 (83.6)	0.02
Ca^{2+} antagonists, n (%)	451 (22.2)	77 (34.2)	<0.001	0.67	112 (24.8)	77 (34.1)	0.01
Aspirin, n (%)	829 (40.7)	168 (74.7)	<0.001	0.26	221 (48.9)	168 (74.3)	<0.001
Warfarin, n (%)	208 (10.2)	22 (9.8)	0.93	0.26	36 (8.0)	22 (9.7)	0.53
Cordarone, n (%)	120 (5.9)	9 (4.0)	0.31	0.26	21 (4.6)	9 (4.0)	0.84
Endpoints							
All-cause mortality, n (%)	335 (16.4)	18 (8.0)	0.001	0	64 (14.2)	18 (8.0)	0.03
Cardiovascular mortality/cardiac transplantation, n (%)	196 (9.6)	9 (4.0)	0.008	0	34 (7.5)	9 (4.0)	0.11
SCD, n (%)	91 (4.5)	3 (1.3)	0.04	0	19 (4.2)	3 (1.3)	0.08

Data are presented as number (percentage) or median (Q1–Q3)

Abbreviations: AHCM, apical hypertrophic cardiomyopathy; DBP, diastolic blood pressure; FHCM, familial hypertrophic cardiomyopathy; IVS, interventricular septum; LA, left atrial; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RBBB, right bundle branch block; RV, right ventricular; VT, ventricular tachycardia

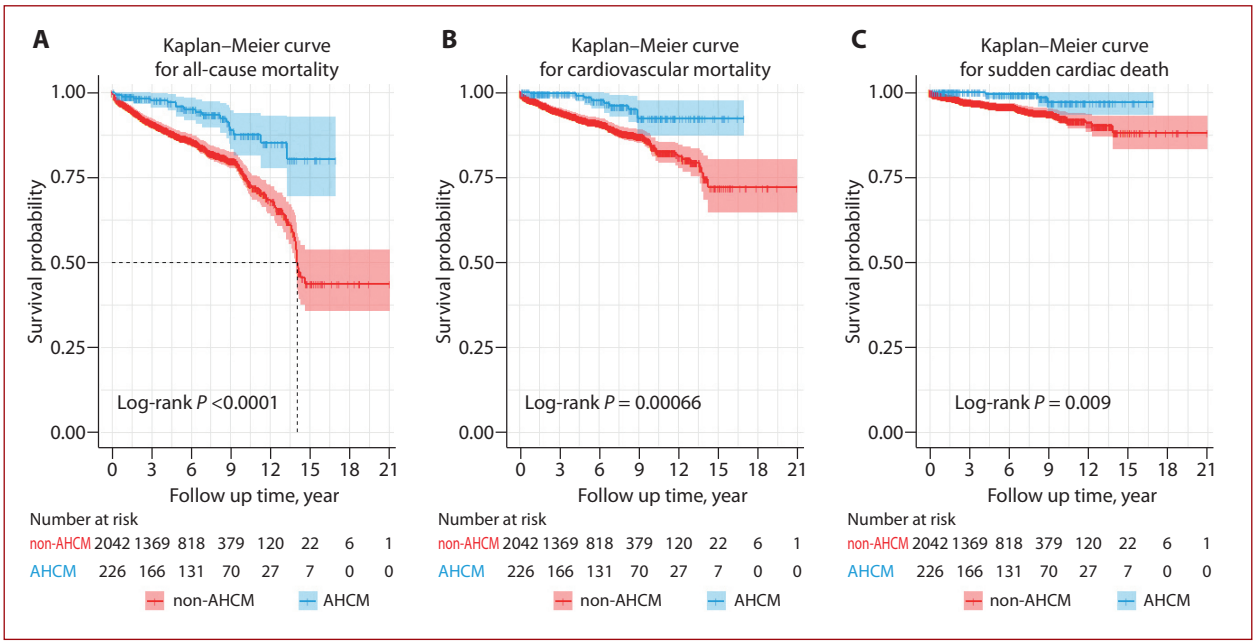


Figure 1. Kaplan–Meier curves for the unmatched cohort. **A.** All-cause mortality. **B.** Cardiovascular mortality/cardiac transplantation. **C.** Sudden cardiac death

Abbreviations: see — Table 1

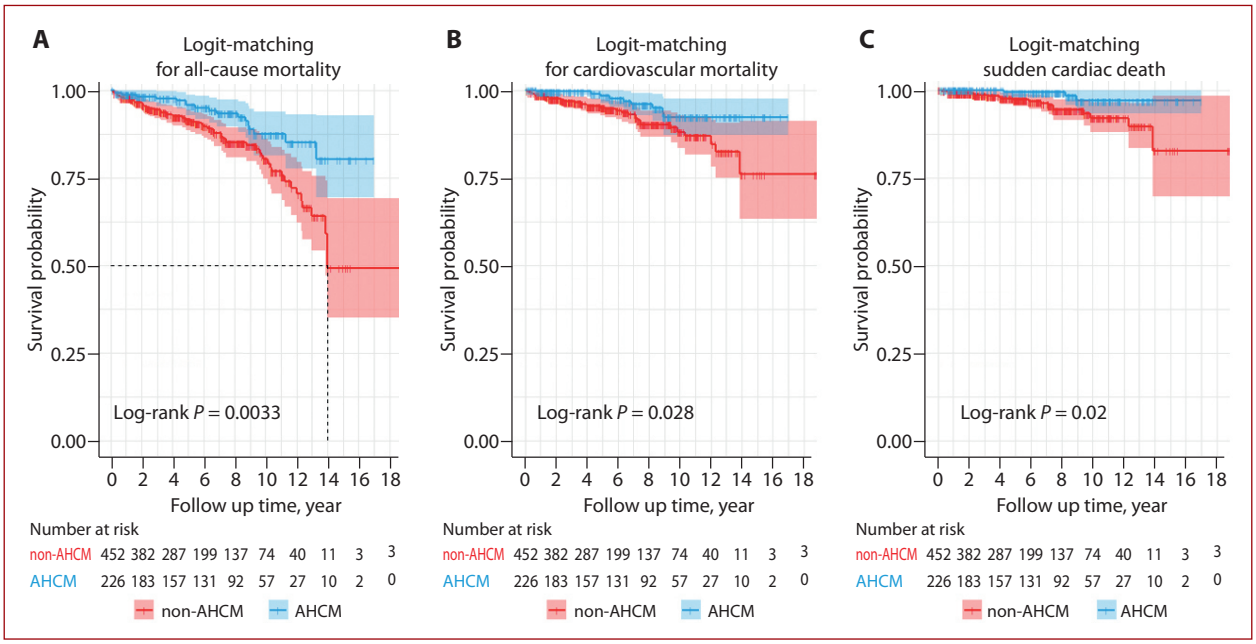


Figure 2. Kaplan–Meier curves for the matched cohort. **A.** All-cause mortality. **B.** Cardiovascular mortality/cardiac transplantation. **C.** Sudden cardiac death

Abbreviations: see — Table 1

Table 2. Multivariable Cox regression for primary all-cause mortality of the unmatched and the propensity score matched cohort

Variables	Unmatched cohort			Matched cohort		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
AHCM	0.608	0.323–1.147	0.13	0.461	0.271–0.784	0.004
Age	1.032	1.020–1.044	<0.001	1.040	1.022–1.059	<0.001
Ventricular arrhythmias	0.878	0.487–1.585	0.67	1.672	0.888–3.146	0.11
RA	0.571	0.299–1.089	0.09	0.224	0.030–1.688	0.15
LVEF	0.965	0.952–0.978	<0.001	0.976	0.953–0.999	0.04
Log (NT-proBNP)	3.658	2.581–5.184	<0.001	7.181	3.767–13.687	<0.001
NSVT	2.534	0.995–6.456	0.051	—	—	—
Atrial fibrillation	1.220	0.850–1.752	0.28	—	—	—
DBP	0.986	0.974–0.997	0.02	—	—	—
QT	0.995	0.992–0.998	<0.001	—	—	—
LV diameter	1.003	0.978–1.029	0.80	—	—	—
Betablocker	0.593	0.417–0.842	0.003	—	—	—
Concordance		0.797			0.730	

Abbreviations: CI, confidence interval; HR, hazard ratio; RA, right atrial; other — see Table 1

Table 3. Multivariable Cox regression for cardiovascular mortality/cardiac transplantation of the unmatched and the propensity score matched cohort

Variables	Unmatched cohort			Matched cohort		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
AHCM	0.506	0.218–1.178	0.11	0.506	0.239–1.069	0.07
Male	1.015	0.685–1.505	0.94	0.485	0.260–0.904	0.02
Ventricular arrhythmias	0.991	0.522–1.882	0.98	2.318	1.064–5.052	0.03
Ca2+ antagonists	1.132	0.728–1.760	0.58	0.536	0.254–1.131	0.10
Log (NT-pro-BNP)	3.168	2.091–4.799	<0.001	10.114	4.085–25.045	<0.001
LVEF	0.956	0.939–0.973	<0.001	—	—	—
Creatinine	1.002	1.000–1.004	0.03	—	—	—
QTc	—	—	—	1.007	1.002–1.013	0.01
Concordance		0.789			0.753	

Abbreviations: see Tables 1 and 2

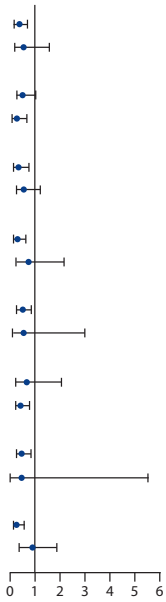
Table 4. Multivariable Cox regression for sudden cardiac death of the unmatched and the propensity score matched cohort

Variables	Unmatched cohort			Matched cohort		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
AHCM	0.189	0.025–1.403	0.10	—	—	—
DBP	0.982	0.960–1.004	0.11	0.955	0.920–0.992	0.02
QT	0.999	0.988–1.009	0.79	1.008	0.998–1.018	0.12
LV diameter	1.057	1.014–1.102	0.01	1.067	1.014–1.123	0.01
RV diameter	0.703	0.229–2.162	0.54	0.876	0.755–1.016	0.08
Log (NT-pro-BNP)	3.042	1.054–6.152	0.002	5.142	1.030–25.670	0.046
Ventricular arrhythmias	—	—	—	2.467	0.885–6.881	0.08
LBBB	—	—	—	8.654	1.665–44.993	0.01
IVS	—	—	—	1.126	1.035–1.226	0.006
Ca^{2+} antagonists	—	—	—	0.313	0.102–0.962	0.04
Concordance		0.769			0.816	

Abbreviations: see Tables 1 and 2

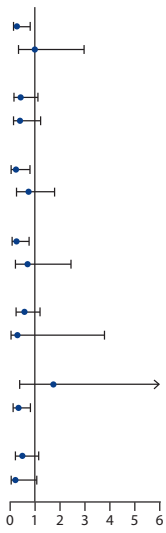
A **Hazard ratio for all-cause mortality**

Group	non-AHCM	AHCM	Adjusted HR (95% CI)	Adjusted *P*-value
Sex				
Male	338 (511)	173 (511)	0.369 (0.196, 0.698)	0.002
Female	114 (167)	53 (167)	0.554 (0.193, 1.586)	0.27
Age				
Age >60	174 (270)	96 (270)	0.514 (0.257, 1.028)	0.06
Age ≤60	278 (408)	130 (408)	0.259 (0.098, 0.679)	0.006
NYHA class				
I–II	300 (440)	140 (440)	0.347 (0.162, 0.740)	0.006
III–IV	152 (238)	86 (238)	0.565 (0.259, 1.230)	0.15
AF				
No	392 (580)	188 (580)	0.306 (0.153, 0.610)	0.001
Yes	60 (98)	38 (98)	0.751 (0.260, 2.169)	0.6
Ventricular arrhythmias				
No	409 (610)	201 (610)	0.500 (0.283, 0.883)	0.02
Yes	43 (68)	25 (68)	0.528 (0.092, 3.023)	0.47
LV diameter				
LV diameter >50	93 (149)	56 (149)	0.670 (0.220, 2.040)	0.48
LV diameter ≤50	359 (529)	170 (529)	0.428 (0.229, 0.799)	0.008
LVEF				
LVEF >55%	421 (641)	220 (641)	0.456 (0.253, 0.820)	0.009
LVEF ≤55%	31 (37)	6 (37)	0.447 (0.036, 5.554)	0.53
Log(NT-proBNP)				
Log(NT-proBNP) >3	249 (361)	112 (361)	0.278 (0.133, 0.583)	0.001
Log(NT-proBNP) ≤3	203 (317)	114 (317)	0.847 (0.377, 1.903)	0.69



B **Hazard ratio for cardiovascular mortality**

Group	non-AHCM	AHCM	Adjusted HR (95% CI)	Adjusted *P*-value
Sex				
Male	338 (511)	173 (511)	0.267 (0.090, 0.791)	0.02
Female	114 (167)	53 (167)	0.935 (0.296, 2.956)	0.91
Age				
Age >60	174 (270)	96 (270)	0.403 (0.145, 1.116)	0.08
Age ≤60	278 (408)	130 (408)	0.347 (0.099, 1.216)	0.098
NYHA class				
I–II	300 (440)	140 (440)	0.181 (0.041, 0.802)	0.02
III–IV	152 (238)	86 (238)	0.709 (0.285, 1.767)	0.46
AF				
No	392 (580)	188 (580)	0.248 (0.084, 0.729)	0.01
Yes	60 (98)	38 (98)	0.669 (0.185, 2.413)	0.54
Ventricular arrhythmias				
No	409 (610)	201 (610)	0.533 (0.238, 1.190)	0.13
Yes	43 (68)	25 (68)	0.283 (0.021, 3.758)	0.34
LV diameter				
LV diameter >50	93 (149)	56 (149)	1.691 (0.406, 7.033)	0.47
LV diameter ≤50	359 (529)	170 (529)	0.296 (0.113, 0.777)	0.01
Log(NT-proBNP)				
Log(NT-proBNP) >3	249 (361)	112 (361)	0.481 (0.202, 1.150)	0.01
Log(NT-proBNP) ≤3	203 (317)	114 (317)	0.193 (0.035, 1.059)	0.06



C **Hazard ratio for SCD**

Group	non-AHCM	AHCM	Adjusted HR (95% CI)	Adjusted *P*-value
Sex				
Male	338 (511)	173 (511)	0.226 (0.051, 1.009)	0.05
Female	114 (167)	53 (167)	0.460 (0.027, 7.986)	0.59
Age				
Age >60	174 (270)	96 (270)	0.092 (0.010, 0.831)	0.03
Age ≤60	278 (408)	130 (408)	0.324 (0.068, 1.551)	0.16
AF				
No	392 (580)	188 (580)	0.238 (0.053, 1.070)	0.06
Yes	60 (98)	38 (98)	0.117 (0.006, 2.227)	0.15
Ventricular arrhythmias				
No	409 (610)	201 (610)	0.241 (0.054, 1.067)	0.06
Yes	43 (68)	25 (68)	0.283 (0.053, 12.631)	0.89
LV diameter				
LV diameter >50	93 (149)	56 (149)	0.914 (0.154, 5.419)	0.92
LV diameter ≤50	359 (529)	170 (529)	0.108 (0.014, 0.835)	0.03
Log(NT-proBNP)				
Log(NT-proBNP) >3	249 (361)	112 (361)	0.257 (0.057, 1.164)	0.08
Log(NT-proBNP) ≤3	203 (317)	114 (317)	0.302 (0.034, 2.654)	0.28

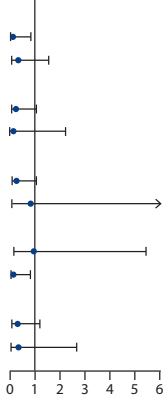


Figure 3. Forest plots of subgroup analyses.
A. All-cause mortality.
B. Cardiovascular mortality/cardiac transplantation.
C. Sudden cardiac death.
The forest plots showing the difference of AHCM on the prognosis of HCM in different populations and different outcomes

Abbreviations: SCD, sudden cardiac death; other — see Tables 1 and 2

(NT-proBNP) >3. In the cardiovascular mortality/cardiac transplantation group, AHCM was also a protective predictor in the subgroups of male patients, with NYHA class I-II, LV diameter≤50 mm (Figure 3b), and, additionally, in the SCD subgroups aged > 60 years and with LV diameter ≤50 mm (Figure 3c).

DISCUSSION

To the best of our knowledge, this is one of the largest cohort studies of HCM in China. In our study, both in the matched and unmatched cohorts, we found that AHCM patients had a favorable prognosis, with lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD. According to the Cox proportional hazard regression model, AHCM was an independent prognostic predictor of all-cause mortality and an univariable prognostic predictor of cardiovascular mortality/cardiac transplantation and SCD in HCM. However, AHCM was not significant in multivariable Cox regression models for cardiovascular mortality/cardiac transplantation and SCD. Eventually, the subgroup analysis showed that in each subgroup AHCM was consistently a protective predictor of all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD.

Generally, the incidence of AHCM is relatively low, which is 3%–25% of HCM [3, 4, 20]. In our study, AHCM patients accounted for 10% of all HCM patients, which was similar to Western countries (1%–11%) but lower than reported in Japan (13%–25%) [3, 4, 21]. Compared with classical HCM, AHCM is more sporadic, with lower frequency of sarcomere mutations, more atrial fibrillation (AF), and different risk factors for SCD [20, 22, 23]. There are no strong specific recommendations to guide AHCM diagnosis, family screening, and patient risk stratification [19]. In our study, similar to previous results, AHCM patients had less familial HCM. AF, which was the most frequent morbid event in AHCM compared with other arrhythmias, was not significantly different in AHCM and non-AHCM. Additionally, ventricular arrhythmias and ventricular tachycardia were rarer in AHCM, which may be the reason for better AHCM prognosis in our study. Previous studies have also reported that malignant ventricular arrhythmias and mortality are associated with apical aneurysms in AHCM patients in Western countries, compared with a 2% incidence of apical aneurysms in HCM patients and a 13%–15% incidence of apical aneurysms in AHCM patients [24–26]. In our study, apical ventricular aneurysm was present in only a few patients, which may be another reason for the favorable prognosis in AHCM. Moreover, the extent of myocardial hypertrophy is also an important prognostic factor in AHCM patients [10, 20, 27]. In this study, both IVS thickness and maximal LV wall thickness of AHCM were smaller than those of non-AHCM, and left ventricular outflow tract obstruction was less common, which may also contribute to the favorable prognosis in AHCM.

In our study, the Cox proportional hazard regression model showed that AHCM was an independent prognostic predictor of all-cause mortality and an univariable protective predictor of cardiovascular mortality/cardiac transplantation and SCD in HCM. To better investigate the effect of AHCM on the prognosis in HCM, we performed a subgroup analysis, and the results suggested that AHCM was invariably a protective predictor of all-cause mortality in the following subgroups: males, NYHA class I–II, age ≤60 years, LV diameter ≤50 mm, LVEF >55%, and Log (NT-proBNP) >3. In the case of cardiovascular mortality/cardiac transplantation, AHCM was also a protective predictor of SCD in these subgroups: male, NYHA class I–II, and LV diameter ≤50 mm subgroups, as well as in the age >60 years and LV diameter ≤50 mm.

Regarding long-term AHCM prognosis, most research has shown that AHCM usually has a favorable prognosis [4–10]. A meta-analysis showed that annual mortality in AHCM was lower than that in non-AHCM patients (0.81% to 1.55%) [28, 29]. Furthermore, Eriksson et al., in their retrospective study of 105 North American ACHM patients followed up for 15 years found that there were no SCD and that cardiovascular mortality was 1.9% [5]. Kim et al. [30] used the inverse probability of treatment weighted method and the propensity score matching method to compare the long-term outcomes of all-cause and cardiac mortality rates between AHCM and asymmetric HCM [30], and the results showed that the all-cause mortality rates of AHCM and asymmetric HCM were similar. However, AHCM had lower cardiovascular mortality [30]. Zadok et al. [28] evaluated the risk of SCD in AHCM patients based on the HCM Risk-SCD 5-year prediction model, and the results showed that AHCM had a lower 5-year SCD risk [28].

In our study, the annual all-cause mortality rates of AHCM and non-AHCM were 0.1% and 2.6%, respectively. The annual rate of cardiovascular mortality/cardiac transplantation in AHCM was 0.07%, and that in non-AHCM was 1.5%. For SCD, annual mortality in AHCM was 0.02% and non-AHCM was 0.7%. The Kaplan–Meier curves showed that AHCM had lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD both before and after matching. However, Moon et al. [4] and Klarich et al. [10] reported that AHCM prognosis was not as favorable as previously reported. Meanwhile, recent data have shown that the annual cardiovascular mortality rate in AHCM is 0.5% to 4%, approaching that of classic HCM [17]. Notably, an earlier study reported that one-third of AHCM patients in Western countries may develop adverse clinical events and potentially life-threatening complications such as myocardial infarction, ventricular arrhythmias, and stroke [5, 24]. Similarly, ACHM patients in our study still experienced ventricular arrhythmias and SCD, but there were fewer patients than those with non-AHCM. Altogether, combining the results of all studies, most of these studies concluded that ACHM patients had a favorable prognosis

compared with other forms of HCM, but not for all AHCM patients [4, 10, 31]. Therefore, it is necessary to consider and manage ACHM patients clinically.

Current management of HCM focuses on symptom relief, risk stratification, prevention of sudden cardiac death, and family screening [32, 33]. Medical therapy for apical HCM patients is similar to that for typical HCM patients [3, 16]. Currently, mavacamten, a first-class, selective, and reversible β-myosin allosteric inhibitor, which can inhibit the binding of myosin and actin and reduce the number of actin-myosin cross-bridges, has been shown to improve NYHA class, health status, cardiac biomarkers, and cardiac structure of patients [33, 34], but mainly for obstructive HCM. However, ACHM patients are less likely to have LVOT obstruction. Therefore, better clinical treatment of AHCM is expected.

In this cohort study, there were numerous covariate imbalances, and the number of patients in the AHCM group was significantly different from that in the non-AHCM group before matching. This can make the accuracy of unmatched cohort results questionable. Therefore, to adjust for potential confounding bias in the clinical features of AHCM and non-AHCM patients, we used 1:2 propensity score matching. Our results showed that the AHCM prognosis was favorable both before and after matching, which was consistent with most previous studies. Given the diversity of prognoses in AHCM in different studies, its role in HCM risk stratification should not be disregarded. Furthermore, the incidence of AHCM is low, and the lack of risk predictors and guidelines makes it a clinical challenge to predict which patients are at risk for adverse events. Therefore, more and larger studies are required to explore the prognosis in AHCM and reach a consensus or issue guidelines.

Study limitations

There are some limitations to this study. First, this is a multicenter cohort study with patients from 13 tertiary centers, so there may be some heterogeneity among the different hospitals. Second, genetic testing of patients was not performed in our study, so differences in gene mutations between AHCM and non-AHCM could not be investigated. Third, LGE is closely related to the prognosis in cardiomyopathy, but there were too many missing data in this study, making it impossible to compare LGE outcomes between the two groups in this study. Fourth, depending on the pattern of hypertrophy, AHCM has been described as "pure AHCM" and "mixed AHCM", but in our study, we did not distinguish between them. Finally, the medications were only recorded during the in-hospital treatment of the patients, and no follow-up data were recorded, which we did not further analyze in our study.

CONCLUSION

Patients with AHCM have a favorable prognosis, with lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD both before and after matching. Furthermore, AHCM was an independent prognostic predictor of all-cause mortality and an univariable prognostic predictor of cardiovascular mortality/ cardiac transplantation and SCD in HCM patients.

Article information

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REFERENCES

1. Antunes M, Scudeler TL. Hypertrophic cardiomyopathy. Int J Cardiol Heart Vasc. 2020; 27: 100503, doi: 10.1016/j.ijcha.2020.100503, indexed in Pubmed: 32309534.
2. Sakamoto T, Tei C, Murayama M, et al. Giant T wave inversion as a manifestation of asymmetrical apical hypertrophy (AAH) of the left ventricle. Echocardiographic and ultrasono-cardiotomographic study. Jpn Heart J. 1976; 17(5): 611–629, doi: 10.1536/ihj.17.611, indexed in Pubmed: 136532.
3. Paluszkiewicz J, Krasinska B, Milting H, et al. Apical hypertrophic cardiomyopathy: diagnosis, medical and surgical treatment. Kardiochir Torakochirurgia Pol. 2018; 15(4): 246–253, doi: 10.5114/kitp.2018.80922, indexed in Pubmed: 30647749.
4. Moon J, Shim CY, Ha JW, et al. Clinical and echocardiographic predictors of outcomes in patients with apical hypertrophic cardiomyopathy. Am J Cardiol. 2011; 108(11): 1614–1619, doi: 10.1016/j.amjcard.2011.07.024, indexed in Pubmed: 21890076.
5. Eriksson MJ, Sonnenberg B, Woo A, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002; 39(4): 638–645, doi: 10.1016/s0735-1097(01)01778-8, indexed in Pubmed: 11849863.
6. Kitaoka H, Doi Y, Casey SA, et al. Comparison of prevalence of apical hypertrophic cardiomyopathy in Japan and the United States. Am J Cardiol. 2003; 92(10): 1183–1186, doi: 10.1016/j.amjcard.2003.07.027, indexed in Pubmed: 14609593.
7. An S, Fan C, Yan L, et al. Comparison of Long-Term Outcome between Apical and Asymmetric Septal Hypertrophic Cardiomyopathy. Cardiology. 2017; 136(2): 108–114, doi: 10.1159/000448239, indexed in Pubmed: 27595481.
8. Yan L, Wang Z, Xu Z, et al. Two hundred eight patients with apical hypertrophic cardiomyopathy in China: clinical feature, prognosis, and comparison of pure and mixed forms. Clin Cardiol. 2012; 35(2): 101–106, doi: 10.1002/clc.20995, indexed in Pubmed: 22125122.
9. Lee CH, Liu PY, Lin LJ, et al. Clinical features and outcome of patients with apical hypertrophic cardiomyopathy in Taiwan. Cardiology. 2006; 106(1): 29–35, doi: 10.1159/000092590, indexed in Pubmed: 16612066.

10. Klarich KW, Attenhofer Jost CH, Binder J, et al. Risk of death in long-term follow-up of patients with apical hypertrophic cardiomyopathy. Am J Cardiol. 2013; 111(12): 1784–1791, doi: 10.1016/j.amjcard.2013.02.040, indexed in Pubmed: 23540548.
11. Okishige K, Sasano T, Yano K, et al. Serious arrhythmias in patients with apical hypertrophic cardiomyopathy. Intern Med. 2001; 40(5): 396–402, doi: 10.2169/internalmedicine.40.396, indexed in Pubmed: 11393409.
12. Wilson P, Marks A, Rastegar H, et al. Apical hypertrophic cardiomyopathy presenting with sustained monomorphic ventricular tachycardia and electrocardiographic changes simulating coronary artery disease and left ventricular aneurysm. Clin Cardiol. 1990; 13(12): 885–887, doi: 10.1002/clc.4960131213, indexed in Pubmed: 2282734.
13. Partanen J, Kupari M, Heikkilä J, et al. Left ventricular aneurysm associated with apical hypertrophic cardiomyopathy. Clin Cardiol. 1991; 14(11): 936–939, doi: 10.1002/clc.4960141115, indexed in Pubmed: 1764832.
14. Cubukçu AA, Scott PJ, Williams GJ. Apical hypertrophic cardiomyopathy presenting as acute subendocardial myocardial infarction. Int J Cardiol. 1993; 38(3): 329–332, doi: 10.1016/0167-5273(93)90254-e, indexed in Pubmed: 8463017.
15. Badhiwala JH, Karmur BS, Wilson JR. Propensity score matching: a powerful tool for analyzing observational nonrandomized data. Clin Spine Surg. 2021; 34(1): 22–24, doi: 10.1097/BSD.0000000000001055, indexed in Pubmed: 32804684.
16. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014; 35(39): 2733–2779, doi: 10.1093/eurheartj/ehu284, indexed in Pubmed: 25173338.
17. Hughes RK, Knott KD, Malcolmson J, et al. Apical hypertrophic cardiomyopathy: the variant less known. J Am Heart Assoc. 2020; 9(5): e015294, doi: 10.1161/JAHA.119.015294, indexed in Pubmed: 32106746.
18. Jan MF, Todaro MC, Oreto L, et al. Apical hypertrophic cardiomyopathy: Present status. Int J Cardiol. 2016; 222: 745–759, doi: 10.1016/j.ijcard.2016.07.154, indexed in Pubmed: 27521551.
19. Minami Y, Kajimoto K, Terajima Y, et al. Clinical implications of midventricular obstruction in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2011; 57(23): 2346–2355, doi: 10.1016/j.jacc.2011.02.033, indexed in Pubmed: 21636036.
20. Patel H, Ko Ko NL, Kumar S, et al. "Acing" the hidden spade: review of diagnosis, follow-up, prognosis, and various associations of apical variant hypertrophic cardiomyopathy. Cureus. 2019; 11(1): e3979, doi: 10.7759/cureus.3979, indexed in Pubmed: 30967979.
21. Ho HH, Lee KLF, Lau CP, et al. Clinical characteristics of and long-term outcome in Chinese patients with hypertrophic cardiomyopathy. Am J Med. 2004; 116(1): 19–23, doi: 10.1016/j.amjmed.2003.09.020, indexed in Pubmed: 14706661.
22. Gruner C, Care M, Siminovitch K, et al. Sarcomere protein gene mutations in patients with apical hypertrophic cardiomyopathy. Circ Cardiovasc Genet. 2011; 4(3): 288–295, doi: 10.1161/CIRCGENETICS.110.958835, indexed in Pubmed: 21511876.
23. Klarich KW, Attenhofer Jost CH, Binder J, et al. Risk of death in long-term follow-up of patients with apical hypertrophic cardiomyopathy. Am J Cardiol. 2013; 111(12): 1784–1791, doi: 10.1016/j.amjcard.2013.02.040, indexed in Pubmed: 23540548.
24. Chen CC, Lei MH, Hsu YC, et al. Apical hypertrophic cardiomyopathy: correlations between echocardiographic parameters, angiographic left ventricular morphology, and clinical outcomes. Clin Cardiol. 2011; 34(4): 233–238, doi: 10.1002/clc.20874, indexed in Pubmed: 21400548.
25. Rowin EJ, Maron BJ, Haas TS, et al. Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. J Am Coll Cardiol. 2017; 69(7): 761–773, doi: 10.1016/j.jacc.2016.11.063, indexed in Pubmed: 28209216.
26. Moro E, D'Angelo G, Nicolosi GL, et al. Long-term evaluation of patients with apical hypertrophic cardiomyopathy. Correlation between quantitative echocardiographic assessment of apical hypertrophy and clinical-electrocardiographic findings. Eur Heart J. 1995; 16(2): 210–217, doi: 10.1093/oxfordjournals.eurheartj.a060887, indexed in Pubmed: 7744093.
27. Huang G, Fadl SA, Sukhotski S, et al. Apical variant hypertrophic cardiomyopathy "multimodality imaging evaluation". Int J Cardiovasc Imaging. 2020; 36(3): 553–561, doi: 10.1007/s10554-019-01739-x, indexed in Pubmed: 31853820.
28. Zadok O, Hasdai D, Witberg G, et al. Calculated risk for sudden cardiac death in patients with apical versus nonobstructive nonapical hypertrophic cardiomyopathy. Am J Cardiol. 2018; 122(9): 1551–1556, doi: 10.1016/j.amjcard.2018.07.014, indexed in Pubmed: 30197054.
29. Pelliccia F, Pasceri V, Limongelli G, et al. Working Group on Cardiomyopathies and Pericardial Diseases of the Italian Society of Cardiology. Long-term outcome of nonobstructive versus obstructive hypertrophic cardiomyopathy: A systematic review and meta-analysis. Int J Cardiol. 2017; 243: 379–384, doi: 10.1016/j.ijcard.2017.06.071, indexed in Pubmed: 28747036.
30. Kim SH, Kim SO, Han S, et al. Long-term comparison of apical versus asymmetric hypertrophic cardiomyopathy. Int Heart J. 2013; 54(4): 207–211, doi: 10.1536/ihj.54.207, indexed in Pubmed: 23924932.
31. Yang K, Song YY, Chen XY, et al. Apical hypertrophic cardiomyopathy with left ventricular apical aneurysm: prevalence, cardiac magnetic resonance characteristics, and prognosis. Eur Heart J Cardiovasc Imaging. 2020; 21(12): 1341–1350, doi: 10.1093/ehjci/jeaa246, indexed in Pubmed: 32888301.
32. Pysz P, Rajtar-Salwa R, Smolka G, et al. Mavacamten — a new disease-specific option for pharmacological treatment of symptomatic patients with hypertrophic cardiomyopathy. Kardiol Pol. 2021; 79(9): 949–954, doi: 10.33963/KP.a2021.0064, indexed in Pubmed: 34268723.
33. Ismayl M, Abbasi MA, Marar R, et al. Mavacamten treatment for hypertrophic cardiomyopathy: a systematic review and meta-analysis of randomized controlled trials. Curr Probl Cardiol. 2023; 48(1): 101429, doi: 10.1016/j.cpcardiol.2022.101429, indexed in Pubmed: 36167226.
34. Tian Z, Li L, Li X, et al. Effect of mavacamten on Chinese patients with symptomatic obstructive hypertrophic cardiomyopathy: The EXPLORER-CN randomized clinical trial. JAMA Cardiol. 2023; 8(10): 957–965, doi: 10.1001/jamacardio.2023.3030, indexed in Pubmed: 37639259.