Clinical, Echocardiographic and Cardiac MRI Predictors of Outcomes in Patients with Apical Hypertrophic Cardiomyopathy

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Research Article

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Abstract

Purpose: The clinical prognosis of apical hypertrophic cardiomyopathy (ApHCM) is still controversial in the previous study. Moreover, there are limited studies on the prognostic risk factors of ApHCM. The present study aimed to observe the clinical prognosis of ApHCM and to identify the predictors of poor prognosis in clinical, echocardiographic and cardiac magnetic resonance imaging.

Methods: A total of 126 patients with ApHCM were identified retrospectively from January 2008 to December 2018. Adverse events were defined as a composite of cardiac death, progressive heart failure, myocardial infarction, thromboembolic stroke, appropriate implantable cardioverter-defibrillator (ICD) interventions for ventricular tachycardia or ventricular fibrillation, and new-onset atrial fibrillation (AF).

Results: During a mean follow-up of 96.8±36.0 months, clinical events were observed in 34 (27.0%) patients. The patients who experienced events were older and had higher incidence of heart failure. The patients with clinical events had higher incidence of non-sustained ventricular tachycardia and had larger LAVI and thicker apical thickness than those without clinical events, and were more frequently with LGE presence. The peak systolic mitral annular velocity (s') was higher in patients with clinical events patients with events.

Conclusions: ApHCM was not as benign as expected. Age≥55 years，LAVI≥36.7 ml/m^2, s'≤6.7cm/s along with NSVT and LGE were independent risk factor for poor prognosis of ApHCM.

Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiovascular disease characterized by left ventricular hypertrophy and no other disease that can explain the degree of hypertrophy with the prevalence rate was 0.2% in the general population(1). Apical hypertrophic cardiomyopathy (ApHCM) is a relatively rare subtype of HCM, which mainly involves the left ventricular apex(2). In the Asian population, ApHCM patients account for about 25% of the total HCM population and 1% to 10% in the non-Asian population(3). Sakamoto et al. first described ApHCM in patients with "giant" T-wave negative and end diastolic left ventricular (LV) “spade-shaped” configuration measured by electrocardiogram and left ventriculography, respectively(4). Although it has been reported that ApHCM has a good prognosis in terms of cardiovascular mortality(5, 6), it has been found in recent years that about one third of ApHCM patients may experience adverse clinical events and potentially life-threatening complications, such as malignant arrhythmia, sudden cardiac death, heart failure, myocardial infarction, atrial fibrillation and stroke(7). Therefore, the aim of this study is to observe the clinical prognosis of ApHCM and to identify the predictors of poor prognosis in clinical, echocardiographic and cardiac magnetic resonance imaging (CMR).

Methods

Study population

A total of 675 patients were diagnosed with HCM in Nanjing Medical University Affiliated Wuxi No. 2 Hospital from January 2008 to December 2018. Among them, 142 ApHCM patients were identified.

The criteria for the diagnosis of ApHCM included a demonstration of otherwise unexplained left ventricular hypertrophy, confined predominantly to the left ventricular apex below the papillary muscle level, with an apical thickness >15 mm or a ratio of maximal apical to posterior wall thickness >1.5 at the end diastole using standard 2-dimensional transthoracic echocardiography or CMR(2). 16 patients were excluded for the following reasons: (1) age <18 years(N=2); (2) severe heart failure (NYHAIV, N=4), liver dysfunction(N=1), renal failure requiring dialysis treatment(N=2), severe valvular disease(N=1) and severe coronary artery disease(N=3); (3) inadequate clinical data(N=3). Finally, 126 patients were included in this retrospective study. The clinical characteristics, electrocardiography (ECG), echocardiography and CMR results of these 126 patients were gathered at presentation (**Figure 1**).

The study was approved by the institutional review boards and all subjects provided informed consent.

Echocardiography

Transthoracic two-dimensional echocardiography was performed with commercially available instruments (HP5500 color Doppler (USA) with the probe frequency of 2.5 and 2.4 MHz). Standard 2-dimensional measurements were obtained as recommended by the American Society of Echocardiography in the left lateral position(8). The maximum apical wall thickness was obtained from the standard apical 4- and 2-chamber views at end-diastole. The left atrial (LA) dimensions were measured at end-systole, and the LA volume was calculated using the area–length methods. The LA volume index was calculated as the LA volume divided by the body surface area. Early mitral inflow velocity (E) and late mitral inflow velocity (A) were measured using the pulsed wave Doppler method. Tissue Doppler-derived early diastolic mitral annular velocity (e’), late diastolic mitral annular velocity (a’), and peak systolic mitral annular velocity (s’) were measured from the septal corner of the mitral annulus in the apical 4-chamber view. The ratio of the E velocity to the e' septal and lateral Left ventricular ejection fraction was calculated from LV annular velocities were averaged to provide an index of diastolic function. Left ventricular ejection fraction was calculated from LV volumes using Simpson’s rule. The echocardiographic data were gathered and analyzed by 2 experienced echocardiographers and were recorded on videotapes or hard disc.

CMR images acquisition and analysis

CMR was performed with a 1.5 T MRI scanner (Magnetom Avanto, Siemens, Germany). Transverse and sagittal dark blood images were obtained by half-Fourier acquisition single-shot turbo spin-echo sequence. Breath-hold cine steady-state free precession images were performed in standard views with full LV coverage, including LV two-chamber, four-chamber, left ventricular outflow tract, and eight slices of short-axis views. Late gadolinium enhancement (LGE) images were acquired 10-15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA with breath-held segmented inversion-recovery sequence (inversion time, 240 to 300 ms) acquired in the same views as the cine images.

Follow-up

Clinical follow-ups were initiated from the time of diagnosis of ApHCM. The primary endpoint was a composite of cardiac death, progressive HF [with an increase of at least one New York Heart Association (NYHA) functional class], myocardial infarction, thromboembolic stroke, appropriate implantable cardioverter-defibrillator (ICD) interventions for ventricular tachycardia or ventricular fibrillation, and new-onset atrial fibrillation (AF).

Statistical analyses

All analyses were performed with IBM SPSS Statistics 20.0 software. Continuous normally distributed data were presented as mean ± SD, and were compared using independent-samples t-test. Non-normally distributed continuous data were displayed as median and interquartile range (25–75%), and were compared using non-parametric test (Mann–Whitney U test). Categorical data were presented as number and percentage, and were compared using the $\chi 2$ or Fisher's exact test. Cox analysis was used to identify univariable and multivariable predictors of clinical events. Variables exhibiting a $p < 0.1$ in the univariate analysis were tested in the multivariable analysis. Receiver operating characteristics curves were used to examine the accuracy of variables in predicting the clinical outcomes. The survival analysis was estimated by the Kaplan–Meier method. Differences in survival between groups were assessed using the log-rank test. A two-tailed P value <0.05 was considered statistically significant.

Results

Prognostic data

The whole study group comprised 126 patients, and their mean age was 58.3±10.4 years (54.0% were male). During a mean follow-up of 96.8±36.0 months, clinical events were observed in 34 (27.0%) patients, representative picture is shown in **Figure 2**. The clinical events during the follow-up periods are listed in **Table 1**. A total of 6 patients (4.8%) died during the monitoring period. There are 17(13.5%) patients had progressive heart failure, and 5 patients (4.0%) experienced thromboembolic stroke. There were 7(5.6%) patients who were appropriate implantable cardioverter-defibrillator (ICD) interventions for ventricular tachycardia or ventricular fibrillation Nonfatal myocardial infarction occurred in 3 (2.4%) patients without significant coronary artery disease and was confirmed by coronary angiography in both cases. In addition, 8(6.3%) patients developed new onset atrial fibrillation.

Baseline characteristics of study patients

The patients were divided into two groups according to whether the clinical event occurred or not. Baseline characteristics of the study population are summarized in **Table 2**. The patients who experienced events were older (62.6±7.0 vs. 56.8±11.0 years, p=0.005) and had higher incidence of heart failure (38.2% vs. 16.3%, p=0.015) than the patients who experienced no events. No significant differences were found in other clinical characteristics between the 2 groups.

ECG and echocardiography results

The patients with clinical events had higher incidence of non-sustained ventricular tachycardia (38.2% vs. 17.4%, p=0.018) and had larger LAVI (45.2±4.4 vs. 40.4±11.3 ml/m2, p=0.001) and thicker apical thickness (21.2±3.3 vs. 18.9±4.0mm, p=0.006) than those without clinical events. The peak systolic mitral annular velocity (s') was lower (5.9±0.8 vs. 6.5±0.9 cm/s, p=0.001) in patients with clinical events. The detailed ECG and echocardiography information are presented in **Table 3** and **Table 4.**

CMR results

CMR results was listed in **Table 5**. Compared with patients without clinical events, patients with events were more frequently with LGE presence (82.4% vs. 62.0, p=0.030). There are no significantly difference in other parameters between the 2 subgroups.

Predictors of clinical events

The results of the Cox Univariate regression analysis are listed in **Table S1-4**(Data in **Supplementary materials**).

The results of the Cox multivariate regression analysis are listed in **Figure 3 and Table S5**(Data in **Supplementary materials**). In multivariate analysis, the age, LAVI, S', NSVT, LGE presence and LGE of LV mass were independent risk factors for poor prognosis. ROC curve analysis of continuous variables in risk factors showed that age≥55 years、LAVI≥36.7 ml/m^2, S'≤6.7cm/s were the best cut-off value. Kaplan-Meier curves of event-free survival since the initial presentation according to the risk factors showed that the patients who also had an older age, a larger LAVI, a lower S' along with NSVT and LGE presence experienced significantly worse clinical outcomes during follow-up (**Figure 4**).

Discussion

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited cardiomyopathy with genetic heterogeneity, characterized by asymmetric ventricular hypertrophy, which is one of the main causes of sudden exercise death in adolescents(9). ApHCM is a phenotypic variation of HCM, with hypertrophy predominantly at the left ventricular (LV) apical portion, with or without middle segment involvement and apical aneurysm formation(10). ApHCM was initially considered not to increase the risk of mortality, but recent data show that cardiac mortality is 0.5% to 4% per year, close to typical HCM(3). In our study, we found a mortality rate of 4.8% for ApHCM, which was similar to previous studies. Moreover, our study demonstrated that age≥55 years、LAVI≥36.7 ml/m^2, S'≤6.7cm/s along with NSVT and LGE were independent risk factor for poor prognosis of ApHCM.

Age and prognosis of ApHCM

Our study found that patients with events were older than those without. Moon et al. and Kim et al. have similar findings, which is related to the fact that older patients may have more cardiovascular risk factors

such as hypertension, diabetes, kidney disease or other complications such as cancer(7, 11). In addition, previous studies have found that sudden death in HCM patients is more common in young people(9, 12), while in our study, most of the patients with adverse events in ApHCM are elderly people, which may be related to the difference of hypertrophic sites for most of the patients with HCM are complicated with left ventricular outflow tract obstruction.

Echocardiographic parameters and prognosis of ApHCM

In our study, patients with adverse events had larger LAVI and lower s' than those without adverse events. Previous study reported that left atrial volume is closely related to left ventricular diastolic dysfunction, which reflects the severity degree of left ventricular diastolic dysfunction(13). Moreover, left atrial volume is considered to be an important prognostic factor, not only in the general population, but also in various cardiovascular diseases(14-16). Futhermore, Yang et al. reported that increased LA volume index was an independent predictor of cardiovascular events in HCM patients with the best cut-off value of 39 mL/m2(17). Our results suggested that increased LA volume was an independent predictor of adverse clinical outcomes such as cardiovascular death, progressive heart failure, and ischemic stroke in patients with ApHCM, and the best cut-off value was 36.7 mL/m2, which was close to previous research. In addition, decreased s’ velocity, which indicated impaired myocardial contractility, was an independent predictor of poor prognosis. Moon et al. have similar findings(7), and the cut-off value of s’ in their study was 6cm / s which is close to ours. Moreover, in their study, E/e’ ratio was also an independent predictor of poor prognosis, which was not in our study for this difference may come from patient selection and sample size.

NSVT and prognosis of ApHCM

NSVT is a risk factor for poor prognosis of ApHCM in our study, which is defined as ≥3 consecutive ventricular beats at a rate of ≥120 bpm and 30 s in duration on Holter monitoring (duration 24 hours) at or prior to evaluation. Previous studies have shown that asymptomatic and symptomatic NSVT accounted for 18% and 5%, and monomorphic ventricular tachycardia often occurs in ApHCM with aneurysm, which may be related to the reentry around the aneurysm(2). In our studies, the prevalence of NSVT was higher, accounted for 38.2% and 17.4% in ApHCM patients with or without adverse events, which may be related to the selected patients and the small sample size. In addition, Monserrat et al. found that NSVT was significantly associated with an increased risk of sudden death during a mean follow-up period of 2.6 years(18). O'mahony et al. confirmed that NSVT was an independent predictor of SCD in 3 765 HCM patients at a median follow-up of 5.7 years(19). Therefore, although ApHCM is a subtype of HCM, our study indicated that NSVT was also a risk factor for poor clinical prognosis.

LGE and prognosis of ApHCM

CMR can provide high-resolution myocardial images and accurately determine the location and degree of myocardial hypertrophy (such as apical hypertrophy) and the presence of apical aneurysms(20). The most important value of CMR is to accurately quantify and visualize the pattern of dense focal

extracellular matrix deposition, such as LGE due to alternative fibrosis, which is related to the clinical severity of ventricular arrhythmia and SCD(21). In HCM, LGE has been shown to be closely associated with disease progression, small intramural coronary artery dysplasia, adverse outcomes, and cardiac mortality(22), however, in patients with ApHCM, the relationship between the prognosis of LGE and ApHCM is unclear. In patients with ApHCM, our study found that LGE was also associated with poor prognosis and was an independent predictor of poor prognosis. A recent study showed that left ventricular weight ≥ 15% showed that the risk of SCD events increased by 2 times in those patients with low risk, and the probability of SCD events was estimated to be 6% at 5 years(23). In this cohort of 1293 patients, for every 10% increase in LGE, the relative risk of SCD events increased by 40%. In our study, LGE of left ventricular mass was not measured due to technical limitations, so further studies are needed to determine this point.

Limitations

First, this was a single center retrospective study. Therefore, our study subjects might not be representative of the overall patient population with ApHCM. Second, the sample size in this study was small and the follow-up was relatively short. Therefore, a study with a larger sample size and a long-term follow-up is needed. Third, no patients had genetic analysis in the present study, the correlation between genetic cause and poor prognosis remains unresolved. Fourth, selection of patients for device therapy may result in some selection bias with respect to the survival analysis. Fifth, previous studies suggested that LVAA was a predictor of poor prognosis(10, 24), but in this study, there was no significant difference between the two groups because there were fewer patients with LVAA. Finally, due to technical limitations, LGE of LV mass is not available in this study.

Conclusions

ApHCM was not as benign as expected. During a mean follow-up of 96.8±36.0 months, clinical events were observed in 34 (27.0%) ApHCM patients. Age≥55 years、LAVI≥36.7 ml/m^2, S'≤6.7cm/s along with NSVT and LGE were independent risk factor for poor prognosis of ApHCM.

Declarations

Acknowledgement

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Tables

Table 1. The clinical events during the follow-up periods in ApHCM patients.

Prognosis	Patients without events (%)
Cardiovascular mortality	6(4.8)
Progressive HF	17(13.5)
Thromboembolic stroke	5(4.0)
Appropriate ICD interventions for ventricular tachycardia or ventricular fibrillation	7(5.6)
Nonfatal myocardial infarction	3(2.4)
New-onset atrial fibrillation	8(6.3)
Any event	34(27.0)

Values are n (%).

ApHCM: apical hypertrophic cardiomyopathy; HF: heart failure; ICD: implantable cardioverter-defibrillator.

Table2. Baseline characteristics between ApHCM patients with or without adverse cardiovascular events.

Baseline clinical characteristics	Patients without events (N=93)	Patients with events (N=34)	*p* Value
Age	56.8±11.0	62.6±7.0	**0.005**
Male	18(47.1)	50(54.3)	1.0
BMI	25.4±2.0	24.7±3.3	0.228
Clinical symptoms			
Chest pain	57(62.0)	18(52.9)	0.416
Palpitation	42(45.7)	19(55.9)	0.323
Dyspnoea	22(23.9)	13(38.2)	0.122
Dizziness	17(18.5)	4(11.8)	0.433
Syncope	4(4.3)	3(8.8)	0.386
Asymptomatic	4(4.3)	1(2.9)	1.000
Medical history			
Ischemic heart disease	5(5.4)	4(11.8)	0.250
Heart failure	15(16.3)	13(38.2)	**0.015**
Diabetes mellitus	11(12.0)	6(17.6)	0.394
Hypertension	36(39.1)	17(50.0)	0.273
Stroke	5(5.4)	3(8.8)	0.444
Medication			
β-blockers	67(72.8)	24(70.6)	0.825
Calcium channel blockers	51(55.4)	19(55.9)	1.000
ACEI/ARBS	33(35.9)	13(38.2)	0.837
Antiplatelet	49(53.3)	17(50.0)	0.841
Statin	54(58.7)	19(55.9)	0.776
Anticoagulation	14(15.2)	8(23.5)	0.297

Values are mean ± standard deviation, n (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ApHCM: apical hypertrophic cardiomyopathy; BMI: body mass index.

Table 3. ECG characteristic between ApHCM patients with or without adverse cardiovascular events.

ECG	Patients without events (N=93)	Patients with events (N=34)	*p* Value
ST-T segment change	85(92.4)	33(97.1)	0.681
Negative T wave	70(76.1)	30(88.2)	0.214
Left ventricular high voltage	54(58.7)	18(52.9)	0.685
Ventricular premature beat	45(48.9)	19(55.9)	0.550
Non-sustained ventricular tachycardia	16(17.4)	13(38.2)	**0.018**
Atrial fibrillation	12(13.0)	9(26.5)	0.104
Abnormal Q wave	9(9.8)	7(20.6)	0.133
CLBBB	7(7.6)	5(14.7)	0.304

Values are n (%). ApHCM: apical hypertrophic cardiomyopathy; CLBBB: Complete left bundle branch block; ECG: electrocardiogram.

Table 4. Echocardiography characteristic between ApHCM patients with or without adverse cardiovascular events.

Echocardiography	Patients without events (N=93)	Patients with events (N=34)	*p* Value
LVEDD, cm	47.0±6.5	48.3±5.0	0.222
LVESD, cm	27.6±5.7	28.2±5.2	0.570
IVST, cm	11.9±3.0	12.0±3.0	0.832
PWT, cm	11.8±2.4	11.7±2.3	0.823
LA, cm	40.8±7.2	45.2±6.5	**0.003**
LAVI, ml/m2	40.4±11.3	45.2±4.4	**0.001**
Apical thickness	18.9±4.0	21.2±3.3	**0.006**
LVEF, %	62.9±5.6	61.0±7.8	0.184
Mitral inflow-E, m/s	0.63±0.16	0.66±0.17	0.364
Mitral inflow-A, m/s	0.69±0.18	0.72±0.25	0.483
Deceleration time, ms	209.3±25.2	217.3±28.3	0.130
Tissue Doppler velocity			
s', cm/s	5.9±0.8	6.5±0.9	**0.001**
e', cm/s	4.8±0.9	4.5±1.1	0.159
a', cm/s	7.5±1.2	7.2±0.9	0.118
E/e' ratio	13.1±5.5	14.9±5.6	**0.098**

Values are mean ±standard deviation.

ApHCM: apical hypertrophic cardiomyopathy; a', late diastolic septal mitral annular velocity of tissue Doppler; e', early diastolic septal mitral annular velocity of tissue Doppler; IVST, interventricular septal thickness; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; PWT, posterior wall thickness; s', systolic septal mitral annular velocity of tissue Doppler.

Table 5. MRI characteristic between ApHCM patients with or without adverse cardiovascular events.

MRI	Patients without events (N=93)	Patients with events (N=34)	*p* Value
LV systolic midcavity obstruction	64(69.6)	26(76.5)	0.511
LGE presence, n (%)	57(62.0)	28(82.4)	**0.030**
LVAA presence, n (%)	4(4.3)	2(5.9)	0.661

Values are n (%).

LGE: late gadolinium enhancement; LVAA: left ventricular apical aneurysm; MRI: magnetic resonance imaging.

Figures

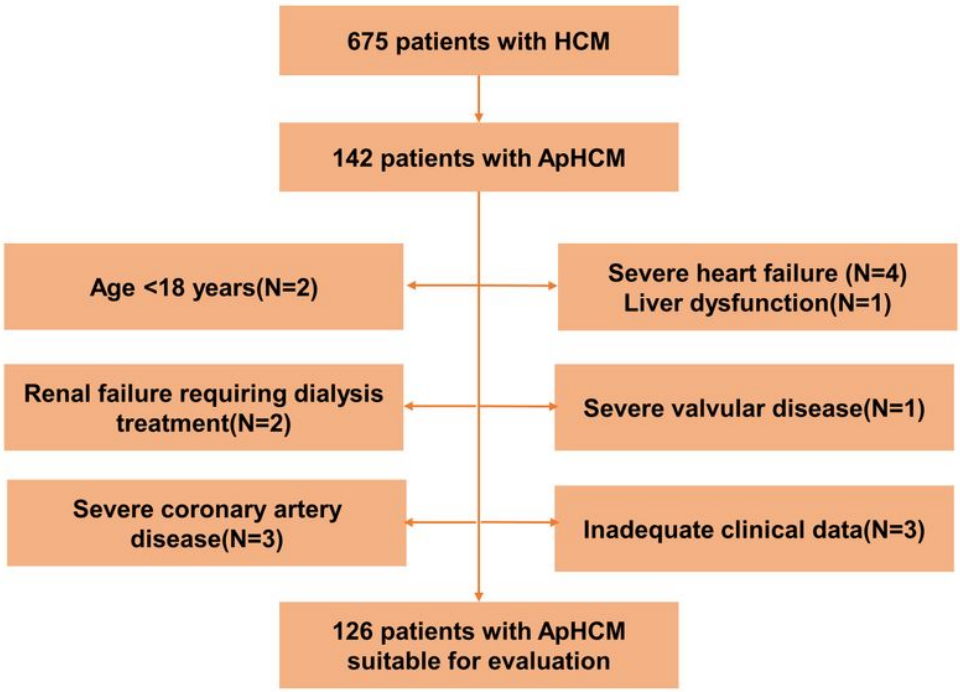

Figure 1

Study Flow Chart. HCM: hypertrophic cardiomyopathy; ApHCM: apical hypertrophic cardiomyopathy.

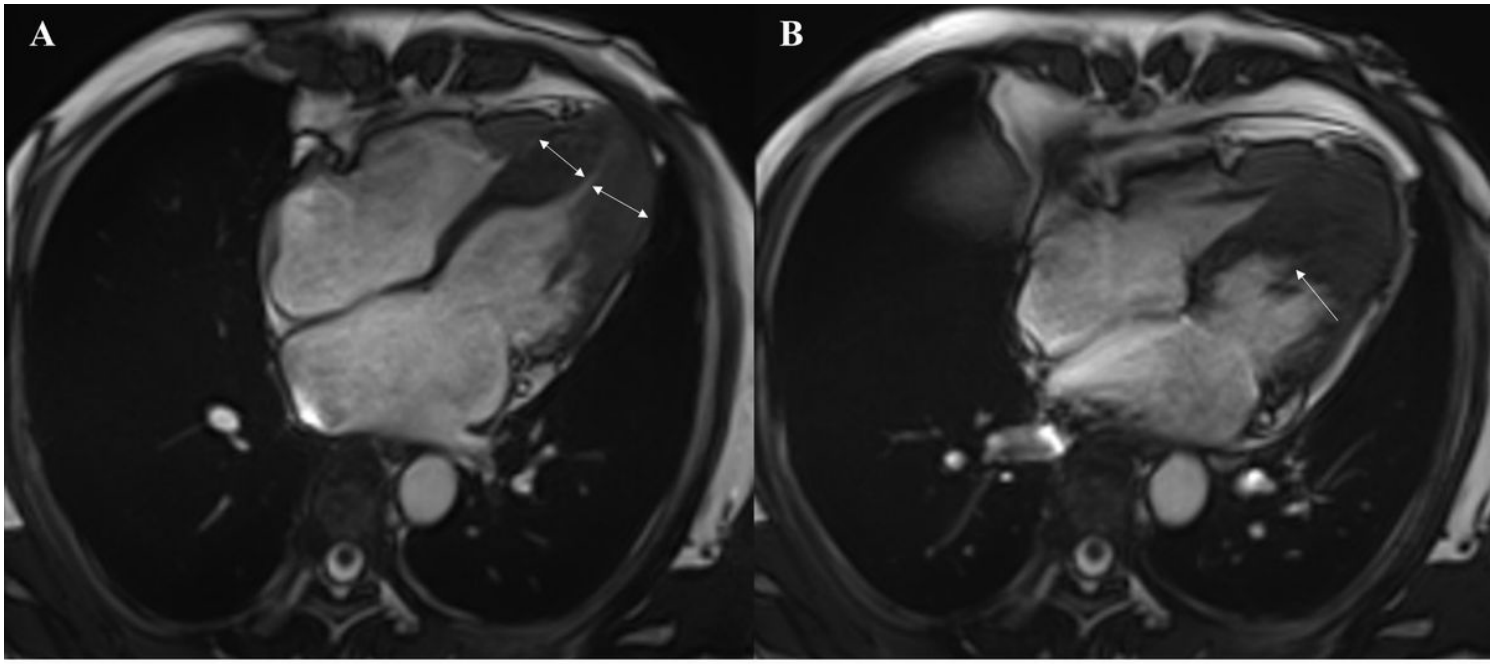

Figure 2

Representative CMR image of ApHCM. (A): Diastolic CMR in patients with ApHCM. White double arrows represent apical myocardial hypertrophy. (B): Systolic CMR in the same ApHCM patient. White single arrow indicates LV midcavity obstruction. CMR: Cardiac magnetic resonance imaging; ApHCM: apical hypertrophic cardiomyopathy.

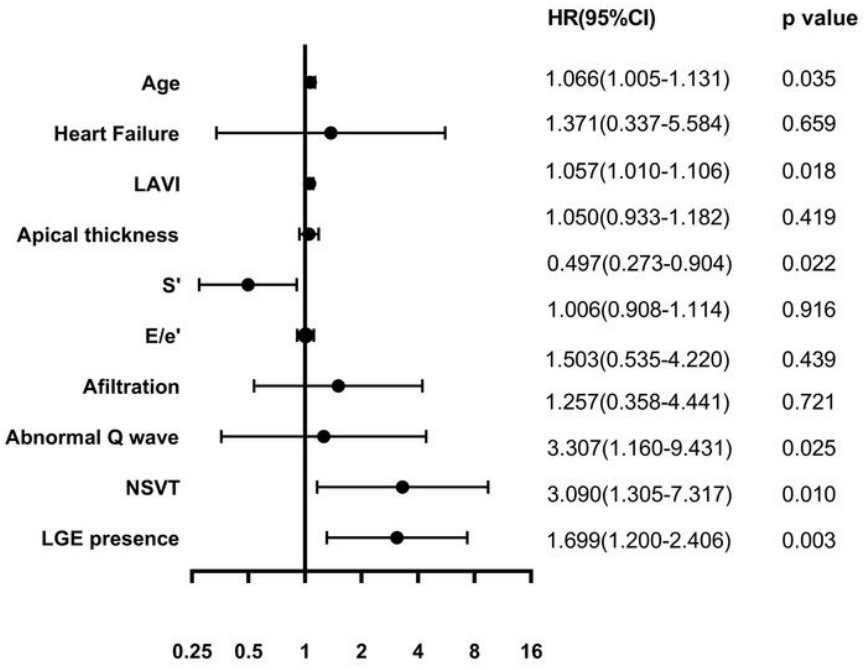

Figure 3

The forest graph for results of the cox multivariate regression analysis. The age, LAVI, s', NSVT, LGE presence were independent risk factors for poor prognosis. E/e': early mitral inflow/mitral annular early diastolic ratio. LAVI, left atrial volume index; LGE: late gadolinium enhancement; NSVT: Non-persistent ventricular tachycardia; s', systolic septal mitral annular velocity of tissue Doppler.

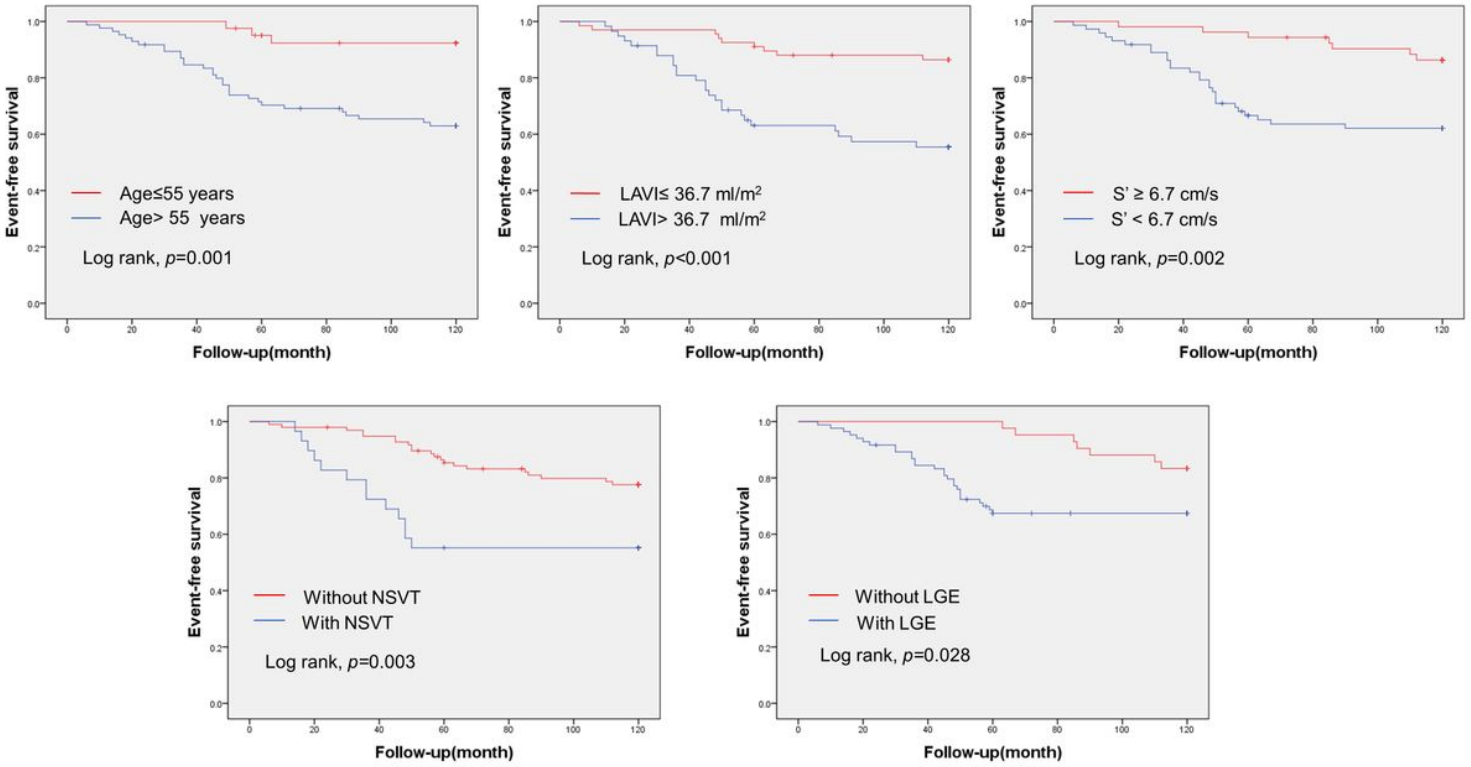

Figure 4

Kaplan-Meier curves of event-free survival since the initial presentation according to the risk factors. (A-E): ApHCM patients who had an older age, a larger LAVI, a lower S' along with NSVT and LGE presence experienced significantly worse clinical outcomes during follow-up. LAVI, left atrial volume index; LGE: late gadolinium enhancement; NSVT: Non-persistent ventricular tachycardia; s', systolic septal mitral annular velocity of tissue Doppler.

Supplementary Files

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- Supplementarymaterials.docx