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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Long-Term Outcomes of Patients With Apical Hypertrophic Cardiomyopathy Utilizing a New Risk Score

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ABSTRACT

BACKGROUND Apical hypertrophic cardiomyopathy (aHCM) is a distinct variant characterized by predominant hypertrophy of the left ventricle apex.

OBJECTIVES This study sought to describe aHCM patients' characteristics and develop a risk score for aHCM patients.

METHODS A total of 462 patients (age 58 ± 15 years, 68% male) diagnosed with aHCM were included. The primary endpoint was death, appropriate defibrillator discharge, or need for cardiac transplantation. Variables showing potential association with the composite endpoint were considered to develop an aHCM-specific risk score.

RESULTS At baseline, 67% patients were asymptomatic and 69% had no risk factors for sudden death. On echocardiography, the mean left ventricle ejection fraction, left atrial volume index, and right ventricular systolic pressure were 64% ± 8%, 36 ± 15 ml/m^2, and 32 ± 10 mm Hg, respectively, with 51(11%) demonstrating an apical aneurysm. Baseline cardiac magnetic resonance, performed in 246 (53%) patients, demonstrated delayed gadolinium enhancement in 170 (71%) patients (mean percentage of 4.9% ± 6.6%). At age 6.3 ± 4.8 years, the composite events occurred in 80 (17%, death in 62 [13%]) patients. The aHCM-specific risk score, incorporating age, apical aneurysm, left atrial volume index, serum creatinine, and right ventricular systolic pressure, demonstrated good discrimination (C-statistic = 0.75) with an expected to observed ratio of 1.02 and a calibration slope of 0.91. The risk score ranged between 0 and 8 points, with a higher score associated with higher composite events.

CONCLUSIONS aHCM constituted 6.8% of our overall HCM cohort with a composite event rate of 2.8%/year. The aHCM risk score provided good discrimination in predicting the composite primary endpoint, with a higher score associated with a higher rate of events. (JACC Adv. 2024;3:101235) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ACC/AHA = American College of Cardiology/American Heart Association

aHCM = apical HCM

CMR = cardiac magnetic resonance

HCM = hypertrophic cardiomyopathy

ICD = internal cardioverter defibrillator

LAVI = left atrial volume index

LGE = late gadolinium enhancement

LVEF = LV ejection fraction

LVOT = left ventricular outflow tract

NT-proBNP = N-terminal pro brain natriuretic peptide

RVSP = right ventricular systolic pressure

SCD = sudden cardiac death

VT = ventricular tachycardia

Hypertrophic cardiomyopathy (HCM) is a complex inherited myocardial disease with an estimated prevalence of 1 in 200 to 500 individuals, although the clinical symptoms and precise phenotypic characteristics vary across these demographics, making the diagnosis and challenging.[1-3] The most common phenotype is obstructive HCM with its characteristic finding of dynamic left ventricular outflow tract (LVOT) obstruction, which is present in ~70% patients.[1-3] The rest have the nonobstructive variant and many such patients have left ventricle (LV) hypertrophy predominantly in the apex.

Apical HCM (aHCM) was first described in Japan by Sakamoto et al in 1976,[4] constituting around 25% of all HCM cases among Asian populations and 1 to 10% of non-Asian populations.[5] In the absence of dynamic LVOT obstruction, a significant proportion of its symptomatology arises from diastolic dysfunction, abnormal lusitropy, microvascular angina, and low-stroke volume from a small cavity.[6,7] In the past, it was perceived that aHCM constituted a more benign variant, in terms of survival and risk of sudden cardiac death (SCD).[8] However, that is being challenged, along with the notion of low prevalence in the western population.[5,9,10] Recent HCM guidelines recommend various clinical and imaging-based characteristics to guide management and risk stratification of the full spectrum of HCM patients.[1-3] Given the phenotypic differences between obstructive hypertrophic cardiomyopathy (oHCM) and aHCM, understanding specific characteristics and their impact on future risk of adverse events in such patients might be important. In the current report, we sought to describe the characteristics and long-term outcomes of aHCM patients, along with developing an aHCM-specific risk score.

METHODS

STUDY DESIGN AND PARTICIPANTS. Out of the HCM registry of 6,785 patients aged ≥18 years, 462 (6.8%) patients had a diagnosis of aHCM following a clinical evaluation at the Cleveland Clinic between January 2001 and February 2021. This was based on typical features, such as asymmetric left ventricular hypertrophy confined primarily to the LV apex, an apical wall thickness of ≥15 mm, and a ratio of maximal apical to the posterior wall thickness of ≥1.5, experienced cardiologists diagnosed aHCM using 2-dimensional echocardiography and/or cardiac magnetic resonance (CMR). No other disease responsible for hypertrophy was detected during the diagnosis.[1-3] The following patients were excluded: 1) obstructive HCM patients (with dynamic LVOT and mid-cavitary obstruction without apical hypertrophy), confirmed following use of maximal provocative maneuvers, due to a different pathophysiologic profile; 2) end-stage renal disease requiring dialysis; 3) a prior myectomy to relieve LVOT obstruction; and 4) phenocopies like amyloidosis, Fabry's disease, and hypertensive heart disease of elderly. The observational registry is approved by the Institutional Review Board with waiver of individual informed consent. Patient data were anonymized to maintain confidentiality and privacy during the study.

Baseline and follow-up data were entered prospectively in the electronic medical records at the time of initial visit and subsequently manually extracted. The data collected included demographics, past medical, surgical, and social history, family history, medications, and laboratory results, as well as baseline surface echocardiogram, CMR (where available), electrocardiogram, and Holter monitor variables. History of non-sustained ventricular tachycardia (VT) (wide complex tachycardia at ≥120 beats/min, lasting >3 beats but <30 seconds or sustained VT lasting >30 seconds) and atrial fibrillation (AF) were recorded, based on history, electrocardiograms, Holter monitoring, and telemetry reviews in all patients.

Transthoracic echocardiography. All patients underwent comprehensive transthoracic echocardiograms at baseline using commercially available equipment (Philips, General Electric, and Siemens). All echocardiographic measurements, including left atrial dimensions and LV wall thickness, were made according to guidelines.[11] Obstructive HCM was excluded by a detailed assessment, including measurement of resting LVOT peak velocity by continuous-wave Doppler echocardiography, and estimation of pressure gradient by using simplified Bernoulli equation. Care was taken to avoid contamination of LVOT waveform by mitral regurgitation if present. In patients with resting LVOT gradients <30 mm Hg, provocative maneuvers, including Valsalva and amyl nitrite were used. Degree

of resting mitral regurgitation was assessed (none-severe) using multiple criteria.[12] In patients with suspected aHCM, imaging was adapted to fully visualize the apex taking care to avoid apical foreshortening.[13] In patients with suspected apical aneurysms with suboptimal endocardial delineation, contrast agent was utilized. Apical aneurysm and thrombus were recorded if present. In patients with missing data on echocardiographic reports, imaging data were manually collected from stored images.

Cardiac magnetic resonance. CMR examinations were performed on standard 1.5- and 3.0-T MR scanners (Philips Medical Systems), using electrocardiographic gating, as described previously.[14] LV ejection fraction (LVEF), maximal end-diastolic left ventricular wall thickness, indexed LV mass, and LV volumes were measured by standard off-line analysis of cine images. The presence and amount of myocardial fibrosis was assessed using phase-sensitive late gadolinium enhancement (LGE), as described previously.[14] LGE was determined semiautomatically, as a percentage of total myocardium (and defined as having an intensity >6 SDs above normal myocardium (identified using a user-specified region of interest). 6 SDs was chosen as it has been previously demonstrated as an optimal threshold for LGE detection, especially in HCM patients, correlating most with manual measurements,[15] as well as on histopathology.[16] Presence of LV apical aneurysm and thrombus were ascertained on cine and LGE images.

Outcomes assessment. The duration of follow-up ranged between initial office visit to event/last office follow-up. In addition to electronic medical record review, state and nationally available databases were queried to ascertain death. In addition, successful resuscitation from cardiac arrest or appropriate internal cardioverter defibrillator (ICD) shocks (with defibrillation threshold of >200 beats on electrogram reviews) was recorded.[17] Need for cardiac transplantation was documented. The primary endpoint was a composite of death, appropriate ICD discharge, and/or need for cardiac transplantation.

STATISTICAL ANALYSIS. Baseline clinical characteristics, echocardiographic, and CMR variables are reported as mean ± SD or median (IQR), as appropriate for continuous variables and as % for categorical variables. Comparison between continuous variables was performed using standard t testing and comparison between categorical variables was performed using chi-square. Univariable survival analysis for the primary endpoint was performed using the Cox regression model. Variables that showed potential association with composite endpoint ($P < 0.05$) were then considered for inclusion in the final model using a multivariable-adjusted Cox regression model with a backward stepwise selection procedure (P for exclusion = 0.20, P for inclusion = 0.10). The proportional hazard assumption was assessed based on scaled Schoenfeld. HRs with 95% CIs are reported. The performance of the final model was evaluated based on discrimination and calibration. Discrimination was via Harrell's C-statistic, while calibration was by comparing the ratio of the expected event-free survival probabilities based on the model to the observed probabilities. We performed an internal validation of the final model using the bootstrapping method with 500 random resampling, and model performance was re-evaluated as optimism-adjusted discrimination and calibration. Potential overfitting was accounted for using the bootstrap shrinkage factor. Lastly, a simple risk-prediction score was developed based on the variables included in the final model, similar to prior reports.[18,19] To create this risk score, each variable was categorized into clinically relevant categories and zero point was allocated to the lowest/reference categories. For all other categories, weighted score was assigned as unit(s) increase that is proportional to the least beta coefficient in the final model. The risk score for each patient is then calculated as the sum of the score across all the variables. All analysis was performed using STATA, 17 (StataCorp), and a 2-tailed P value <0.05 was considered statistically significant.

RESULTS

The baseline clinical and demographic characteristics of the study sample are shown in **Table 1**. The mean age was 58 ± 15 years, with 148 (32%) women. In the study sample, 47 patients (10%) had a family history of HCM, 45 (10%) had a family history of SCD, 78 (17%) had an ICD implanted for primary/secondary SCD prevention, 185 (40%) had a history of at least 1 episode of AF, and 310 (67%) reported no symptoms at baseline. Beta-blocker therapy was prescribed in 364 patients (79%), non-dihydropyridine calcium channel blockers in 138 patients (30%), warfarin in 78 patients (17%), and direct thrombin inhibitor anticoagulants in 42 patients (9%). Out of the patients who underwent genetic testing, 18/57 (32%) were gene-positive for an HCM-specific mutation.

TABLE 1 Baseline Clinical and Demographic Characteristics of the Study Sample (N = 462)

Age	58 ± 15
Age at first diagnosis of HCM, y	53 ± 16
Female	148 (32%)
White race	323 (70%)
Body surface area (kg/m^2)	1.99 ± 0.26
Hypertension	282 (61%)
Diabetes	84 (18%)
Hyperlipidemia	262 (56%)
Chronic obstructive pulmonary disease	45 (10%)
Stroke	35 (8%)
Family history of hypertrophic cardiomyopathy	47 (10%)
Genotype status (available in 57 patients)	
Negative	32 (56%)
Positive for HCM-specific mutation	18 (32%)
Variant of uncertain significance	7 (12%)
Family history of sudden cardiac death	45 (10%)
History of non-sustained ventricular tachycardia	76 (16%)
History of atrial fibrillation	185 (40%)
NYHA functional class	
I	310 (67%)
II	108 (23%)
III	39 (8%)
IV	5 (1%)
ACC/AHA SCD risk factors	
0	319 (69%)
1	120 (26%)
2 or more	23 (5%)
European Society of Cardiology SCD risk score	2.4 ± 1.9
European Society of Cardiology risk score categories	
<4%	397 (86%)
4%-6%	42 (9%)
>6%	23 (5%)
Giant T-wave inversions in precordial leads on electrocardiogram	45 (10%)
Beta-blocker	364 (79%)
Calcium channel blocker	138 (30%)
Disopyramide	15 (3%)
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	229 (50%)
New oral anticoagulants	42 (9%)
Warfarin	78 (17%)
Brain natriuretic peptide (data available in 65 patients), pg/dL	362.17 ± 353.94
N-terminal pro brain natriuretic peptide (data available in 192 patients), pg/dL	1,769.73 ± 2,663.38
Serum creatinine, mg/dL	1.09 ± 0.70
Internal cardioverter defibrillator	78 (17%)
Permanent pacemaker	14 (3%)

Values are mean ± SD or n (%).

ACC/AHA = American College of Cardiology/American Heart Association; HCM = hypertrophic cardiomyopathy; SCD = sudden cardiac death.

The data on imaging are reported in Table 2. The mean LVEF was 64% ± 8%, the mean LV mass index was 112.4 ± 36.0 g/m^2, and 51 (11%) had an apical aneurysm. A baseline CMR was done for 246 (53%) patients, with delayed gadolinium enhancement in 170 (71%) patients with a mean percentage of 4.9% ± 6.6% (median 2.7% [IQR: 0%-6.2%]). An apical aneurysm was reported in 29 (12%) of the patients who underwent CMR. The mean LGE% was significantly higher in patients with a documented apical aneurysm vs no apical aneurysm (14% ± 6% vs 3% ± 3%, $P < 0.001$).

FOLLOW-UP. During a mean follow-up period of 6.3 ± 4.8 years (median 5.3 years [IQR: 2.5-9.1 years]), the composite event occurred in 80 patients (17%), with 1-, 5-, and 10-year freedom from composite primary events of 97%, 87%, and 75%, respectively (Central Illustration). The breakdown of composite events was as follows: death in 62 patients, appropriate ICD discharge in 19 patients, and cardiac transplantation in 4 patients. In patients with multiple events, time to first event was utilized for censoring. Freedom from death at 1, 5, and 10 years was observed in 98%, 91%, and 80% patients, respectively. Based on that, the composite event rate and death rate were 2.8% and 2.1%/year, respectively. A transaortic apical myectomy was performed in 15 patients with zero in-hospital mortality. There were 9 additional pacemakers, and 54 ICDs implanted during follow-up, while 24 patients underwent percutaneous AF ablation. There were no documented additional strokes in follow-up. At the last follow-up, 74 (16%) patients had a documented apical aneurysm.

SURVIVAL ANALYSIS. Univariable analysis for the composite primary outcome, performed using the Cox regression model identified the following statistically significant variables: age (HR: 1.06; 95% CI: 1.04-1.08; $P < 0.001$), the presence of apical aneurysm (HR: 2.32; 95% CI: 1.24-4.34; $P = 0.008$), lower LVEF (HR: 0.96; 95% CI: 0.94-0.99; $P = 0.002$), left atrial volume index (LAVI) (HR: 1.82; 95% CI: 1.28-2.59; $P = 0.001$), higher right ventricular systolic pressure (RVSP) (HR: 1.04; 95% CI: 1.02-1.06; $P < 0.001$), hypertension (HR: 1.81; 95% CI: 1.04-3.12; $P = 0.03$), NYHA functional class IV (HR: 11.69; 95% CI: 3.59-38.08; $P < 0.001$), presence of AF (HR: 1.77; 95% CI [1.14-2.76] $P = 0.012$), serum creatinine (HR: 1.26; 95% CI: 1.09-1.45; $P < 0.001$), and 2 or more American College of Cardiology/American Heart Association (ACC/AHA) risk factors (HR: 2.68; 95% CI: 1.07-6.57, $P = 0.03$) (Table 3). In addition, in the subset where N-terminal pro brain natriuretic peptide (NT-ProBNP) and % LGE data were available, each were significantly associated with primary composite outcomes on univariable analysis: NT-ProBNP (HR: 1.21; IQR: 1.07-1.52; $P < 0.001$) and LGE% (HR: 1.04 IQR: 1.01-1.08; $P = 0.03$). Within the

CMR subset, 4/17 (23.5%) patients with LGE ≥ 15% and 6/70 (9%) with LGE% ≥5% had a primary composite event during 5.47 ± 4.3 years of follow-up, suggesting an event rate of 4.3%/year and 1.6%/year, respectively.

DEVELOPMENT OF aHCM RISK SCORE. Subsequently, variables were then considered for inclusion in the final multivariable-adjusted Cox regression model with a backward stepwise selection procedure (P for exclusion = 0.20, P for inclusion = 0.10). The 5 variables that remained statistically significant in the multivariable model were age, presence of an apical aneurysm, creatinine level, LAVI, and RVSP (Table 4). Ultimately, an aHCM-specific risk-prediction score was developed based on the beta coefficient of the variables included in the final model. Because LGE% and NT-ProBNP were not available in all patients, these were not entered into the model. Similarly, as ACC/AHA risk factors and European risk score represent a composite of multiple risk factors, they were not entered into the model.

The model demonstrated good discrimination with C-statistics of 0.75 and good calibration with expected to observed ratio = 1.02 and calibration slope = 0.91 (P value for the difference between expected and observed probabilities = 0.22) (Figure 1A). With an internal validation using the bootstrapping method with 500 random resampling, the model continued to show good discrimination with optimism-adjusted C-statistic = 0.71 and good calibration with expected to observed ratio = 0.99, optimism-adjusted calibration slope = 0.89 (P value for the difference between expected and observed probabilities = 0.23) (Figure 1B).

Over the study period, there was a graded increase in the observed rate of the composite primary endpoint with an increasing aHCM risk score with distribution as follows: 17/214 (8% overall or 1.3%/year) among those with a risk score of 0, 22/146 (15% overall or 2.4%/year) among those with risk score of 1, 24/64 (38% overall or 6%/year) and 17/38 (45% overall or 7%/year) among those with a risk score of ≥3. Compared to patients with risk score = 0, the HRs for the composite endpoints were 2.85 (95% CI: 1.50-5.41), 6.28 (95% CI: 3.36-11.7), and 11.3 (95% CI: 5.69-22.6) for those with risk score = 1, 2, and ≥3, respectively (Figure 2) ($P < 0.001$ for all).

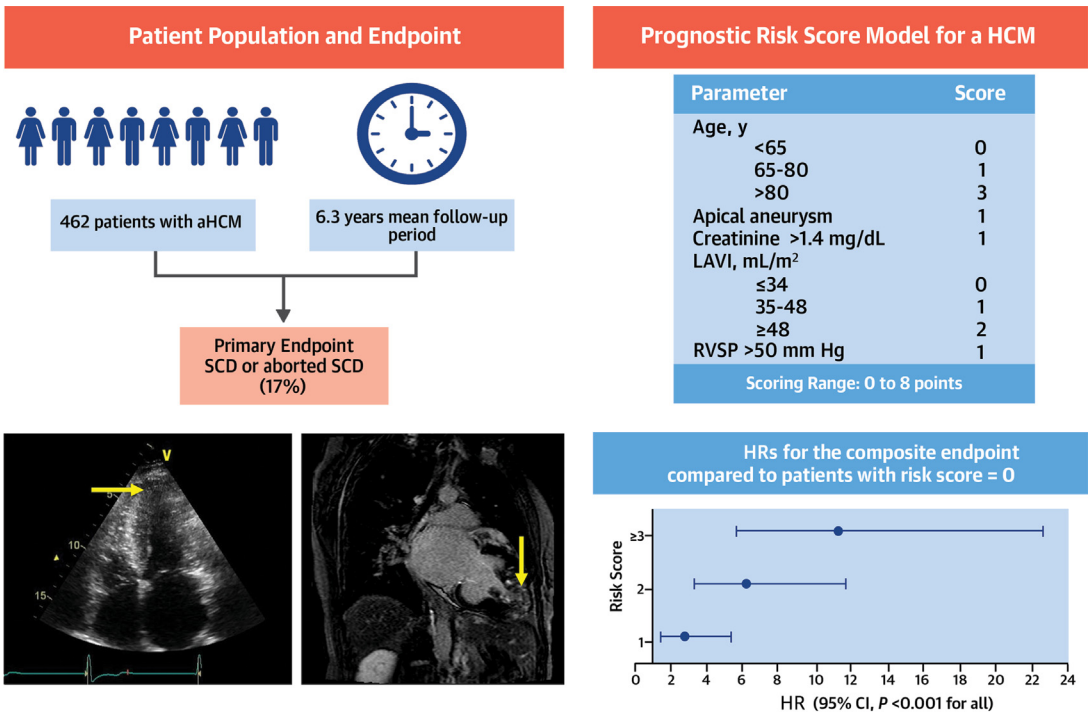
In comparison, as shown in Table 3, ESC risk score was not significantly associated with the primary outcome on univariable analysis with a much lower C-statistic of 0.54, P = 0.13. On the other hand, while ≥2 ACC/AHA risk factors were significantly associated with primary events, the C-statistic was significantly lower than the newer aHCM risk score (0.64 vs 0.75, respectively, both $P < 0.001$).

TABLE 2 Baseline Imaging Characteristics of the Study Sample (N = 462)

Echocardiographic data (n = 462)	
Left ventricular ejection fraction, %	63.6 ± 8.1
Left ventricular ejection fraction <50%	10 (2%)
Left atrial volume index, mL/m^2	36.2 ± 15.3
Indexed left ventricular end-systolic volume, mL/m^2	17 ± 6.3
Indexed left ventricular end-diastolic volume, mL/m^2	46.4 ± 15.4
Left ventricular stroke volume index, mL/m^2	30.4 ± 11.1
Interventricular septum thickness, cm	1.4 ± 0.4
Posterior wall thickness, cm	1.2 ± 0.3
Maximal apical wall thickness, cm	1.8 ± 0.4
LV mass index, g/m^2	112.4 ± 36.0
Peak left ventricular outflow tract gradient rest, mm Hg	11.2 ± 17.6
Mean left ventricular outflow tract gradient rest, mm Hg	5.6 ± 8.1
Presence of intra-cavitary obliteration	35 (7.6%)
Apical aneurysm at presentation	51 (11.0%)
Diastolic function	
Normal	80 (17%)
Stage I dysfunction	125 (27%)
Stage II dysfunction	54 (12%)
Stage III dysfunction	8 (2%)
Indeterminate	195 (42%)
Mitral annular septal E/e'	12.8 ± 5.4
Mitral annular lateral E/e'	9.3 ± 4.7
e/a ratio	1.4 ± 0.7
Mitral regurgitation grade	
None	102 (22%)
Mild	337 (73%)
At least moderate	23 (5%)
Right ventricular systolic pressure, mm Hg	32.7 ± 10.2
Cardiac magnetic resonance data (n = 246)	
Left ventricular ejection fraction, %	62.4 ± 7.7
Left ventricular ejection fraction ejection fraction <50%	8 (3%)
Indexed left ventricular end-systolic volume	29.5 ± 19.3
Indexed left ventricular end-diastolic volume	75.0 ± 52.0
Left ventricular stroke volume index	46.9 ± 35.4
Interventricular septum thickness	1.33 ± 0.33
Maximal apical wall thickness	1.7 ± 0.4
Left ventricular mass index	101.1 ± 36.2
Presence of late gadolinium enhancement	170 (71%)
Late gadolinium enhancement %	4.9 ± 6.6 2.7 (0-6.2)
Patients with LGE	
≥15% of left ventricular mass	17 (7%)
≥5% of left ventricular mass	70 (28%)
Apical aneurysm	29 (12%)
Apical thrombus	5 (2.4%)

Values are mean ± SD, n (%), or median (IQR).
LGE = late gadolinium enhancement.

CENTRAL ILLUSTRATION **Long-Term Outcomes in Patients With Apical Hypertrophic Cardiomyopathy: A New Risk Score**



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Key details of the study, including the study population, representative images, follow-up, endpoints, and key findings. LAVI = left atrial volume index; RVSP = right ventricular systolic pressure; SCD = sudden cardiac death; other abbreviation as in Figure 2.

DISCUSSION

The current study describes the characteristics of aHCM patients evaluated at our tertiary care institution. In addition, we describe the longer-term outcomes of these patients and develop an aHCM specific risk score. Two-thirds of the study sample were men and patients also had a high proportion of established cardiovascular risk factors like hypertension, diabetes mellitus, and hyperlipidemia. In addition, 40% patients had a history of at least one episode of AF at baseline with only 26% patients on appropriate anticoagulation therapy. Vast majority (69%) patients had no ACC/AHA risk factors for SCD or were in the lowest ESC SCD risk category (86%) and 17% had an ICD. Interestingly, giant T waves were only observed in 10% of our cohort, similar to Klarich et al with 11%[5] but much lower than other studies (where 47%-100% was reported).[4,8,20-23] The LVEF was preserved (≥50%) in 98% patients and as expected, the maximal wall thickness was present in the apex. Apical aneurysm was present in 51 (11%) patients. In the subgroup of patients who underwent a CMR, at least some LGE was present in 71%, with mean LGE% of 4.9 ± 6.6 and 17 (7%) and 70 (28%) patients demonstrating significant LGE (defined as ≥15% of LV mass, respectively). There were an additional 23 apical aneurysms identified during follow-up. Whether this reflects newly formed aneurysms vs improved recognition due to enhanced imaging is uncertain. Also, there is no conclusive data about routine use of anticoagulation in patients with documented apical aneurysms.

Unlike the obstructive HCM patients where symptomatology is primarily driven by dynamic LVOT obstruction and concomitant mitral regurgitation, aHCM patients represent a unique subset where symptomatology is mostly driven by diastolic dysfunction, microvascular angina, impaired lusitropy, and small LV cavity. However, the current guidelines do not differentiate between these very

different subtypes (oHCM vs nonobstructive hypertrophic cardiomyopathy [nHCM], especially aHCM) in terms of risk stratification.[1,2] As a result, we also sought to understand longer-term outcomes of aHCM patients and develop a unique risk score for aHCM patients. Despite most patients reporting no symptoms or demonstrating guideline described SCD risk factors at baseline, the 5- and 10-year freedom from composite events were 87% and 75%, respectively. The aHCM-specific risk score considered unique features that are associated with adverse outcomes in such patients, predominantly driven by diastolic dysfunction, small LV cavity size, abnormal lusitropy, and apical aneurysm (likely driven in part by increased mid LV cavity pressure).[24] These features included age, LAVI, RVSP, and apical aneurysm formation. Indeed, the current aHCM risk score provides improved prognostication for longer-term composite events in aHCM patients vs that provided by ACC/AHA or ESC risk stratification tools which were not developed for this specific subgroup of HCM patients.[1,2] We converted the various parameters to clinically relevant categories in order to create a simple risk prediction score that will be easy to use without the need for cumbersome computation. However, it requires external validation.

aHCM, which was first described in Japan, represents 13% to 25% of Japanese HCM patients.[25] However, it is less common outside of Japan, with reported frequencies of 3% to 11% of all HCM patients.[20,25] However, a recent study has challenged that notion and demonstrated that up to 27% of French-Canadians of Caucasian descent have the aHCM variant associated with an increased risk for ventricular arrhythmia.[10] In our study, aHCM represented 6.8% of all confirmed HCM patients seen at our institution. Also, autosomal dominant mutation rates in aHCM have been reported to be lower (13%-25%) than in classic HCM (60%)[26,27] and biopsies have shown a lower incidence of myocyte disarray in aHCM, but both subtypes have similar interstitial fibrosis severity and extent.[28] In the current study, within the genetically tested subgroup, only 32% were gene-positive.

While aHCM was initially thought to be a benign condition with no increased mortality risk, recent studies have shown mortality rates of 0.5% to 4.8% per year, like those in typical HCM.[5,9] In our cohort, the composite event rate and death rate were 2.8% and 2.1%/year, respectively. This was higher than our previously reported results in obstructive HCM patients where the composite event rate (death and appropriate ICD discharge) and death were 1.3% and 1.1%/year, respectively.[29] This likely reflects lack of proven medical/surgical therapies in aHCM patients (nHCM patients in general) vs oHCM patients where septal reduction therapies have been demonstrated to provide excellent symptom relief and longer-term survival.[30-33] Previous cohort studies have reported predictors of worse prognosis in aHCM patients. Eriksson et al, in 2002, found that age at presentation <41 years, NYHA functional class ≥II at baseline, and left atrial enlargement were predictors of cardiovascular morbidity.[8] In 2011, Moon et al identified LAVI, S′ velocity, and E/e′ ratio along with older age, hypertension, and diabetes as independent predictors of worse prognosis.[34] Klarich et al found that higher age at presentation, female sex, and the presence of AF at baseline were predictors of poorer

TABLE 3 Univariable Cox Regression Analysis of Composite Primary Events

	HR (95% CI)	*P* Value
Age at presentation	1.06 (1.04-1.08)	<0.001
Female	1.46 (0.93-2.28)	0.10
Hypertension	1.81 (1.04-3.12)	0.03
Diabetes mellitus	1.69 (0.97-2.97)	0.11
Hyperlipidemia	1.22 (0.77-1.93)	0.39
COPD	2.10 (0.95-4.68)	0.12
Stroke	1.87 (0.95-3.26)	0.11
Apical aneurysm	2.32 (1.24-4.34)	0.008
Family history of HCM	0.72 (0.31-1.65)	0.434
Family history of sudden death	1.26 (0.58-2.73)	0.566
History of non-sustained VT	1.64 (0.88-3.09)	0.11
Atrial fibrillation	1.77 (1.14-2.76)	0.01
ACC/AHA SCD risk factors		
0 (reference)		
1	1.47 (0.58-3.76)	0.41
2 or more	2.68 (1.07-6.57)	0.03
ESC risk score	1.07 (0.96-1.20)	0.23
NYHA (reference NYHA functional class I)		
II	1.34 (0.79-2.28)	0.28
III	1.49 (0.70-3.16)	0.29
IV	11.69 (3.59-38.08)	<0.001
Beta-blockers	0.88 (0.50-1.55)	0.69
Non dihydropyridine calcium channel blockers	0.79 (0.36-1.76)	0.56
Serum creatinine	1.26 (1.09-1.45)	<0.001
Serum NT-proBNP (in the subgroup of 192 patients with available data)	1.21 (1.07-1.52)	<0.001
LV ejection fraction	0.96 (0.94-0.99)	0.002
LA volume index	1.82 (1.28-2.59)	0.001
Indexed LVEDV	0.99 (0.98-1.00)	0.061
Maximal LV wall thickness	1.46 (0.88-2.41)	0.13
E/e′	1.02 (0.96-1.08)	0.58
e/a ratio	1.30 (0.83-2.04)	0.24
RVSP	1.04 (1.02-1.06)	<0.001
LGE% (in the subgroup of 246 patients with CMR)	1.04 (1.01-1.08)	0.03

CMR = cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; ESC = European Society of Cardiology; LA = left atrium; LVEDV = left ventricular end-diastolic volume; NT-Pro BNP = N-terminal pro brain natriuretic peptide; RVSP = right ventricular systolic pressure; VT = ventricular tachycardia; other abbreviations as in Tables 1 and 2.

TABLE 4 Multivariable Cox Regression Analysis of Composite Primary Events With aHCM-Specific Risk Score

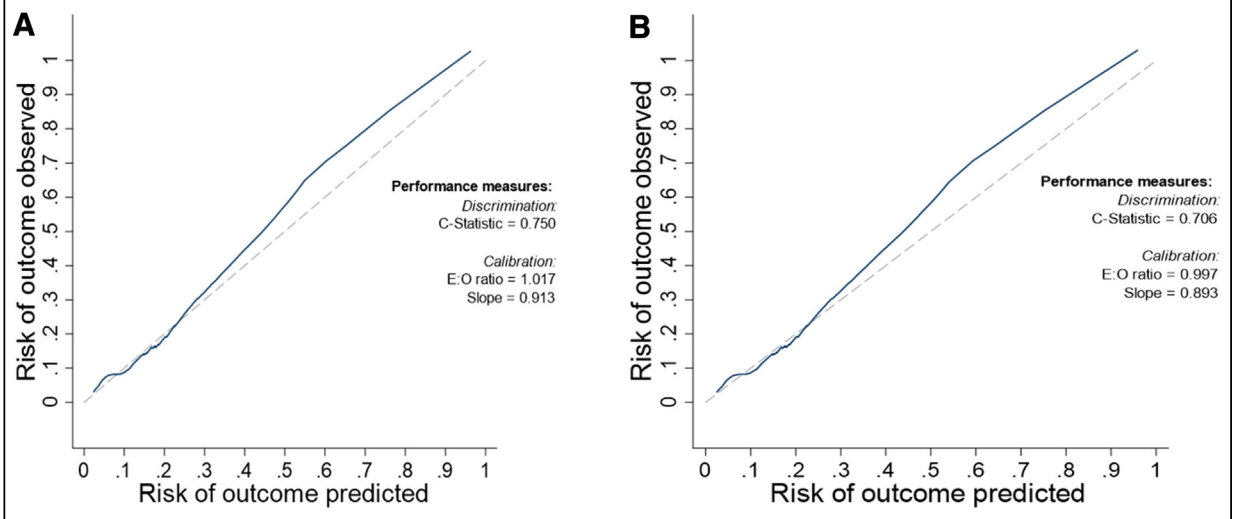
	HR (95% CI)	*P* Value	Beta Coefficient (95% CI)	Risk Score for Primary Composite Events
Age, y				
<65	Reference		Reference	0
65-80	2.23 (1.34-3.72)	0.002	0.79 (0.29-1.32)	1
>80	4.71 (2.10-10.6)	<0.001	1.55 (0.74-2.36)	3
Apical aneurysm at baseline	1.92 (1.00-3.72)	0.05	0.65 (−0.01 to 1.31)	1
Creatinine >1.4 mg/dL	1.68 (0.93-3.1)	0.08	0.53 (−0.07-1.12)	1
LAVI, ml/m^2				
≤34	Reference		Reference	0
35-48	0.84 (0.47-1.50)	0.55	−0.17 (−0.75 to 0.40)	0
≥48	2.31 (1.31-4.04)	0.009	0.84 (0.27-1.40)	2
RVSP>50 mm Hg	1.75 (0.92-3.35)	0.08	0.56 (−0.09 to 1.21)	1

aHCM = apical hypertrophic cardiomyopathy; LAVI = left atrial volume index; other abbreviation as in Table 3.

survival.[5] More recently, in a study by Yin et al in 2021, assessing clinical, echocardiographic, and CMR variables as prognostic predictors of outcomes in 126 patients with aHCM, 5 variables were identified as poor markers, and these are age ≥55 years, LAVI ≥36.7 ml/m^2, S′≤6.7 cm/s, non-sustained VT, and LGE.[9] In recent years, with increased utilization of multimodality imaging, apical aneurysms have been demonstrated to have worse prognosis with event rates as high as 4.7%/year.[35-37] In a follow-up study, an aneurysm size ≥2 cm was associated with a 5-year SCD rate of 9.7%, compared with 2.9% for aneurysm size <2 cm.[38] Indeed, the current aHCM risk score corroborates many of the findings of prior studies. In addition, in a smaller subset, it also suggests that LGE% and NT-ProBNP might have incremental prognostic utility. The results of the ongoing HCMR (Hypertrophic Cardiomyopathy Magnetic Resonance) registry will shed light on the role of multiparametric CMR imaging (including LGE) in ascertaining long-term prognosis of such patients.[39]

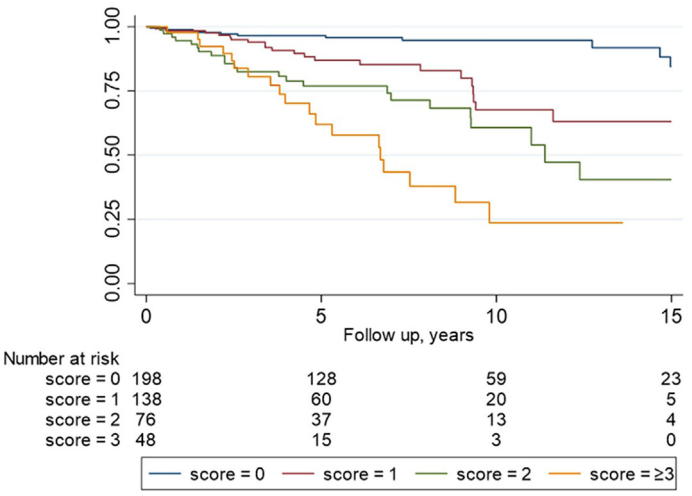
Based on the body of evidence thus far, it is important to recognize that aHCM patients do not have a benign prognosis and should undergo diligent phenotypic characterization and risk stratification. It appears that reliance on abnormal T-wave inversions on electrocardiogram and the standard guideline-recommended risk stratification tools may not be

FIGURE 1 Model Performance for Original Dataset and Internal Validation



(A) Graph of model performance in the original data set. The thick blue line represents a calibration plot of observed and expected event-free survival probabilities based on the adaptive linear spline method (calibration intercept was −0.005 (95% CI: −0.06-0.05). The dashed blue line represents a hypothetical perfect calibration. The E:O ratio is the ratio of the expected and observed event-free survival probabilities (ideal value = 1); the slope refers to the model fit (ideal value = 1). (B) Model performance with internal validation. Graph of model performance with internal validation using the bootstrapping method. The thick blue line represents a calibration plot of observed and expected event-free survival probabilities based on the adaptive linear spline method (Calibration intercept was −0.006 (95% CI: −0.05-0.05). The dashed blue line represents a hypothetical perfect calibration. E:O ratio is the ratio of the expected and observed event-free survival probabilities (ideal value = 1); slope refers to the model fit (Ideal value = 1).

FIGURE 2 Kaplan-Meier Survival Analysis for Primary Composite Events Separated on Basis of Increasing Apical Hypertrophic Cardiomyopathy Risk Score



sufficient in this subset and specific factors that are unique to this population might have to be considered. Importantly, once aHCM is suspected, every effort should be made to identify the area with maximal wall thickness and identify apical aneurysm formation (and possibly thrombus) using multimodality imaging. In the future, an earlier diagnosis would hopefully allow earlier initiation of effective therapies and prevent formation of apical aneurysms which carry an adverse prognosis.[40] While the emergence of cardiac myosin inhibitors like mavacamten and aficamten have further opened more therapeutic avenues in oHCM, ongoing trials will determine its efficacy in nHCM (and specifically in aHCM) patients (ODYSSEY-HCM, NCT05582395 and ACACIA-HCM, NCT06081894). Indeed, there is a growing body of evidence that a subgroup of severely symptomatic aHCM patients may benefit from a debulking apical myectomy as an alternative to cardiac transplantation.[41] However, the results and experience are relegated to few specialized centers with no prospective trials.[42]

STUDY LIMITATIONS. While the current study reports results of one of the largest available cohorts of aHCM patients, the results should be interpreted in the context of its limitations. First, this is an observational study from a large tertiary care center with its inherent referral biases. Only associations and not causality can be inferred. In addition, details like heart failure admissions, especially at local hospitals, were not available. However, follow-up myectomy or heart transplantations were only performed in patients with advanced heart failure. As mentioned above, potential markers like LGE% and NT-ProBNP were not included in risk score development as data were only available in a subset, reflecting inclusion of patients over a long interval of time with significant evolution in diagnostic and therapeutic tools. It is likely that in earlier phase of the study, echocardiography was not advanced enough (eg, optimal visualization of LV apex, inconsistent use of contrast) to diagnose apical aneurysms and whether the newer aneurysms diagnosed during follow-up represent progression of disease vs improved imaging techniques remains uncertain. Additionally, LV strain assessment or serial imaging was not uniformly available to ascertain changes in regional LV systolic function or progression of disease in the entire study cohort. While the newer aHCM risk score provided good discrimination in predicting the composite endpoint, future studies are needed to assess an external validation of our risk score, along with incorporation of newer laboratory and imaging markers which would potentially further improve its ability to predict outcomes.

CONCLUSIONS

The current study reports the characteristics and outcomes of one of the largest aHCM cohorts in the western population. They constituted 6.8% of our overall HCM cohort with a composite event rate of 2.8%/year. While the newer aHCM-specific risk score provided good discrimination in predicting the composite endpoint, future studies are needed to assess

external validation of the risk score, along with incorporation of newer laboratory and imaging markers like LGE.

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