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Complementary classification of hypertrophic cardiomyopathy using unsupervised cluster analysis on left ventricular function

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Contemporary classification of hypertrophic cardiomyopathy (HCM) was mainly based on the site of myocardial hypertrophy and left ventricular outflow tract obstruction. A complementary classification based on left ventricular function could provide a powerful tool to identify individuals with high risk of adverse cardiovascular outcomes and guide individualized managements. Multi-dimensional echocardiographic parameters of left ventricular function derived from conventional echocardiography, tissue Doppler imaging, and speckle tracking echocardiography were obtained in 266 HCM patients and 169 healthy controls (HCs). According to these parameters, HCM subtypes were calculated by principal component analysis and unsupervised cluster analysis. Variables of different groups were compared. The prognosis between HCM subtypes were evaluated. There were two HCM subtypes generated, subtype 1 HCMs (n = 123) and subtype 2 HCMs (n = 143). Compared to HCs, left ventricular diastolic and systolic function were significantly declined to varying degrees in both subtype 1 HCMs and subtype 2 HCMs, especially in subtype 1 HCMs (all *P* value < 0.001). Subtype 1 HCMs characterized as increased LAVI and E/E′, decreased mean E′ and untwist rate, increased global and segmental longitudinal strains, circumferential strains and radial strains, decreased rotation degree, twist degree, and twist rate, in comparison with subtype 2 HCMs (all *P* value < 0.001). Notably, subtype 1 HCMs were more susceptible to adverse prognosis of atrial fibrillation (HR: 4.34; 95% CI 1.08–17.53; *P* value: 0.039). Collectively, we stratified HCM patients into two subtypes with different diastolic and systolic performance and risk of atrial fibrillation. This complementary classification might eventually help to target management of HCM patients who would benefit most.

Keywords Hypertrophic cardiomyopathy, Cluster analysis, Multi-dimensional echocardiographic parameters, Atrial fibrillation

Hypertrophic cardiomyopathy (HCM) was the most common myocardial disease, affecting 0.2–0.5% of the population worldwide[1]. Up to 30% to 40% HCM patients would experience adverse outcomes[2]. Left ventricular hypertrophy, myocardial hypercontractility, reduced compliance, myofibrillar disarray, and fibrosis could be observed in the hearts of HCM patients[3,4]. Symptomatic HCM patients often experienced heterogenous phenotypic manifestations, such as shortness of breath, especially with physical exertion, atrial fibrillation, chest pain, syncope, dizziness and sudden cardiac death[5].

With the development of clinical and molecular research, especially the promotion of family pedigree screening and the implementation of more sensitive cardiac imaging diagnosis, asymptomatic HCM patients were often disclosed during treatments for other disease and routinely medical examination[6,7]. As the population of HCM patients gradually expanded, so had their unmet medical needs. The overall principle of HCM treatment was to reduce symptoms, improve cardiac function, and delay disease progression[8]. As novel pharmacotherapies targeting the molecular underpinnings of HCM emerged, assessment of both asymptomatic and symptomatic HCM patients needed to be updated[9,10].

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Among the many modalities, echocardiography was widely utilized in clinical practice as the most common initial tests recommended by guidelines for patients with suspected HCM[11,12]. Multi-dimensional echocardiographic parameters, such as diastolic and systolic velocities of mitral annulus, global longitudinal strain, twist mechanics, and so on, had refined our understanding of mechanisms of left ventricular dysfunction, and emerged as sensitive methods to noninvassively assess left ventricular function[13,14]. Our study made full use of multi-dimensional echocardiographic parameters in the evaluation of HCM patients in the hope of describing a broad group of HCM patients who were actually characterized by different clinical, pathophysiological, and prognostic characteristics.

Clustering, also known as cluster analysis, was an unsupervised machine learning technique that could explore naturally occurring groups and group data points together based on their similarities[15]. Since classification was performed by the clustering algorithms, not by humans[16]. To date, attempts to describe disease heterogeneity in HCM patients by cluster algorithms had been limited to the analysis of clinical variables[17]. Easy and objective identification of this heterogeneity through multi-dimensional echocardiographic parameters could assist in identifying, within the broad HCM classification, patients with different risk profile.

In this study, we utilized unsupervised cluster analysis to identify and validate complementary classification of HCM by exploring and exploiting multi-dimensional echocardiographic parameters of left ventricular function. We identified echocardiographic markers that enabled a delineation of HCM into complementary subtypes with different degree of left ventricular dysfunction and risk profile. Specially, we evaluated the prognostic value across the identified complementary subtypes of HCM. Our study provided innovative risk stratification strategy and new decision point for therapy.

Materials and methods

Study population

The study included a total of 435 participants consisting of 266 HCM patients and 169 healthy controls (HCs), who were recruited from the inpatient and outpatient services of the People's Hospital of China Medical University and the First Affiliated Hospital of China Medical University, and the local community at Shenyang, from July 2017 to June 2023. Inclusion criteria were echocardiographic evidence of left ventricular hypertrophy defined as a diastolic maximum wall thickness ≥ 15 mm or ≥ 13 mm in case of a first-degree relative with HCM, in the absence of other cardiac or systemic diseases that could account for the observed hypertrophy[18]. Exclusion criteria were as follows: (1) poor acoustic windows; (2) history of atrial fibrillation or atrial fibrillation status; (3) history of myocardial infarction or coronary artery disease; (4) history of septal myectomy or alcoholic septal ablation; and (5) impaired renal function, or metallic implants. Age- and sex-matched HCs were included, who had no evidence or no family history of HCM, hypertension, diabetes mellitus, or any other disease. The study was approved by the Institutional Review Board of the People's Hospital of China Medical University or the First Affiliated Hospital of China Medical University. All participants provided written informed consent after receiving a detailed description of the study and all experiments were performed in accordance with relevant guidelines and regulations.

Clinical variables

The clinical examinations consisted of standardized questionnaires, physical examinations and laboratory examinations. The questionnaire included age, sex, smoking, alcohol consumption, family medication history, and self-reported health status. Smokers were defined as having smoked at least one cigarette per day for more than one year. Drinkers were defined as having consumed at least one alcoholic beverage a day for a minimum period of six months. The physical examinations included measurements of height, weight, body mass index (BMI), body surface area (BSA), systolic blood pressure (SBP), diastolic blood pressure (DBP), and 12-lead electrocardiogram. The laboratory examinations included total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), fasting blood glucose (FBG), 2 h blood glucose (2hBG), glycosylated hemoglobin Alc (HbAlc), serum creatinine (Cr), serum urea nitrogen (UN), serum uric acid (UA), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), cardiac troponin T (cTNT), and N-terminal pro-brain natriuretic peptide (NT-proBNP).

Echocardiographic parameters

For each subject, conventional and advanced echocardiography were recorded with a Vivid 7 Dimension ultrasound system (GE Healthcare, Waukesha, WI) using the protocol of American Society of Echocardiography[19]. Conventional echocardiographic parameters included left ventricle end-diastolic dimension (LVEDD), left ventricle end-systolic dimension (LVESD), left ventricular ejection fraction (LVEF), maximum wall thickness (MWT), left ventricular mass index (LVMI), left ventricular outflow tract obstruction (LVOTO), left ventricular outflow tract obstruction peak gradient at rest (LVOTG), left atrial volume (LAV), derived LAV index (LAVI) (LAVI = LAV/BSA), peak early and late diastolic mitral inflow velocities (E and A), and derived E/A ratio. According to the echocardiographic morphology, there were three HCM types, including septal hypertrophy, apical hypertrophy, and mixed hypertrophy. Tissue Doppler imaging parameters included early diastolic velocities (E′), late diastolic velocities (A′), and systolic velocities (S′) of mitral annulus from both posterior septal and lateral sides. Mean E′, mean A′, mean S′ and E/E′ values were calculated. Speckle tracking echocardiographic parameters included left ventricular strains and twist mechanics which were generated from collected echocardiography cine clips after post-processing on professional software provided by GE Healthcare. Strains included global and segmental longitudinal strains, circumferential strains, and radial strains. Twist mechanics included segmental rotations, twist degree, peak twist rate in systolic phase and peak untwist rate in early and late diastolic phase[20].

Adverse cardiovascular outcomes

After study enrollment, HCM patients were evaluated every six months. At each visit, adverse cardiovascular outcomes were documented and assessed, which included atrial fibrillation, heart failure, stroke, syncope, and cardiovascular hospitalization. Enrollment date was defined as the first visit to the outpatient clinic. Follow-up surveys were taken up for two and a half years. Follow-up surveys were completed in 113 HCM patients. The missing follow-up HCM patients were due to out of contact and refusal to our follow-up after multiple contacts.

Unsupervised clustering

Eleven variables representing left ventricular function, including LAVI, E/E′, E′, S′, A′, global longitudinal strain, global circumferential strain, global radial strain, twist degree, twist rate, untwist rate were identified for cluster analysis. Generally, K-means clustering and principal component analysis (PCA) were applied to identify potential subtypes of interest[21]. K-means clustering was one of the simplest and popular unsupervised machine learning algorithms to partition a given data set into a set of K clusters effectively[15]. The HCM patients with a similar diastolic and systolic function pattern could group into the same cluster. Moreover, PCA was the main linear technique for dimensionality reduction, in order to simplify visual inspection of multivariate data by a linear transformation of data from high dimensional space into a low dimensional space that still retained the meaningful properties of the original data. The clustering workflows were described as below.

First, data normalization: Z-score normalization was used to transform data from multiple features to the same scale. It was calculated by subtracting the mean value for each field from the values of the file and then dividing by the standard deviation of the field. Second, K-means clustering: K-means clusters were specified as $k=2$ to ensure that there were a reasonable number of HCM patients within each cluster for interpretability. Meanwhile, the iteration was set as ten. The HCM patients were randomly clustered into the defined clusters until a local minimum was found by using the Euclidean sum of squares as a descriptor. Third, PCA: PCA was used to convert high dimensional data to three-dimensional data (the first three principal components). Then PCA results were presented in an interactive 3D scatterplot. Z-score normalization, K-means clustering and PCA were carried out using Python 3.7.

Statistical analysis

Statistical analysis was performed using SPSS statistics 23.0 (SPSS Inc., Chicago, IL). Categorical variables were expressed as counts (n) and percentages (%) and continuous variables as mean and standard deviation (SD) whenever appropriate. Between-group differences of continuous variables among HCM subtypes and HCs were compared by one-way analysis of variance (ANOVA) followed by least significant difference (LSD) post-hoc test. Categorical variables were compared using the chi-square test (χ^2) test. To further evaluate the prognostic and discriminative utility of the HCM subtypes, Kaplan–Meier curves were plotted with the duration from the enrollment to the last follow-up or adverse cardiovascular outcomes and compared with the log-rank test. Cox proportional hazard analysis was performed to evaluate the association between the adverse cardiovascular outcomes and the HCM subtypes, with or without adjusting by basic characteristics (age and sex). A P value less than 0.05 was considered statistically significant.

Results

Identified subtypes

The ensemble cluster analysis identified two subtypes in HCM patients ($n=266$) (Fig. 1). Subtype 1 included 123 HCM patients (Subtype 1 HCMs), and Subtype 2 included 143 HCM patients (Subtype 2 HCMs). Clinical variables according to subtypes were shown in Table 1. The levels of cTNT and NT-proBNP were significantly different among Subtype 1 HCMs, Subtype 2 HCMs and HCs ($P=0.049$ and $P=0.018$, respectively). Compare to HCs, Subtype 1 HCMs showed significant higher levels of cTNT and NT-proBNP ($P=0.015$ and $P=0.005$, respectively). There was no significant difference among Subtype 1 HCMs, Subtype 2 HCMs and HCs in demographic characteristics, physical variables, blood sugar, blood lipid, liver function, kidney function, and thyroid function (all P value >0.05).

There were significant differentces among Subtype 1 HCMs, Subtype 2 HCMs and HCs in the conventional parameters of echocardiography, including LVEDD, MWT, LVMI, LVOTO, and E (all P value <0.001). Compared to HCs, Subtype 1 HCMs and Subtype 2 HCMs showed significant smaller LVEDD, thicker MWT, higher LVMI, and lower E (all P value <0.001). However, there was no significant difference between Subtype 1 HCMs and Subtype 2 HCMs in the above parameters (all P value >0.05). In addition, no statistical differences of LVOTO and LVOTG were observed between Subtype 1 HCMs and Subtype 2 HCMs (all P value >0.05), as well as morphological types of HCM (all P value >0.05).

Subtype-related diastolic function alterations

There was significant difference in diastolic function among Subtype 1 HCMs, Subtype 2 HCMs and HCs (all P value <0.001) (Table 2). Subtype 1 HCMs had the most severe diastolic dysfunction, expressed as the highest LAVI value and E/E′ ratio, and the lowest mean E′ and A′ value compared to Subtype 2 HCMs and HCs (all P value <0.001). Subtype 2 HCMs had moderate diastolic dysfunction as the higher LAVI value and E/E′ ratio, and the lower mean E′ value compared to HCs (all P value <0.001). The detailed data were illustrated in Table 2.

Subtype-related systolic function alterations

There was significant difference in systolic function among Subtype 1 HCMs, Subtype 2 HCMs and HCs (all P value <0.001). Subtype 1 HCMs had the most severe systolic dysfunction, characterized as the lowest global and segmental longitudinal strains, circumferential strains, and radial strains, as well as the disturbed twist mechanics, including the lowest segmental rotation degree in the basal, middle, and apical levels, twist degree, peak twist

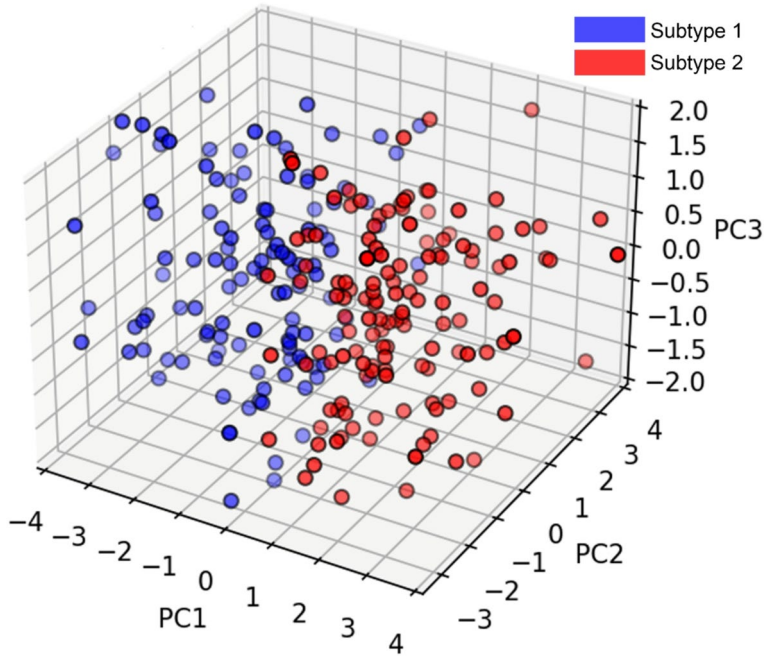

Fig. 1. Clustering of HCM subtypes in three-dimensional space. HCM, hypertrophic cardiomyopathy; PC, principal component.

rate and peak untwist rate compared to Subtype 2 HCMs and HCs (all *P* value < 0.05). Moreover, compared to HCs, Subtype 2 HCMs had moderate systolic dysfunction as lower global and segmental longitudinal strains, circumferential strains, and radial strains, and reduced twist mechanics as lower segmental rotation degree in basal, middle, and apical levels, and lower twist degree (all *P* value < 0.05) (Figs. 2 and Fig. 3). The detailed data were illustrated in Table 3 and Table S1.

Subtype-related adverse cardiovascular outcomes

Follow-up data were available for 113 of the 266 (42.48%) HCM patients included in the cluster analysis (follow-up duration: 30 months, interquartile range: 6–30 months). The composite endpoint occurred in 31 patients (27.43%), including nine atrial fibrillation (7.96%), seven heart failure (6.19%), four stroke (3.54%), four syncope (3.54%), and seven cardiovascular hospitalization (6.19%). As shown in Fig. 4, survival analysis found a trend toward statistical significance in adverse cardiovascular outcomes between Subtype 1 HCMs and Subtype 2 HCMs (log-rank *P*-value = 0.093) (Table S2). Moreover, it showed that there was significant difference in atrial fibrillation between Subtype 1 HCMs and Subtype 2 HCMs (log-rank *P*-value = 0.022). Using Cox proportional hazards modeling, Subtype 1 HCMs were more like to suffer from atrial fibrillation compared to Subtype 2 HCMs after adjusting for age and sex (HR: 4.34; 95% CI 1.08–17.53; *P*-value: 0.039) (Table 4).

Discussion

The widely used clinical classification of HCM was mainly based on hemodynamic characteristics and the site of myocardial hypertrophy[3]. Periodic risk stratification for HCM related sudden cardiac death was carried out clinically[22,23]. However, there were still lack of well established protocols for risk assessment of adverse cardiovascular outcomes in HCM patients. There was a pressing need for a HCM classification that could distinguish patients with higher risk of adverse cardiovascular outcomes. To our knowledge, this was the first application of cluster analysis in disclosing classification of HCM patients according to multi-dimensional echocardiographic parameters of left ventricular function other than demographic characteristics and clinical variables. Our study achieved a binary classification of HCM mainly featured with different cardiac diastolic and systolic dysfunction, myocardial mechanic disorder and susceptibility of atrial fibrillation.

In this study, we successfully found two complementary subtypes of HCM based on data-driven cluster analysis, which was quantified by multi-dimensional echocardiographic parameters, from conventional echocardiography, tissue Doppler imaging, and speckle tracking echocardiography. The two subtypes mainly differed in left ventricular diastolic and systolic function featured by E′, E/E′, LAVI, longitudinal strain, circumferential strain, radial strain, rotation and twist parameters. Subtype 1 HCMs demonstrated poorer left ventricular diastolic and systolic function compared to subtype 2 HCMs. However, demographic characteristics, physical variables, blood sugar, blood lipid, liver function, kidney function, and thyroid function showed no significant difference. As conventional echocardiographic parameters could hardly fully represent left ventricular function, multi-dimensional echocardiographic parameters, like E′ and E/E′ in tissue Doppler imaging, longitudinal strain, circumferential strain, radial strain, rotation and twist in speckle tracking echocardiography, were introduced to quantify myocardial reflexation and contraction[24]. A few researchers showed that E′ and

Variables	Subtype 1 HCMs		Subtype 2 HCMs		HCs		F/χ2	*P* value
	N	mean ± SD/%	N	mean ± SD/%	N	mean ± SD/%		
Age (years)	123	50.05 ± 13.38	143	48.05 ± 14.63	169	48.21 ± 12.74	0.837	0.434
Male (n, %)	123	63 (53.8)	143	78 (56.1)	169	92 (54.4)	0.149	0.928
Smoker (n, %)	123	23 (24.0)	143	32 (24.4)	169	54 (32.0)	2.903	0.234
Drinker (n, %)	123	17 (17.7)	143	29 (22.1)	169	40 (23.7)	1.300	0.522
Height (m)	123	1.68 ± 0.07	143	1.68 ± 0.09	169	1.67 ± 0.09	1.285	0.278
Weight (kg)	123	69.23 ± 13.02	143	71.16 ± 13.07	169	68.59 ± 10.48	1.627	0.198
BMI (kg/m^2)	123	24.52 ± 3.55	143	25.08 ± 3.57	169	24.96 ± 2.91	0.944	0.390
BSA (m^2)	123	1.76 ± 0.20	143	1.78 ± 0.21	169	1.76 ± 0.19	0.682	0.506
HR (bmp)	123	67.44 ± 13.31	143	70.43 ± 10.61	169	70.25 ± 6.96	2.483	0.085
SBP (mmHg)	123	131.58 ± 22.60	143	128.95 ± 21.66	169	127.62 ± 12.55	1.255	0.286
DBP (mmHg)	123	80.48 ± 11.94	143	79.47 ± 11.12	169	81.02 ± 7.46	0.704	0.495
TC (mmol/L)	123	4.61 ± 0.99	143	4.60 ± 1.04	169	5.31 ± 3.91	0.844	0.432
TG (mmol/L)	123	1.66 ± 1.04	143	1.97 ± 1.50	169	1.98 ± 2.48	0.223	0.800
HDL (mmol/L)	123	1.42 ± 0.51	143	1.35 ± 0.54	169	1.44 ± 0.44	0.531	0.589
LDL (mmol/L)	123	3.08 ± 0.86	143	2.97 ± 0.78	169	3.19 ± 0.89	0.857	0.426
FBG (mmol/L)	123	5.42 ± 0.91	143	5.58 ± 0.69	169	5.82 ± 1.49	1.385	0.253
2hBG (mmol/L)	123	7.28 ± 2.42	143	7.66 ± 2.90	169	7.30 ± 3.51	0.047	0.954
HbA1C (%)	123	6.09 ± 1.19	143	5.77 ± 0.29	169	6.73 ± 2.38	1.143	0.321
Cr (mmol/L)	123	69.15 ± 13.55	143	67.68 ± 11.67	169	65.45 ± 13.44	0.955	0.387
UN (mmol/L)	123	4.85 ± 1.08	143	4.85 ± 1.02	169	4.84 ± 1.15	0.009	0.991
UA (mmol/L)	123	306.25 ± 59.05	143	319.74 ± 55.45	169	294.10 ± 87.43	0.858	0.426
ALT (U/L)	123	19.65 ± 7.90	143	19.01 ± 7.19	169	20.43 ± 14.07	0.647	0.524
AST (U/L)	123	20.13 ± 4.75	143	19.94 ± 4.91	169	20.35 ± 6.73	0.192	0.825
FT3 (pmol/L)	123	4.21 ± 0.66	143	5.04 ± 2.58	169	4.37 ± 1.44	1.633	0.200
FT4 (pmol/L)	123	13.55 ± 2.51	143	13.14 ± 2.16	169	13.30 ± 1.87	0.206	0.815
TSH (mIU/L)	123	1.75 ± 0.95	143	1.62 ± 1.14	169	1.78 ± 0.71	0.275	0.760
cTNT (pg/ml)	123	57.94 ± 80.04*	143	44.40 ± 68.88*	169	6.67 ± 4.43	**3.118**	**0.049**
NT-proBNP (pg/ml)	123	644.29 ± 115.89*	143	402.27 ± 153.12*	169	78.94 ± 15.86	**4.309**	**0.018**

Table 1. Clinical and laboratory characteristics stratified by HCM subtypes. *P* value in bold was indicated $P < 0.05$ among three groups; * $P < 0.05$, LSD post-hoc analysis compared to HCs; $^{\#}P < 0.05$, LSD post-hoc analysis compared to subtype 2 HCMs. HCMs, patients with hypertrophic cardiomyopathy; HCs, healthy controls; BMI, body mass index; BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; Triglyceride, triglyceride; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; FBG, fasting blood glucose; 2hBG, 2 h blood glucose; HbA1C, glycosylated hemoglobin A1c; Cr, serum creatinine; UN, blood urea nitrogen; UA, blood uric acid; ALT, alanine transaminase; AST, aspartate aminotransferase; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; cTNT, cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; LSD, least significant difference.

E/E′ were associated with worse prognosis in HCM patients[25]. Moreover, they also pointed out that there were a close correlation of abnormal regional and global strains, myocardial fibrosis, and myocardial contraction in HCM patients[26–28].

Our study could well distinguish HCM patients who were susceptive to atrial fibrillation with specific echocardiographic characteristics. Atrial fibrillation was the most common sustained tachyarrhythmia in HCM patients, and had been regarded as a turning point of living status and prognosis when effective atrial fibrillation management strategies were not available. Approximately 20% of HCM patients could develop atrial fibrillation mostly in their fifties. It was well established that age, BMI, height, hypertension, diabetes, obstructive sleep apnea, myocardial infarction, heart failure, and smoking were risk factors for atrial fibrillation development and perpetuation[29–31]. Elevated filling pressure due to left ventricular diastolic dysfunction, myocardial hypertrophy, mitral regurgitation and left ventricular outflow tract obstruction was fully acknowledged determinant of left atrial enlargement in HCM clinical course[32,33]. In the meantime, myocardial fibrosis also contributed to left atrial enlargement and functional impairment. Previous researcheres had pointed out that increased left atrial volume could lead to increased risk of atrial fibrillation[34]. This was consistent with our study. In our study, no significant difference was noticed among subtype 1 HCMs, subtype 2 HCMs and HCs in demographic characteristics, physical variables, blood sugar, blood lipid, liver function, kidney function, and thyroid function. It was reasonable to conclude that left atrial size and echocardiographic parameters were better biological markers of atrial fibrillation risk assessment in HCM patients.

Variables	Subtype 1 HCMs		Subtype 2 HCMs		HCs		F/χ2	*P* value
	N	Mean ± SD/%	N	Mean ± SD/%	N	Mean ± SD		
LVEDD	123	43.17 ± 8.93*	143	43.08 ± 8.72*	169	47.20 ± 3.48	**15.980**	**< 0.001**
LVESD	123	29.13 ± 7.98	143	28.03 ± 6.12	169	29.49 ± 3.78	2.305	0.101
LVEF	123	62.86 ± 4.20	143	63.15 ± 4.56	169	63.92 ± 3.75	2.683	0.070
MWT	123	22.24 ± 5.78*	143	21.34 ± 5.33*	169	9.57 ± 1.18	**470.859**	**< 0.001**
LVMI	123	157.64 ± 67.17	143	150.27 ± 62.74	169	89.54 ± 19.68	**78.301**	**< 0.001**
LVOTO (n, %)	123	32 (26.4)	143	35 (24.5)	–	–	0.169	0.681
LVOTG (mmHg)	123	31.51 ± 33.64	143	26.18 ± 29.61	–	–	1.817	0.180
Hypertrophic type	123	–	143	–	–	–	1.973	0.373
Septal type	41 (33.3)		55 (38.4)	–	–	–	–	
Apical type	19 (15.5)		27 (18.9)	–	–	–	–	
Mixed type	63 (51.2)		61 (42.7)	–	–	–	–	
LAVI	123	40.73 ± 19.19*#	143	33.09 ± 10.85*	169	21.53 ± 14.49	**59.110**	**< 0.001**
E	123	0.70 ± 0.24*	143	0.71 ± 0.20*	169	0.79 ± 0.19	**9.282**	**< 0.001**
A	123	0.71 ± 0.24	143	0.75 ± 0.21	169	0.73 ± 0.15	1.320	0.268
E/A	123	1.10 ± 0.54	143	1.03 ± 0.47	169	1.14 ± 0.38	2.293	0.102
E/E′	123	11.97 ± 4.66*#	143	9.12 ± 3.02*	169	7.54 ± 1.71	**66.596**	**< 0.001**
E′	123	6.04 ± 1.36*#	143	8.04 ± 1.41*	169	10.74 ± 2.29	**244.939**	**< 0.001**
S′	123	5.31 ± 1.90*#	143	7.07 ± 2.17*	169	10.30 ± 1.96	**226.833**	**< 0.001**
A′	123	6.98 ± 2.06*#	143	9.36 ± 1.99	169	9.23 ± 1.04	**79.093**	**< 0.001**

Table 2. The characteristics of conventional echocardiography and tissue Doppler imaging stratified by HCM subtypes. *P* value in bold was indicated $P < 0.05$ among three groups; * $P < 0.05$, LSD post-hoc analysis compared to HCs; # $P < 0.05$, LSD post-hoc analysis compared to subtype 2 HCMs. HCMs, patients with hypertrophic cardiomyopathy; HCs, healthy controls; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVOTG, left ventricular outflow tract obstruction peak gradient at rest; LVEF, left ventricular ejection fraction; MWT, maximum wall thickness; LVMI, left ventricular mass index; LVOTO, left ventricular outflow tract obstruction; LAVI, left atrial volume index; E and A, velocity of mitral valve in early and late diastolic phase; E′, A′ and S′, velocity of mitral annulus in early and late diastolic phase and systolic phase; LSD, least significant difference.

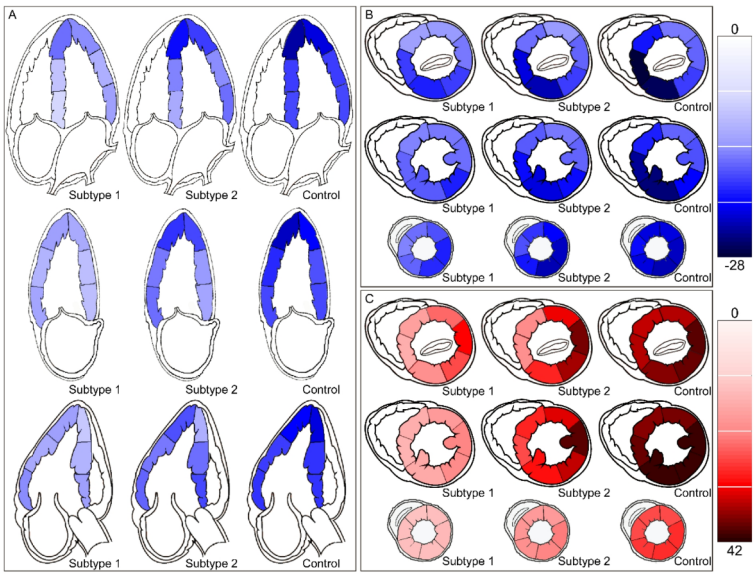

Fig. 2. Distinct strain patterns of subtype 1 HCMs, subtype 2 HCMs and HCs. (**A**) Longitudinal strain pattern of subtype 1 HCMs, subtype 2 HCMs and HCs. (**B**) Circumferential strain pattern of subtype 1 HCMs, subtype 2 HCMs and HCs. (**C**) Radial strain pattern of subtype 1 HCMs, subtype 2 HCMs and HCs. This figure represented the distribution of mean strain value in different myocardial segments. The darker the color was, the larger its absolute value was. HCMs, patients with hypertrophic cardiomyopathy; HCs, healthy controls.

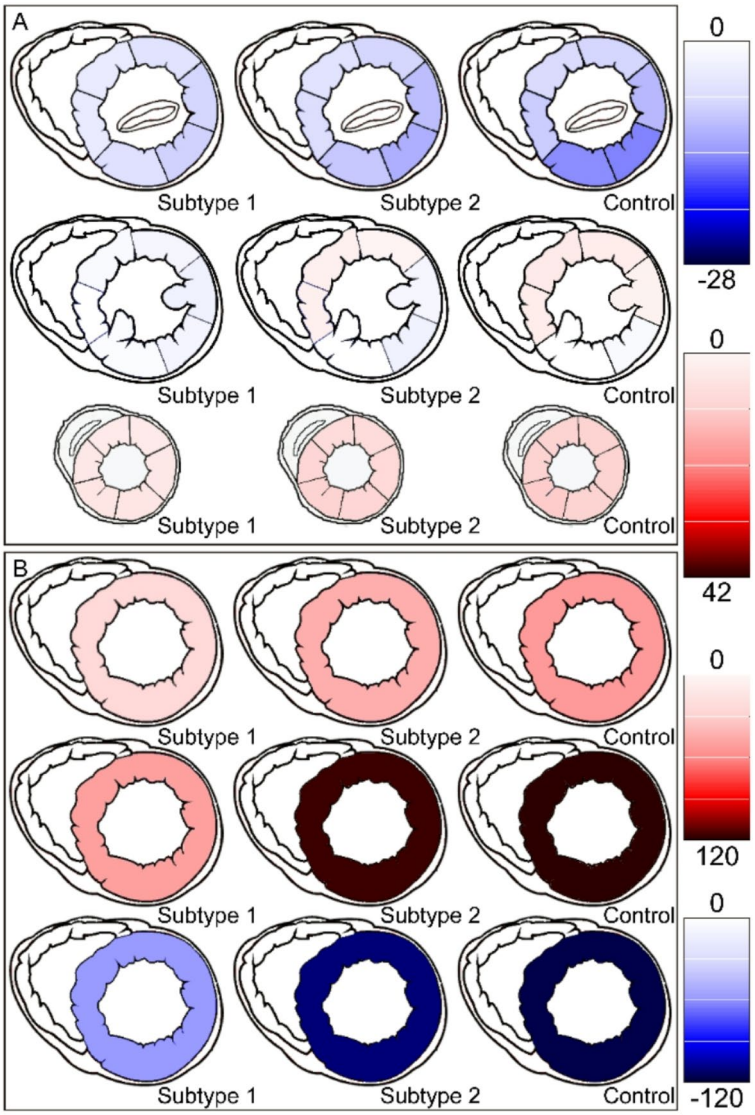

Fig. 3. Distinct twist mechanics patterns of subtype 1 HCMs, subtype 2 HCMs and HCs. (**A**) Rotation pattern of subtype 1 HCMs, subtype 2 HCMs and HCs. (**B**) twist degree pattern, twist rate pattern and untwist rate pattern of subtype 1 HCMs, subtype 2 HCMs and HCs. This figure represented the distribution of mean twist mechanics value in different myocardial segments. The darker the color was, the larger its absolute value was. HCMs, patients with hypertrophic cardiomyopathy; HCs, healthy controls.

For the first time, our study conducted cluster analysis using a large number of noninvasive multi-dimensional echocardiographic parameters of HCM patients. Contemporary risk stratification for HCM patients mainly focused on sudden cardiac death and syncope[22,35]. Moreover, contemporary stratification strategy of atrial fibrillation in HCM patients exhibited not enough concordance for clinical practice. The findings of our study could help to fill a gap in this area, and to identify HCM patients at risk for atrial fibrillation quantitatively. We also achieved in utilizing an unbiased approach to find out existed, distinct, and mutually independent patient clusters that could be used for individualized HCM management[36,37].

There were several limitations in our study. First, deformation parameters were afterload dependent. Follow-up studies should introduce afterload independent parameters, such as myocardial work, to differentiate abnormal parameters resulting from systolic dysfunction and abnormal parameters resulting from abnormal afterload. Second, the relative small sample size, especially of the follow-up HCM patients, was a drawback of our study. Multicenter, longitudinal studies with larger sample size should be conducted in order to reveal the correlations of the strain, rotation, and twisting patterns and morphorlogical types of HCM in Subtype 1 HCMs and Subtyper 2 HCMs. Our cohort enrolled relatively fewer patients with severe LVOT obstruction. For further enhancement of this model, more severe obstructive patients should be recruited in subsequent studies. Meanwhile more detailed follow-up should be pay more attention in the furure. Third, all HCM patients in this study didn't experience cardiac MRI screening, which forbad us to analyze the cardiac structure with fibrosis in

Variables	Subtype 1 HCMs		Subtype 2 HCMs		HCs		F	*P* value
	N	mean ± SD	N	mean ± SD	N	mean ± SD		
LS4Ch	123	− 11.91 ± 3.30*#	143	− 15.98 ± 3.93*	169	− 19.76 ± 3.26	**162.859**	**< 0.001**
LS2Ch	123	− 11.55 ± 3.22*#	143	− 15.77 ± 3.86*	169	− 19.41 ± 3.74	**152.454**	**< 0.001**
LS3Ch	123	− 12.01 ± 3.83*#	143	− 15.83 ± 4.41*	169	− 19.90 ± 3.97	**121.984**	**< 0.001**
GLS	123	− 11.80 ± 2.93*#	143	− 15.86 ± 3.58*	169	− 19.69 ± 2.73	**210.565**	**< 0.001**
CSbas	123	− 16.39 ± 3.67*#	143	− 18.31 ± 3.28*	169	− 20.63 ± 3.52	**48.524**	**< 0.001**
CSmid	123	− 16.80 ± 3.46*#	143	− 18.74 ± 3.70*	169	− 20.55 ± 3.46	**36.652**	**< 0.001**
Csapi	123	− 17.24 ± 5.09*#	143	− 20.77 ± 6.68*	169	− 22.22 ± 5.09	**26.059**	**< 0.001**
GCS	123	− 16.81 ± 3.06*#	143	− 19.27 ± 3.27*	169	− 21.13 ± 2.67	**67.734**	**< 0.001**
RSbas	123	27.37 ± 13.87*#	143	33.54 ± 15.20*	169	38.67 ± 16.81	**17.509**	**< 0.001**
RSmid	123	23.32 ± 12.16*#	143	35.16 ± 18.13*	169	41.06 ± 19.16	**36.490**	**< 0.001**
RSapi	123	17.50 ± 11.07*#	143	26.25 ± 15.46*	169	31.70 ± 17.29	**29.369**	**< 0.001**
GRS	123	22.73 ± 8.35*#	143	31.65 ± 9.36*	169	37.14 ± 11.43	**69.946**	**< 0.001**
Rotbas	123	− 6.19 ± 5.93*#	143	− 8.60 ± 5.41*	169	− 10.61 ± 5.65	**19.864**	**< 0.001**
Rotmid	123	− 1.43 ± 6.53*#	143	− 0.07 ± 5.72*	169	1.87 ± 6.25	**9.550**	**< 0.001**
Rotapi	123	5.33 ± 6.08*#	143	11.86 ± 6.65*	169	13.49 ± 7.01	**54.278**	**< 0.001**
TD	123	11.52 ± 6.84*#	143	20.46 ± 7.53*	169	24.10 ± 9.83	**79.057**	**< 0.001**
TR	123	67.20 ± 37.74*#	143	118.69 ± 44.00	169	119.90 ± 44.07	**63.974**	**< 0.001**
UTR E	123	− 55.67 ± 32.44*#	143	− 104.18 ± 55.45	169	− 109.62 ± 45.97	**52.753**	**< 0.001**

Table 3. Speckle tracking echocardigraphic characteristics stratified by HCM subtypes. *P* value in bold was indicated $P < 0.05$ among three groups; * $P < 0.05$, LSD post-hoc analysis compared to HCs; $^{\#}P < 0.05$, LSD post-hoc analysis compared to subtype 2 HCMs. HCMs, patients with hypertrophic cardiomyopathy; HCs, healthy controls; LS, longitudinal strain; GLS, global longitudinal strain; CS, circumferential strain; GCS, global circumferential strain; RS, radial strain; GRS, global radial strain; 4Ch, 2Ch and 3Ch, apical four-, two-, and three-chamber view; bas, basal; mid, middle; api, apical; Rot, rotation; TD, twist degree; TR, twist rate; UTR E, untwist rate in early diastolic phase; LSD, least significant difference.

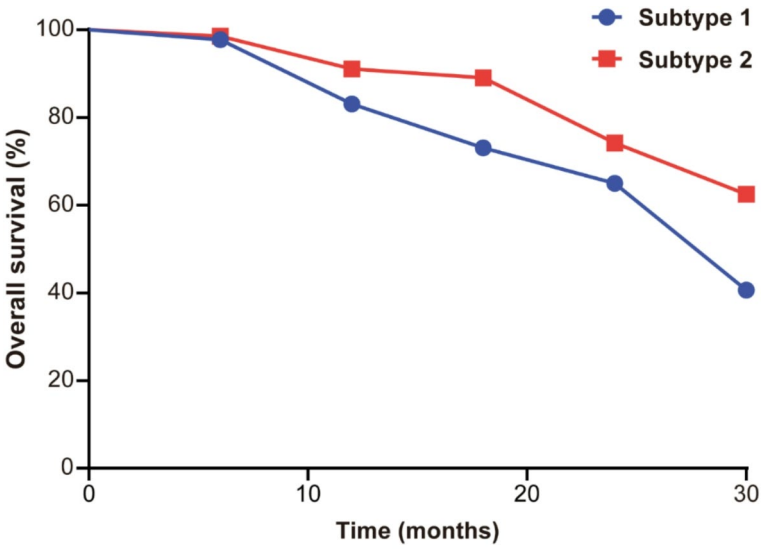

Fig. 4. Survival outcomes in subtype 1 HCMs and subtype 2 HCMs. HCMs, patients with hypertrophic cardiomyopathy.

detail. Last, most data of HCM patients were recorded in rest. Further studies should be pay more attention to provocative data, especially in LVOTO and LVOTG.

As far as we know, this was the first complementary classification of HCM patients utilizing multi-dimensional echocardiographic parameters of left ventricular function, not only conventional echocardiographic measurements, tissue Doppler imaging data, but also speckle tracking echocardiographic assessments. This classification was composed of two clinically meaningful subtypes with significant differences in diastolic and systolic dysfunction. Notably, the complementary classification could well distinguish HCM patients with

Variables	Group	Log-rank analysis	Univariate analysis		Multivariate analysis	
		P value	*P* value	HR(95%CI)	*P* value	HR(95%CI)
Adverse outcome	Subtype 2 HCMs			1(ref)		1(ref)
	Subtype 1 HCMs	0.093	0.118	1.76(0.87–3.56)	0.141	1.71(0.84–3.49)
Atrial fibrillation	Subtype 2 HCMs			1(ref)		1(ref)
	Subtype 1 HCMs	**0.022**	**0.043**	**4.30(1.05–17.70)**	**0.039**	**4.34(1.08–17.53)**
Heart failure	Subtype 2 HCMs			1(ref)		1(ref)
	Subtype 1 HCMs	0.618	0.625	1.45(0.33–6.49)	0.604	1.49(0.33–6.65)
Stroke	Subtype 2 HCMs			1(ref)		1(ref)
	Subtype 1 HCMs	0.448	0.463	2.08(0.29–14.81)	0.411	2.29(0.32–16.49)
Syncope	Subtype 2 HCMs			1(ref)		1(ref)
	Subtype 1 HCMs	0.841	0.843	0.80(0.08–7.69)	0.883	0.84(0.09–8.32)
Cardiovascular hospitalization	Subtype 2 HCMs			1(ref)		1(ref)
	Subtype 1 HCMs	0.602	0.608	1.48(0.33–6.63)	0.595	1.51(0.33–6.84)

Table 4. Association of HCM subtypes with adverse cardiovascular outcomes. *P* value in bold was indicated $P < 0.05$ when subtype 1 HCMs compared to subtype 2 HCMs. HCMs, patients with hypertrophic cardiomyopathy; HR, hazard risk; CI, confidence interval.

adverse cardiovascular outcome of atrial fibrillation. Our study could lead to new target of HCM managements. Moreover, our study could help in design and execution of clinical trials of HCM patients.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data used and/or analysed during the current study will be available from the corresponding author on reasonable request.

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Author contributions

J.Y., D.S. and C.M. designed and conceptualized the study. D.S., X.F., Y.Z. and Z.Z. collected clinical and echocardiographic data. D.S. and X.F. analyzed data and wrote the manuscript. J.Y. revised the manuscript. All authors contributed to data interpretation.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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