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THREE-DIMENSIONAL SPECKLE TRACKING ECHOCARDIOGRAPHY FOR ASSESSING THE DEGREE OF MYOCARDIAL FIBROSIS AND PREDICTING PROGNOSIS IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Objective	To investigate the correlation between three-dimensional speckle tracking echocardiography (3D-STE) parameters and degree of myocardial fibrosis in patients with hypertrophic cardiomyopathy (HCM), and to evaluate the prognostic value of 3D-STR.
Material and methods	A retrospective analysis of 300 HCM patients diagnosed between January 2022 and December 2024 was conducted. All the patients had been examined with 3D-STE and cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE). Based on the LGE percentage, the patients were stratified into mild fibrosis (LGE%<15%, n=168) and moderate-to-severe fibrosis groups (LGE% ≥15%, n=115). Pearson/Spearman correlation analysis was used to assess the relationship between 3D-STE parameters and LGE%, ROC curve analysis to evaluate the diagnostic performance of 3D-STE, and Cox regression analysis to determine the prognostic value 3D-STE. The primary composite end-point encompassed cardiac death, heart failure hospitalization, malignant ventricular arrhythmias, cardiogenic syncope, and stroke.
Results	283 patients completed a median follow-up of 18.0 mos. The 3D-GS absolute value demonstrated a strong correlation with LGE% findings ($r=-0.714$, $p<0.001$), outperforming other strain and torsion parameters. Multivariate linear regression identified the 3D-GS absolute value as an independent predictor of myocardial fibrosis (as quantified by LGE%) ($\beta=-0.486$, $p<0.001$). The AUC of 3D-GS absolute value for predicting moderate-to-severe fibrosis was 0.896 (95% CI: 0.860–0.932), with an optimal cutoff value of 12.1% (sensitivity 86.1%, specificity 82.7%). During follow-up, 92 patients (32.5%) experienced primary composite endpoint events. Multivariate Cox regression revealed that the 3D-GS absolute value independently predicted major adverse cardiovascular events (HR=0.754, $p<0.001$), with a model C-index of 0.824.
Conclusion	3D-STE parameters, particularly 3D-GS, demonstrate close correlation with the degree of myocardial fibrosis in HCM patients. It exhibited excellent diagnostic performance and prognostic value and may serve as a practical, non-invasive tool for assessment of myocardial fibrosis.
Keywords	Hypertrophic cardiomyopathy; three-dimensional speckle tracking echocardiography; myocardial fibrosis; cardiac magnetic resonance; prognosis
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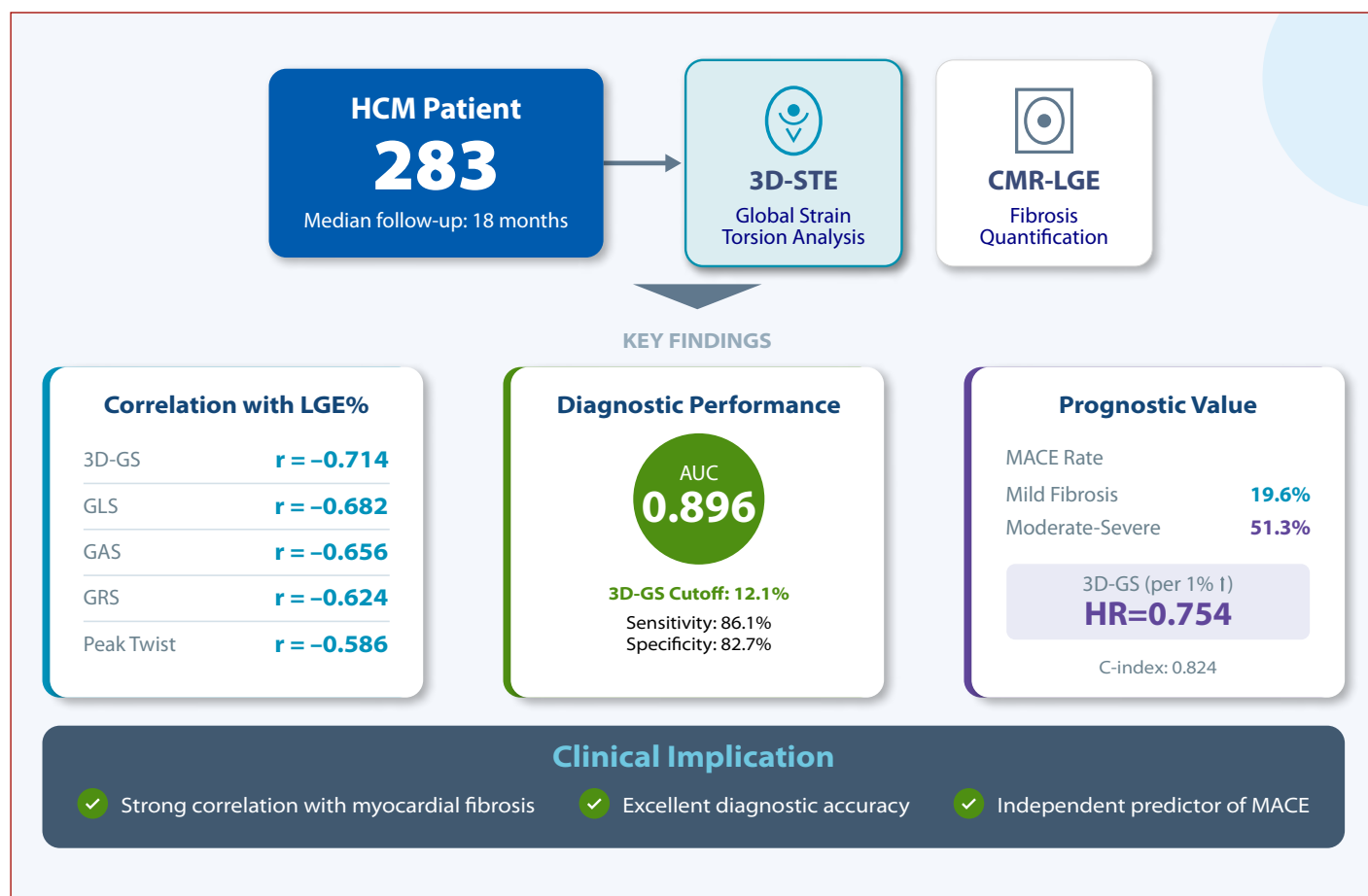
Introduction

Hypertrophic cardiomyopathy (HCM) represents the most prevalent inherited cardiovascular disorder, affecting approximately 1 in 500 individuals. It manifests as asymmetric left ventricular wall thickening with heterogeneous clinical presentations ranging from asymptomatic states to heart failure, malignant arrhythmias, and sudden cardiac death [1]. Myocardial fibrosis constitutes a pivotal pathological hallmark of HCM, with its formation involving multifactorial mechanisms including myocardial cell disarray, microvascular dysfunction, and excessive collagen deposition [2]. Myocardial fibrosis correlates intimately with symptom severity in HCM patients and serves as

a critical predictor of adverse cardiovascular events including arrhythmias, heart failure, and sudden death [3]. Consequently, accurate assessment of the degree of myocardial fibrosis is of substantial clinical significance for risk stratification, treatment decision-making, and prognostic evaluation in HCM patients.

Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) imaging directly visualizes region of myocardial fibrosis and is widely acknowledged as the non-invasive gold standard for assessment of myocardial fibrosis [4]. Nevertheless, CMR examination is hampered by several limitations. Elevated cost, prolonged examination duration, and contraindications in specific patient pop-

Central Illustration. 3D Speckle Tracking Echocardiography for Myocardial Fibrosis Assessment and Prognosis Prediction in Hypertrophic Cardiomyopathy



ulations, including patients with cardiac pacemaker implantation, renal insufficiency, or restricted clinical accessibility, limit its widespread application in the long-term follow-up of HCM patients. Therefore, it is important to identify a straightforward, cost-effective, and reproducible alternative approach for assessing myocardial fibrosis.

Developed in recent years, three-dimensional speckle tracking echocardiography (3D-STE) is a novel technique to assess myocardial function. Through tracking spatial motion trajectories of acoustic speckles within myocardial tissue, it quantitatively evaluates left ventricular global and segmental myocardial strain [5]. Fibrotic myocardium exhibits reduced strain values that are attributable to impaired contractile function. Compared with conventional two-dimensional strain imaging, 3D-STE simultaneously acquires longitudinal, circumferential, radial, and area strain parameters, so it more comprehensively reflects myocardial deformation characteristics. Furthermore, being independent of cardiac plane angles, it theoretically enables more accurate identification of fibrotic regions [6]. Beyond assessment of myocardial strain parameters, 3D-STE automatically calculates left ventricular torsion parameters. Left ventricular torsion represents a anatomical phenomenon, generated by the helical arrangement

of the myocardial fibers. It is manifested as clockwise systolic cardiac rotation at the base that is opposed by counterclockwise rotation at the apex. Myocardial fibrosis potentially affects torsional motion by disrupting the normal arrangement myocardial fibers, increasing myocardial stiffness, and reducing myocardial contractility. Therefore, it is important to systematically evaluate relationships between strain parameters, torsion parameters, and myocardial fibrosis, along with a comparison their diagnostic efficacy, in order to identify the most effective indicators of fibrosis.

However, current evidence regarding the correlation between 3D-STE parameters and CMR with late gadolinium enhancement (CMR-LGE) quantitative assessment myocardial fibrosis, as well as the prognostic value of 3D-STE for HCM patients, remains limited. This investigation aimed to explore the correlation between 3D-STE parameters and CMR-LGE quantitative assessment of myocardial fibrosis, in order to evaluate diagnostic efficacy of 3D-STE in predicting moderate-to-severe fibrosis, and to analyze its prognostic value in HCM patients. Thus, the goals were to provide a straightforward, practical tool for assessing myocardial fibrosis and for improving risk stratification.

Materials and Methods

Study population

Case source. Clinical data were retrospectively collected from clinical records of patients hospitalized in the cardiology department and diagnosed with HCM between January 2022 and December 2024. Based on the inclusion and exclusion criteria listed below, 300 HCM patients were ultimately enrolled in this investigation. The investigation was approved by the hospital Ethics Committee, with informed consent waived due to its retrospective nature.

Inclusion criteria:

- 1) Meeting the 2014 European Society of Cardiology HCM diagnostic criteria, i.e., echocardiography demonstrating left ventricular wall thickness ≥ 15 mm (≥ 13 mm for individuals with family history of HCM), and/or with ventricular hypertrophy of the above degree unexplained by abnormal loading conditions;
- 2) Age 18–75 yrs;
- 3) Completion of conventional echocardiography and 3D-STE examination within 7 days following admission;
- 4) Completion of CMR examination, including LGE sequences within 14 days following admission, with interval between examinations not exceeding 10 days;
- 5) Complete clinical and imaging data;
- 6) Completion of follow-up with duration ≥ 6 months and availability of outcome data, including major adverse cardiovascular events (MACE) and survival status.

Exclusion criteria:

- 1) Secondary myocardial hypertrophy due to other identifiable causes, including hypertensive heart disease, valvular heart disease, congenital heart disease, cardiac amyloidosis, Fabry disease, or other infiltrative/storage cardiomyopathy;
- 2) Coexisting coronary artery disease or acute myocardial infarction;
- 3) Severe arrhythmias that compromised image quality;
- 4) Poor quality of ultrasound images that precluded 3D-STE analysis;
- 5) Contraindications of CMR examination or inadequate image quality;
- 6) Coexisting malignant tumors, severe hepatic or renal insufficiency, or other severe systemic diseases;
- 7) Pregnancy or lactating;
- 8) Absence of more than 10% of critical clinical or imaging variables; patients with such incomplete data were excluded from the analysis, whereas cases with $\leq 10\%$ missing data were retained and analyzed using complete-case methods for the relevant variables.

Clinical data collection

The following data were extracted from the hospital electronic medical record system:

- 1) General information, including gender, age, height, weight, body surface area (BSA), cardiac function classification (New York Heart Association (NYHA) classification);
- 2) Clinical symptoms, including chest pain, dyspnea, palpitations, syncope or presyncope, family history of HCM (defined as first-degree relatives with confirmed HCM diagnosis), sudden cardiac death (< 50 years), or unexplained sudden death;
- 3) Laboratory tests including N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin I (cTnI), hemoglobin, creatinine, estimated glomerular filtration rate (eGFR), collected within 24 h following admission;
- 4) Electrocardiographic findings, including rhythm, QRS duration, presence of pathological Q waves, ST-T changes;
- 5) Treatment regimen, including pharmacological therapy (β -blockers, calcium channel blockers, antiarrhythmic drugs), septal reduction therapy, implantable cardioverter-defibrillator (ICD).

Echocardiographic examination

Equipment and methods. All ultrasound examinations were performed utilizing a GE Vivid E95 ultrasound diagnostic system (GE HealthCare, Horten, Norway) equipped with M5S probe (frequency 1.5–4.6 MHz) and a 4V probe. The patients were positioned in the left lateral decubitus position, connected to the electrocardiograph, and breathing calmly. All examinations followed the ultrasound department's standard operating procedures and were performed by ultrasound physicians with more than five years of cardiac ultrasound experience.

Conventional echocardiographic measurements

Following the the American Society of Echocardiography (ASE) guidelines, images were acquired from parasternal long-axis, short-axis, and apical four-chamber, two-chamber, three-chamber views. Conventional echocardiographic assessment included cardiac chamber size, ventricular wall thickness, left ventricular systolic function, diastolic function, left ventricular outflow tract obstruction, and systolic anterior motion of the mitral valve. The main variables analyzed in this study included:

1. Left ventricular end-diastolic diameter (LVEDd), end-systolic diameter (LVESd);
2. Interventricular septal thickness (IVS), left ventricular posterior wall thickness (LVPW), maximum wall thickness (MWT);
3. Left atrial diameter (LAD), left atrial volume index (LAVI);
4. Left ventricular ejection fraction (LVEF, biplane Simpson's method);
5. Mitral valve early diastolic peak velocity (E wave), late diastolic peak velocity (A wave), and calculation of E/A ratio;

6. Mitral annular lateral wall and septal early diastolic peak velocity (e') and calculation of E/e' ratio (Tissue Doppler imaging (TDI));
7. Left ventricular outflow tract pressure gradient (LVOT gradient), measured at rest and following a Valsalva maneuver;
8. Systolic anterior motion (SAM) of mitral valve. All echocardiographic parameters were extracted from the ultrasound reporting system.

Three-dimensional speckle tracking echocardiography

1. **Image retrieval:** Three-dimensional images that had been acquired from the apical four-chamber view utilizing the 4V probe in full-volume mode were extracted from the hospital picture archiving and communication system (PACS). Cases with satisfactory image quality (volume frame rate ≥ 50 frames/sec, complete left ventricle coverage, absence of significant artifacts) were selected for analysis.
2. **Image analysis:** Extracted three-dimensional images were imported into the workstation and uniformly analyzed offline utilizing 4D Auto LVQ (EchoPAC version 203, GE HealthCare, Horten, Norway) software. The mitral annulus and apex were manually marked; the software automatically identified endocardial borders, with manual adjustment as needed to ensure accurate border tracking. The software automatically divided the left ventricle into 17 segments and tracked myocardial speckle motion throughout the cardiac cycle.
3. **Parameters measured:** Values of global longitudinal strain (GLS), global circumferential strain (GCS), global radial strain (GRS), global area strain (GAS), and three-dimensional global strain (3D-GS) of the left ventricle were obtained.

The 3D-STE parameters obtained included global longitudinal strain (GLS), global circumferential strain (GCS), global radial strain (GRS), global area strain (GAS), and three-dimensional global strain (3D-GS). Longitudinal strain reflects longitudinal shortening of myocardial fibers along the long axis, circumferential strain reflects circumferential shortening, radial strain reflects wall thickening in the radial direction, area strain reflects endocardial surface area changes. 3D-GS integrates multidirectional myocardial deformation and therefore provides a comprehensive estimate of global three-dimensional left ventricular mechanics.

Segmental longitudinal strain values for 17 left ventricular segments were simultaneously recorded. Inter-segmental strain differences (defined as the difference between maximum and minimum longitudinal strain absolute values among 17 segments in each patient) were calculated. These values were utilized to assess myocardial strain heterogeneity.

The standard deviation of time to peak strain (SDT) was determined to evaluate myocardial synchrony.

Cardiac magnetic resonance imaging examination

Scanning protocol. All CMR examinations were performed utilizing a 3.0T magnetic resonance scanner (Skyra, Siemens Healthineers, Erlangen, Germany) with a dedicated cardiac phased-array coil using respiratory gating. Patients were positioned supine and connected to the electrocardiograph (ECG). Scanning sequences included steady-state, free precession (SSFP) sequences that acquired three-chamber cine images of the cardiac short-axis, and long-axis, four-chamber, and two-chamber views. Scanning was performed for 10–15 min following intravenous injection of gadolinium contrast agent (gadopentetate dimeglumine, 0.2 mmol/kg). Phase-sensitive inversion recovery (PSIR) sequence was employed for LGE imaging, with slice thickness 8 mm, interslice gap 2 mm, and covering the entire left ventricle.

Image analysis. CMR image data were extracted from the PACS system and analyzed offline using cvi42 software (version 5.13, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) to measure left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), LVEF, left ventricular mass index (LVMI).

LGE quantitative analysis was performed by utilizing the signal intensity threshold method on each short-axis slice [4]. Endocardial and epicardial contours were manually delineated by selecting normal myocardial regions without obvious enhancement in the contralateral ventricular wall (area $\geq 10 \text{ cm}^2$) as reference. The mean signal intensity and standard deviation were calculated from the reference normal myocardium. Regions with signal intensity that exceeded the mean signal of the mean normal myocardium plus five standard deviations were defined as LGE-positive regions. For 12 cases suspected of diffuse fibrosis and lacking clear normal reference regions, the myocardial region with the lowest relative signal intensity was selected as reference. Considering that this method might overestimate the degree of fibrosis, these 12 patients (four in the mild fibrosis group, eight in the moderate-to-severe fibrosis group) were excluded from the sensitivity analysis to assess the robustness of the results. The software automatically identified and quantified LGE regions by:

- 1) Calculating total LGE mass (units, g) and LGE percentage ($\text{LGE\%} = \text{LGE mass} / \text{total left ventricular mass} \times 100\%$);
- 2) Recording LGE distribution pattern (focal, diffuse, septal insertion point enhancement);
- 3) Recording the number of involved segments. To ensure measurement consistency, all LGE quantitative analyses employed the same software version and threshold criteria.

Based on the CMR-LGE results, the patients were stratified into a mild fibrosis group ($\text{LGE\%} < 15\%$) or a moderate-to-severe fibrosis group ($\text{LGE\%} \geq 15\%$).

Intra-observer and inter-observer reproducibility analysis

To evaluate the reliability of 3D-STE and selected CMR measurements, including LGE quantification and CMR-derived left ventricular ejection fraction (CMR-LVEF), 30 patients were randomly selected from the study cohort for reproducibility analysis. Two independent observers, each with more than five years experience analyzing cardiac ultrasound and CMR images, separately analyzed the images. Intra-observer reproducibility assessment: Observer A re-analyzed the same batch of images following a 4-wk interval. Inter-observer reproducibility assessment: Observer B independently analyzed the same batch of images datasets that had been initially analyzed by Observer A. For intra-observer reproducibility assessment, Observer A re-analyzed the same datasets after a 4-week interval. Both observers remained blinded to each other's measurement results and patient clinical information during analysis. Intraclass correlation coefficient (ICC), coefficient of variation (CV), and Bland-Altman analysis were employed to assess measurement consistency. ICC ≥ 0.90 was defined as excellent, 0.75–0.89 as good. All 3D-STE strain parameters and CMR-LGE parameters demonstrated excellent intra-observer and inter-observer reproducibility (Supplementary Table S1).

Follow-up and endpoint events

All patients underwent follow-up through outpatient visits, telephone contacts, and electronic medical record system queries. The *primary composite endpoint* was major adverse cardiovascular events (MACE), defined as occurrence of any of the following events during follow-up:

1. Cardiac death, including sudden cardiac death, heart failure death, and post-myocardial infarction death. Sudden cardiac death was defined as an unexpected death occurring within 1 hour of symptom onset in a witnessed case, or within 24 hours after the patient was last seen alive and in a stable condition in an unwitnessed case. Cause of death was determined based on medical records, death certificates, and autopsy reports, when available;
2. Heart transplantation or left ventricular assist device implantation;
3. Heart failure hospitalization, defined as hospitalization (≥ 24 h) attributable to worsening heart failure signs and symptoms (such as dyspnea, peripheral edema) requiring intravenous diuretics or vasoactive drug therapy, with diagnosis meeting 2021 ESC heart failure management guideline criteria;
4. Malignant ventricular arrhythmic events, sustained ventricular tachycardia (duration ≥ 30 sec or < 30 sec but requiring urgent termination), ventricular fibrillation, or appropriate implantable cardioverter-defibrillator (ICD) discharge, with event diagnosis based on electrocardiogram, Holter monitoring, or ICD interrogation records

documented in hospitalization or outpatient medical records;

5. Syncope with clear cardiogenic evidence, loss of consciousness caused by arrhythmias, outflow tract obstruction, or acute cardiac output reduction following exclusion of vasovagal syncope, orthostatic hypotension, neurogenic causes, and other causes documented in medical records; 6) Stroke or transient ischemic attack (TIA), diagnosis based on head computed tomography (CT) or magnetic resonance imaging (MRI) imaging and neurology consultation opinions documented in medical records.

For each patient, only the first occurring primary composite endpoint event was recorded for primary analysis. Event occurrence time was defined as the interval (mos) from admission date to the date of the event occurrence.

Secondary endpoint events included:

1. Cardiac death (defined as above);
2. New-onset atrial fibrillation, defined as newly diagnosed atrial fibrillation documented in medical records during follow-up (based on electrocardiogram or Holter monitoring);
3. Significant deterioration of left ventricular systolic function, defined as LVEF decrease $\geq 10\%$ from baseline and reduction to $< 50\%$, or LVEF reduction to $< 35\%$ on follow-up echocardiography;
4. Need for septal reduction therapy, including surgical septal myectomy or percutaneous septal alcohol ablation, with treatment indications meeting 2014 ESC guideline recommendations.

All endpoint event information was extracted from electronic medical record system, outpatient, and hospitalization records, and independently determined by two researchers according to the above criteria, with disagreements resolved through discussion.

Statistical methods

Statistical analysis was performed utilizing SPSS 26.0 and R 4.2.0 software. Two-tailed tests were employed for all analyses, with $p < 0.05$ considered statistically significant.

Normality testing was conducted utilizing the Kolmogorov-Smirnov test. Continuous variables with normal distribution are expressed as mean $\pm$ standard deviation (SD), with independent samples t-tests used for between-group comparisons. Continuous variables with non-normal distribution are expressed as median (interquartile range), with Mann-Whitney U tests used for between-group comparisons. Categorical variables are expressed as number (percentage), with χ^2 or Fisher's exact tests used for between-group comparisons. Pearson correlation analysis (for normally distributed data) or Spearman rank correlation analysis (for non-normally distributed data) was employed to assess the correlation between 3D-STE parameters and LGE%.

Variables with $p < 0.10$ in the univariate analysis were entered into the multivariate linear regression model, including age, interventricular septal thickness (IVS), maximum wall thickness (MWT), left atrial volume index (LAVI), left ventricular ejection fraction (LVEF), E/e' ratio, global longitudinal strain (GLS), global circumferential strain (GCS), global radial strain (GRS), global area strain (GAS), three-dimensional global strain (3D-GS), peak twist, twist rate, and standard deviation of time to peak strain (SDT). Multicollinearity was assessed utilizing the variance inflation factor (VIF). $VIF < 5$ considered an indication of no severe multicollinearity.

ROC curve analysis was used to evaluate the diagnostic performance of each parameter in predicting moderate-to-severe fibrosis. The area under the curve (AUC), sensitivity, specificity, and Youden index were calculated. The DeLong test was used to compare the AUCs of different parameters.

Comparisons of segmental strain values employed Bonferroni correction (corrected $\alpha' = 0.003$). Intra-observer and inter-observer reproducibility were assessed utilizing ICC, CV, and Bland-Altman analysis. Survival analysis employed the Kaplan-Meier method to plot survival curves, with a log-rank test for between-group comparisons. Univariate and multivariate Cox proportional hazards regression analyses were used to evaluate prognostic predictors, with the Schoenfeld residuals test used to verify the proportional hazards assumption. Model discrimination was assessed with Harrell's C-index

Results

Baseline characteristics of study population

This investigation enrolled 300 HCM patients. In the mild fibrosis group, 12 patients were lost to follow-up (12/180, 6.7%), and in the moderate-to-severe fibrosis group, 5 patients were lost to follow-up (5/120, 4.2%). The total loss to follow-up rate was 17/300, 5.7%. The 283 patients who completed at least six months of follow-up were included in the final analysis. Based on the CMR-LGE% results, patients were stratified into a mild fibrosis group (LGE% $< 15\%$, $n = 168$) or into a moderate-to-severe fibrosis group (LGE% $\geq 15\%$, $n = 115$).

The baseline clinical data of the two groups are compared in Table 1. The moderate-to-severe fibrosis group were older ($p = 0.003$), had a higher proportion of patients with NYHA functional class III–IV cardiac function ($p < 0.001$), and higher incidence of dyspnea ($p < 0.001$) and syncope or presyncope ($p = 0.023$). The moderate-to-severe fibrosis group exhibited NT-proBNP ($p < 0.001$) and higher cTnI ($p < 0.001$). The moderate-to-severe fibrosis group manifested higher incidence of atrial fibrillation ($p = 0.039$), longer QRS duration ($p = 0.015$), and higher incidence of pathological Q waves ($p = 0.021$).

Table 1. Comparison of baseline clinical data between the two groups

Variable	Mild Fibrosis Group (n=168)	Moderate-to-Severe Fibrosis Group (n=115)	Test Statistic	p Value
Male	98 (58.3)	72 (62.6)	$\chi^2 = 0.531$	0.466
Age (yrs)	51.2 $\pm$ 12.8	55.7 $\pm$ 11.6	$t = 3.035$	0.003
Height (cm)	167.4 $\pm$ 8.6	168.2 $\pm$ 9.1	$t = 0.768$	0.443
Weight (kg)	69.8 $\pm$ 11.2	70.6 $\pm$ 12.4	$t = 0.579$	0.563
BSA (m ²)	1.78 $\pm$ 0.19	1.80 $\pm$ 0.21	$t = 0.859$	0.391
NYHA class III–IV CF	32 (19.0)	51 (44.3)	$\chi^2 = 20.963$	< 0.001
Clinical Symptoms				
Chest pain	89 (53.0)	65 (56.5)	$\chi^2 = 0.359$	0.549
Dyspnea	76 (45.2)	78 (67.8)	$\chi^2 = 14.693$	< 0.001
Palpitations	72 (42.9)	54 (47.0)	$\chi^2 = 0.489$	0.484
Syncope or presyncope	28 (16.7)	32 (27.8)	$\chi^2 = 5.158$	0.023
Family history	45 (26.8)	36 (31.3)	$\chi^2 = 0.740$	0.39
Laboratory Tests				
NT-proBNP (pg/ml)	850 (430, 1520)	2130 (1190, 3630)	$Z = -6.892$	< 0.001
cTnI (ng/ml)	0.04 (0.02, 0.08)	0.12 (0.06, 0.21)	$Z = -5.741$	< 0.001
Hemoglobin (g/l)	138.6 $\pm$ 15.2	136.4 $\pm$ 16.8	$t = 1.141$	0.255
Creatinine (μ mol/l)	78.5 $\pm$ 18.3	81.2 $\pm$ 19.7	$t = 1.195$	0.233
eGFR (ml/min/1.73 m ²)	91.3 $\pm$ 16.8	88.7 $\pm$ 18.2	$t = 1.258$	0.209
Electrocardiogram				
Atrial fibrillation	18 (10.7)	22 (19.1)	$\chi^2 = 4.268$	0.039
QRS duration (ms)	98.4 $\pm$ 14.6	102.8 $\pm$ 16.2	$t = 2.437$	0.015
Pathological Q wave	23 (13.7)	28 (24.3)	$\chi^2 = 5.339$	0.021
ST-T changes	124 (73.8)	95 (82.6)	$\chi^2 = 3.168$	0.075
Treatment Regimen				
β -blockers	116 (69.0)	91 (79.1)	$\chi^2 = 3.639$	0.032
Calcium channel blockers	64 (38.1)	49 (42.6)	$\chi^2 = 0.619$	0.431
Antiarrhythmic drugs	28 (16.7)	34 (29.6)	$\chi^2 = 7.341$	0.006
Baseline septal reduction therapy	6 (3.6)	7 (6.1)	Fisher's exact test	0.389
Baseline ICD implantation	15 (8.9)	24 (20.9)	$\chi^2 = 8.642$	0.003

Data are mean $\pm$ SD, median (interquartile range), or number (percentage). NYHA, New York Heart Association; CF, cardiac function; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator.

Regarding treatment regimens, the moderate-to-severe fibrosis group had higher utilization rates of β -blockers ($p = 0.032$) and antiarrhythmic drugs ($p = 0.006$), and they had a higher baseline ICD implantation rate ($p = 0.003$). No statistically significant differences existed between the two groups in gender, height, weight, BSA, chest pain, palpitations, family history, hemoglobin, creatinine, eGFR, calcium channel blocker utilization rate, and baseline septal reduction therapy ($p > 0.05$ for all).

Table 2. Comparison of three-dimensional speckle tracking echocardiographic parameters between two groups

Parameters	Mild Fibrosis Group (n=168)	Moderate-to-Severe Fibrosis Group (n=115)	Test Statistic	p Value
GLS (%)	-16.8±2.4	-12.6±2.8	t=13.529	<0.001
GCS (%)	-22.4±3.6	-17.8±4.2	t=9.859	<0.001
GRS (%)	38.6±8.2	28.4±7.6	t=10.736	<0.001
GAS (%)	-28.2±4.1	-21.6±4.8	t=12.482	<0.001
3D-GS (%)	-14.2±2.2	-10.4±2.6	t=13.178	<0.001
Peak twist (°)	12.8±3.4	9.6±3.2	t=8.064	<0.001
Twist rate (°/s)	86.4±18.6	68.2±16.4	t=8.524	<0.001
SDT (ms)	42.6±12.8	58.4±16.2	t=9.138	<0.001

Data are mean±SD. 3D-STE, three-dimensional speckle tracking echocardiography; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; GAS, global area strain; 3D-GS, three-dimensional global strain; SDT, standard deviation of time to peak strain.

Comparison of conventional echocardiographic parameters

Compared with the mild fibrosis group, the moderate-to-severe fibrosis group had larger IVS ($p<0.001$), LVPW ($p=0.002$), and MWT ($p<0.001$) (Supplementary Table S2). The moderate-to-severe fibrosis group exhibited larger LAD ($p<0.001$) and LAVI ($p<0.001$), and lower LVEF ($p<0.001$). The moderate-to-severe fibrosis group had higher E/A ratio ($p=0.001$) and E/e' ratio ($p<0.001$). The moderate-to-severe fibrosis group exhibited higher resting and post-Valsalva LVOT gradient ($p<0.001$, $p<0.001$, respectively), and higher SAM positivity rate ($p=0.015$).

Comparison of three-dimensional speckle tracking echocardiographic parameters

The moderate-to-severe fibrosis group had a significantly lower GLS absolute value, GCS absolute value, GRS, GAS absolute value, and 3D-GS absolute value ($p<0.001$ for all) (Table 2). The moderate-to-severe fibrosis group exhibited significantly reduced peak twist and twist rate ($p<0.001$ for both). The moderate-to-severe fibrosis group had a larger myocardial synchrony index SDT ($p<0.001$).

Comparison of left ventricular 17-segment strain values

The longitudinal strain values of left ventricular segments in both groups were analyzed according to the AHA 17-segment model (Supplementary Table S3) [6]. Utilizing the Bonferroni correction for the significance level ($\alpha'=0.003$), the moderate-to-severe fibrosis group demonstrated lower longitudinal strain absolute values in all segments compared with the mild fibrosis group ($p<0.003$). Regional mean strain values for basal segments (segments 1–6), mid segments (segments 7–12), and apical segments (segments 13–17) were calculated by first computing the mean strain of segments

within that region for each patient, then calculating the mean and SD across all patients. The mean absolute longitudinal strain in the basal segments was 17.2 ± 2.8 in the mild fibrosis group and 13.1 ± 3.2 in the moderate-to-severe fibrosis group, with values expressed as percentages of myocardial deformation ($t=11.526$, $p<0.001$). The mid segment mean longitudinal strain absolute values were $-16.9 \pm 2.6\%$ for the mild fibrosis group and $-12.8 \pm 3.0\%$ for the moderate-to-severe fibrosis group ($t=12.284$, $p<0.001$). The apical segment mean longitudinal strain absolute values were $16.1 \pm 3.2\%$ for the mild fibrosis group and $-11.8 \pm 3.6\%$ for the moderate-to-severe fibrosis group ($t=10.528$, $p<0.001$).

Septal segments (segments 2, 3, 8, 9, 14) demonstrated more pronounced strain impairment, particularly in the moderate-to-severe fibrosis group. Inter-segmental strain difference was $4.8 \pm 2.1\%$ for the mild fibrosis group and $7.6 \pm 3.2\%$ for the moderate-to-severe fibrosis group ($t=8.264$, $p<0.001$), indicating more significant myocardial strain heterogeneity in the moderate-to-severe fibrosis group (Supplementary Table S3).

Comparison of cardiac magnetic resonance imaging parameters

The moderate-to-severe fibrosis group demonstrated larger LVEDV index ($p=0.004$), larger LVESV index ($p<0.001$), lower LVEF ($p<0.001$), and higher LVMI ($p<0.001$) values. The moderate-to-severe fibrosis group exhibited greater LGE mass ($p<0.001$), higher LGE% ($p<0.001$), and more LGE-involved segments ($p<0.001$). Regarding LGE distribution pattern, the moderate-to-severe fibrosis group demonstrated a higher proportion of diffuse distribution ($p<0.001$) (Supplementary Table S4).

Correlation between three-dimensional speckle tracking echocardiographic and other parameters with degree of myocardial fibrosis

The results of the correlation analyses between 3D-STE parameters, clinical parameters, conventional echocardiographic parameters, and LGE% are presented in Supplementary Table S5. All the 3D-STE parameters correlated negatively with LGE% ($p<0.001$ for all), but there was some variation in the strength of the correlation. Among conventional echocardiographic parameters, MWT, LAVI, and E/e' ratio were positively correlated with LGE%, while LVEF was negatively correlated with LGE% ($p<0.001$ for all). The clinical parameters, were positively correlation with LGE% ($p<0.001$ for all), but the correlation with age was weak.

Multivariate linear regression analysis of myocardial fibrosis degree

To screen for independent predictors of the degree of myocardial fibrosis, univariate linear regression analysis was

Table 3. Multivariate linear regression analysis of myocardial fibrosis degree

Parameter	Unstandardized Coefficient β	Standard Error SE	Standardized Coefficient β	t Value	p Value	VIF
Constant	2.846	3.124	–	0.911	0.363	–
3D-GS absolute value	–2.134	0.286	–0.486	–7.462	<0.001	2.18
SDT	0.096	0.024	0.218	4	<0.001	1.86
MWT	0.312	0.098	0.195	3.184	0.002	2.42
E/e' ratio	0.228	0.086	0.162	2.651	0.008	1.94

Model adjusted $R^2=0.624$, $F=115.682$, $p<0.001$. 3D-GS, three-dimensional global strain; SDT, standard deviation of time to peak strain; MWT, maximum wall thickness; E/e', ratio of early diastolic transmitral peak velocity to early diastolic mitral annular velocity; SE, standard error; VIF, variance inflation factor. Adjusted R^2 , adjusted coefficient of determination.

Table 4. ROC curve analysis of three-dimensional speckle tracking echocardiographic parameters for predicting moderate-to-severe fibrosis

Parameter	AUC	95% CI	Optimal Cutoff	Sensitivity (%)	Specificity (%)	Youden Index	Positive Predictive Value (%)	Negative Predictive Value (%)	Comparison with 3D-GS
GLS absolute value (%)	0.872	0.833–0.911	14.5	83.5	81	0.645	76.8	86.7	$Z=2.184$; $p=0.029$
GCS absolute value (%)	0.801	0.754–0.848	19.8	76.5	75.6	0.521	70.4	81	$Z=3.486$; $p<0.001$
GRS (%)	0.818	0.773–0.863	32.6	78.3	77.4	0.557	72	82.6	$Z=2.982$; $p=0.003$
GAS absolute value (%)	0.862	0.821–0.903	24.2	80.9	82.1	0.63	76.2	85.8	$Z=2.256$; $p=0.024$
3D-GS absolute value (%)	0.896	0.860–0.932	12.1	86.1	82.7	0.688	78.6	88.9	Reference
Peak twist (°)	0.806	0.760–0.852	10.8	77.4	76.2	0.536	71.2	81.6	$Z=3.642$; $p<0.001$
Twist rate (°/s)	0.782	0.734–0.830	75.6	73.9	74.4	0.483	68.4	79.2	$Z=4.286$; $p<0.001$
SDT (ms)	0.784	0.735–0.833	51.2	73.9	74.4	0.483	68	79.4	$Z=4.182$; $p<0.001$

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; GAS, global area strain; 3D-GS, three-dimensional global strain; SDT, standard deviation of time to peak strain.

first performed for each parameter. Univariate linear regression of age, clinical symptoms, laboratory indicators, conventional echocardiographic parameters, and 3D-STE parameters were significantly associated with LGE%. Specifically, age ($p=0.002$), IVS ($p<0.001$), MWT ($p<0.001$), LAVI ($p<0.001$), LVEF ($p<0.001$), E/e' ratio ($p<0.001$), GLS ($p<0.001$), GCS ($p<0.001$), GRS ($p<0.001$), GAS ($p<0.001$), 3D-GS ($p<0.001$), peak twist ($p<0.001$), twist rate ($p<0.001$), and SDT ($p<0.001$) were associated with LGE% (all $p<0.10$).

Variables with $p<0.10$ in the univariate analyses were first entered into an initial multivariable linear regression model. A stepwise selection procedure was then applied, with $p<0.05$ as the criterion for retention in the final model and $p>0.10$ as the criterion for removal. Multicollinearity testing demonstrated the following VIF values: 3D-GS (VIF=2.18), peak twist (VIF=2.64), twist rate (VIF=2.58), SDT (VIF=1.86), MWT (VIF=2.42), E/e' ratio (VIF=1.94), all less than five, indicating absence of severe multicollinearity. Results demonstrated that 3D-GS absolute value ($\beta=-0.486$, $p<0.001$), SDT ($\beta=0.218$, $p<0.001$), MWT ($\beta=0.195$, $p=0.002$), and E/e' ratio ($\beta=0.162$, $p=0.008$) were independent predictors of LGE%, with model adjusted $R^2=0.624$ (Table 3). Notably, although peak twist and twist rate were significantly associated with LGE% in the variate analysis, in the multivariate

stepwise regression analysis, when 3D-GS was included in the model, torsion parameters did not enter the final model due to not meeting the inclusion criterion ($p<0.05$), suggesting their predictive value was inferior to 3D-GS.

Diagnostic performance of three-dimensional speckle tracking echocardiographic parameters in predicting moderate-to-severe myocardial fibrosis

ROC curve analysis demonstrated that 3D-GS absolute value achieved the highest AUC for predicting moderate-to-severe fibrosis (0.896, 95% CI: 0.860–0.932), with an optimal cutoff value of 12.1%, sensitivity of 86.1%, and specificity of 82.7%. The AUC of GLS absolute value was 0.872 (95% CI: 0.833–0.911), with an optimal cutoff value of 14.5%, sensitivity of 83.5%, and specificity of 81.0%. The AUC of GAS absolute value was 0.862 (95% CI: 0.821–0.903), with an optimal cutoff value of 24.2%, sensitivity of 80.9%, and specificity of 82.1%. The AUC of peak twist was 0.806 (95% CI: 0.760–0.852), and that of twist rate was 0.782 (95% CI: 0.734–0.830), both significantly lower than the 3D-GS absolute value.

DeLong test demonstrated that the AUC of 3D-GS absolute value was significantly higher than all other parameters: compared with GLS absolute value ($Z=2.184$, $p=0.029$), compared with GCS absolute value ($Z=3.486$, $p<0.001$),

Table 5. Endpoint event occurrence during follow-up

Endpoint Event	Total (n=283)	Mild Fibrosis Group (n=168)	Moderate-to-Severe Fibrosis Group (n=115)	χ^2 Value	p Value
Primary composite endpoint event (first event)	92 (32.5)	33 (19.6)	59 (51.3)	30.624	<0.001
First Event Type Distribution					
Cardiac death	8 (2.8)	1 (0.6)	7 (6.1)	Fisher's exact test	0.005
Heart failure hospitalization	58 (20.5)	21 (12.5)	37 (32.2)	16.518	<0.001
Malignant ventricular arrhythmic events	18 (6.4)	6 (3.6)	12 (10.4)	5.428	0.02
Cardiogenic syncope	5 (1.8)	2 (1.2)	3 (2.6)	Fisher's exact test	0.391
Stroke or TIA	3 (1.1)	3 (1.8)	0 (0)	Fisher's exact test	0.288
Secondary Endpoint Events (Total Occurrence):					
New-onset atrial fibrillation	38 (13.4)	16 (9.5)	22 (19.1)	5.578	0.018
Significant deterioration of left ventricular systolic function	24 (8.5)	7 (4.2)	17 (14.8)	10.341	0.001
Need for septal reduction therapy	16 (5.7)	8 (4.8)	8 (7.0)	0.658	0.417

Data are number (percentage). Primary composite endpoint events only record the first event type occurring for each patient according to the study protocol, therefore the sum of each event type equals the total MACE cases (92 cases). Secondary endpoint events represent total occurrence statistics.

compared with GRS ($Z=2.982$, $p=0.003$), compared with GAS absolute value ($Z=2.256$, $p=0.024$), compared with peak twist ($Z=3.642$, $p<0.001$), compared with twist rate ($Z=4.286$, $p<0.001$), compared with SDT ($Z=4.182$, $p<0.001$) (Table 4).

Follow-up Endpoint Events

During a median follow-up of 18.0 mos (interquartile range 12.0–24.0 mos), 92 of 283 patients (32.5%) experienced the primary composite endpoint, defined as major adverse cardiovascular events (MACE). According to the study protocol, the distribution of first primary endpoint event types was as follows: cardiac death eight cases (2.8%), encompassing sudden cardiac death five cases and heart failure death three cases; heart failure hospitalization 58 cases (20.5%); malignant ventricular arrhythmic events 18 cases (6.4%), encompassing sustained ventricular tachycardia 11 cases, ventricular fibrillation four cases, and appropriate ICD discharge three cases; cardiogenic syncope five cases (1.8%); stroke or TIA three cases (1.1%). No cases of heart transplantation or left ventricular assist device implantation occurred.

Total occurrence of each endpoint event type during follow-up (encompassing non-first events) was as follows: secondary endpoint events included cardiac death eight cases (2.8%), new-onset atrial fibrillation 38 cases (13.4%), significant deterioration of left ventricular systolic function 24 cases (8.5%), need for septal reduction therapy 16 cases (5.7%), surgical septal myectomy 11 cases, and percutaneous septal alcohol ablation 5 cases (Table 5).

The MACE incidence rate in the moderate-to-severe fibrosis group (51.3%, 59/115) was higher than in the mild fibrosis group (19.6%, 33/168), with statistically significant difference ($\chi^2=30.624$, $p<0.001$).

Survival analysis

Kaplan-Meier survival curves demonstrated that the MACE-free survival rate in the moderate-to-severe fibrosis group was lower than in the mild fibrosis group (log-rank $\chi^2=35.842$, $p<0.001$). MACE-free survival rates at 6, 12, 18, and 24 mos for the mild fibrosis group were 94.6% ($n=168$), 88.7% ($n=165$), 83.9% ($n=142$), and 80.4% ($n=98$), respectively. For the moderate-to-severe fibrosis group, these rates were 78.3% ($n=115$), 64.3% ($n=110$), 53.0% ($n=92$), 48.7% ($n=58$), respectively.

Based on the 3D-GS absolute value cutoff of 12.1%, the MACE-free survival rate of patients with an 3D-GS absolute value $\leq 12.1\%$ was lower than in those patients with 3D-GS absolute value $>12.1\%$ (log-rank $\chi^2=42.168$, $p<0.001$).

Univariate cox regression analysis of primary composite endpoint events

Univariate Cox regression analysis results demonstrated that age, NYHA III–IV CF, syncope or presyncope, NT-proBNP, atrial fibrillation, pathological Q wave, MWT, LAVI, LVEF, E/e' ratio, GLS absolute value, GCS absolute value, GRS, GAS absolute value, 3D-GS absolute value, SD, LGE%, and moderate-to-severe fibrosis were associated with MACE. Male sex, BSA, and family history were not associated with MACE (Supplementary Table S6).

Multivariate Cox regression analysis of primary composite endpoint events

Variables with $p<0.10$ in the univariate analysis were included in the multivariate Cox regression model. Multicollinearity testing demonstrated that all variables had VIF values less than five, indicating absence of severe multicollinearity. Schoenfeld residuals test demonstrated that both models met the proportional hazards assumption.

Table 6. Multivariate Cox regression analysis of primary composite endpoint events

Variable	HR	95% CI	Wald χ^2	p Value	VIF
Model 1 (including 3D-GS)					
3D-GS absolute value (per 1% increase)	0.754	0.672–0.847	20.486	<0.001	2.36
NT-proBNP (per 100 pg/ml increase)	1.001	1.000–1.001	7.584	0.006	1.92
E/e' ratio (per 1-unit increase)	1.056	1.018–1.096	8.264	0.004	2.08
NYHA III–IV	2.142	1.368–3.354	11.286	0.001	1.68
Model 2 (including LGE%)					
LGE% (per 1% increase)	1.082	1.058–1.106	32.468	<0.001	2.54
NT-proBNP (per 100 pg/ml increase)	1.001	1.000–1.001	6.312	0.012	1.88
E/e' ratio (per 1-unit increase)	1.048	1.010–1.088	6.184	0.013	2.12
NYHA III–IV	2.036	1.296–3.200	9.642	0.002	1.72

Model 1 Harrell's C-index=0.824 (95% CI: 0.781–0.867); Model 2 Harrell's C-index=0.838 (95% CI: 0.797–0.879); Comparison of the two model C-indices: $Z=1.426$, $p=0.154$; Model 1 proportional hazards assumption test: Schoenfeld residual $\chi^2=3.682$, $p=0.451$; Model 2 proportional hazards assumption test: Schoenfeld residual $\chi^2=4.126$, $p=0.389$; All variables $VIF<5$, no multicollinearity. HR, hazard ratio; CI, confidence interval; VIF, variance inflation factor; 3D-GS, three-dimensional global strain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; E/e', ratio of early diastolic transmitral peak velocity to early diastolic mitral annular velocity; NYHA, New York Heart Association; LGE, late gadolinium enhancement. Harrell's C-index was used to assess model discrimination, and Schoenfeld residuals were used to test the proportional hazards assumption.

tion (Model 1: $\chi^2=3.682$, $p=0.451$; Model 2: $\chi^2=4.126$, $p=0.389$).

For Model 1 (including 3D-GS), the results demonstrated that 3D-GS absolute value, NT-proBNP, E/e' ratio, and NYHA III–IV were significant, independent predictors of MACE (Table 6). The model's Harrell's C-index was 0.824 (95% CI: 0.781–0.867).

When LGE% was employed to replace 3D-GS absolute value in constructing the model (Model 2), LGE%, NT-proBNP, E/e' ratio, and NYHA III–IV were independent predictors of MACE (Table 6). The model's Harrell's C-index of 0.838 (95% CI: 0.797–0.879). The DeLong test demonstrated no statistically significant difference between the two models' C-indices ($Z=1.426$, $p=0.154$).

Sensitivity Analysis

Sensitivity analysis of lost to follow-up cases demonstrated that when lost to follow-up cases were considered as having endpoint events, i.e., the worst-case scenario, the MACE incidence rates in the moderate-to-severe fibrosis group and mild fibrosis group were 55.7% (64/115) and

21.4% (36/168) respectively ($\chi^2=35.482$, $p<0.001$). When the lost to follow-up cases were considered as not having endpoint events (best-case scenario), the MACE incidence rates were 51.3% (59/115) and 19.6% (33/168) respectively ($\chi^2=30.624$, $p<0.001$). Results from analyses of both extreme scenarios were consistent with the conclusions of the main analysis, suggesting that lost to follow-up cases had no substantial impact on the study conclusions.

For the 12 cases employing myocardium with the lowest relative signal intensity as the LGE reference region (mild fibrosis group: 4 cases, LGE% range 8.2%–13.6%; moderate-to-severe fibrosis group: 8 cases, LGE% range 16.8%–32.4%), an exclusion sensitivity analysis was performed. All 12 cases completed follow-up and were included in the main analysis. Following exclusion, the remaining 271 patients were included in a sensitivity analysis. For this subgroup, the correlation coefficient between 3D-GS absolute value and LGE% was -0.708 ($p<0.001$), essentially consistent with the main analysis result ($r=-0.714$). In the multivariate Cox regression analysis, the 3D-GS absolute value remained an independent predictor of MACE (HR=0.761, 95% CI: 0.677–0.855, $p<0.001$), while NT-proBNP (HR=1.001, 95% CI: 1.000–1.001, $p=0.008$), E/e' ratio (HR=1.054, 95% CI: 1.016–1.094, $p=0.005$), and NYHA III–IV (HR=2.186, 95% CI: 1.382–3.459, $p=0.001$) were also independent predictors. The model's C-index equaled 0.819 (95% CI: 0.774–0.864). These results of the sensitivity analyses were consistent with the main analysis, suggesting that the different LGE quantification methods did not substantially affect the main conclusions, and also that the study results were robust.

Discussion

This investigation systematically evaluated the relationship between 3D-STE parameters and the degree of myocardial fibrosis in patients with HCM, and it explored the prognostic predictive value of these parameters. The main findings were:

1. 3D-GS absolute value demonstrated strong correlation ($r=-0.714$) with the CMR-LGE quantitative assessment of the degree of fibrosis. The AUC for predicting moderate-to-severe fibrosis was 0.896, outperforming other strain parameters and torsion parameters.
2. Multivariate analysis demonstrated that the 3D-GS absolute value was an independent predictor of the degree of myocardial fibrosis and adverse prognosis. These results suggest that 3D-STE may become a practical tool for assessing myocardial fibrosis in HCM patients.

Myocardial fibrosis constitutes a critical pathological feature of HCM, intimately associated with disease progression and adverse prognosis [7]. Previous investigations predominantly employed two-dimensional speckle tracking techniques to assess fibrosis, but they were constrained

by angle dependence and single-plane analysis limitations [8]. This investigation employed 3D-STE technology, capable of simultaneously acquiring multiple strain parameters and accurately assessing three-dimensional myocardial deformation. The investigation found that all strain parameters were significantly correlated with LGE%, with 3D-GS demonstrating optimal performance, consistent with previous research findings in dilated cardiomyopathy [9]. 3D-GS integrates longitudinal, circumferential, and radial strain information, so it more comprehensively reflects overall myocardial deformation capacity. Fibrotic myocardium exhibits comprehensively impaired deformation capacity in three-dimensional space which is attributable to increased stiffness and decreased contractility from collagen deposition. Therefore 3D-GS can more sensitively identify fibrotic changes [10].

This investigation found that peak twist and twist rate demonstrated moderate negative correlation with fibrosis degree, but their diagnostic efficacy was lower than 3D-GS. Left ventricular torsion represents a motion pattern generated by the helical arrangement of the myocardial fibers, so fibrosis can affect torsion by disrupting fiber structure and increasing myocardial stiffness [11]. However, multivariate regression analysis demonstrated that torsion parameters did not enter the final model following inclusion of 3D-GS, suggesting that their predictive value was relatively limited. This may result from torsion parameters being more reflective of the overall myocardial coordination rather than to local changes due to fibrosis [12]. Additionally, torsion measurement requires elevated image quality and is subject to large measurement variability, factors that constrain its clinical application [13].

Regarding myocardial synchrony, this investigation found that SDT was significantly increased in the moderate-to-severe fibrosis group, and that SDT was an independent predictor of fibrosis degree. Fibrosis leads to increased electromechanical activity heterogeneity of myocardium, resulting in uncoordinated contraction among different segments [14]. This dyssynchrony not only reflects the degree of fibrosis, but it is also associated with increased arrhythmia risk [15]. Segmental strain analysis demonstrated that septal region strain impairment was particularly obvious in hypertrophic cardiomyopathy [16], consistent with the pathological characteristic of predominant septal involvement in HCM patients [10]. Difference in intersegmental strain was significantly increased in the moderate-to-severe fibrosis group, suggesting heterogeneity of fibrosis distribution [17].

Within this cohort of patients with HCM stratified by myocardial fibrosis burden, the incidence of MACE was significantly higher in the moderate-to-severe fibrosis group than in the mild fibrosis group (51.3% vs. 19.6%,

$p < 0.001$), supporting the association between greater fibrosis burden and worse clinical outcomes. Multivariate Cox regression demonstrated that the 3D-GS absolute value was an independent predictor of MACE, with model C-index comparable to the model incorporating LGE% [18]. This indicates that 3D-STE can provide prognostic assessment capability similar to CMR. Previous investigations have confirmed that LGE is a strong predictor of sudden death and cardiovascular events in HCM patients [19], and this investigation further expands the application value of echocardiography in prognostic assessment. It is noteworthy that NT-proBNP, E/e' ratio, and NYHA classification were also independent predictors of MACE, suggesting that clinical indicators, hemodynamic parameters, and myocardial structural changes jointly influence prognosis [20].

It should be noted that 3D-STE is currently employed predominantly in research and has not been recommended for routine practice by clinical guidelines. Thus, the important potential clinical applications of 3D-STE demonstrated in this investigation require verification through additional large-sample, multi-center investigations to provide sufficient evidence for incorporation into clinical guidelines [21].

This investigation has several limitations. First, this was a single-center retrospective investigation with potential selection bias [22]. Second, the 3D-STE image quality depends on operator technique and patient cooperation [23], and some cases were excluded due to poor image quality. Third, the follow-up time was relatively short, and long-term prognostic value requires further observation [24]. Fourth, in cases of diffuse fibrosis, LGE quantification may be biased because threshold-based LGE analysis requires a reference region of apparently normal myocardium, which may be absent in diffuse disease. As a result, use of the lowest-signal myocardial region as a surrogate reference may shift the threshold for LGE positivity and lead to misestimation of fibrosis burden, potentially resulting in overestimation. Diffuse interstitial fibrosis is also a recognized limitation of LGE-based assessment, for which mapping-based techniques are often considered more suitable [25]. Finally, this investigation did not include genotype information, and different genetic mutations may affect fibrosis patterns and prognosis [26].

Despite limitations, this investigation confirmed that 3D-STE parameters, particularly 3D-GS, are closely correlated with the degree of myocardial fibrosis in HCM patients and that 3D-STE parameters have prognostic value. 3D-STE is straightforward to operate, radiation-free, and has good reproducibility. In the future, 3D-STE potentially will become an important tool for follow-up monitoring of HCM patients. For patients unable to undergo CMR ex-

amination, 3D-STE can serve as an alternative method for assessing fibrosis. Clinical practice should combine clinical symptoms, biomarkers, conventional ultrasound parameters, and 3D-STE indicators for comprehensive assessment. Future research should focus on establishing standardized measurement protocols, clarifying cutoff values for different subgroups, and exploring artificial intelligence-assisted analysis to improve efficiency and accuracy.

Conclusion

In patients with hypertrophic cardiomyopathy, 3D-STE parameters, particularly 3D-GS, were significantly associat-

ed with the extent of myocardial fibrosis and showed favorable diagnostic and prognostic value. As a practical, non-invasive, and radiation-free imaging technique, 3D-STE may serve as a useful adjunctive tool for myocardial fibrosis assessment and risk stratification, especially when CMR-LGE is unavailable or not feasible.

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