Elevated level of N-terminal pro B-type natriuretic peptide is associated with myocardial fibrosis in hypertrophic cardiomyopathy patients with preserved ejection fraction

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Abstract

Background: Myocardial fibrosis assessed by late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) has been reported to be significantly correlated with cardiovascular outcomes in hypertrophic cardiomyopathy (HCM) patients. However, data regarding non-invasive markers for detecting myocardial fibrosis were inconsistent and, not systematically evaluated in HCM patients with preserved ejection fraction (EF).

Methods: In this study, 86 HCM patients with preserved EF and 33 controls were enrolled. The left ventricular function, end-diastolic maximum wall thickness (MWT), global systolic strains and extent of LGE (% LGE) were assessed. The biochemical indices were also recorded before the CMR examination.

Results: Serum high-sensitivity cardiac troponin I (hs-cTnI) and N-terminal pro b-type natriuretic peptide (Nt-proBNP) levels were elevated in LGE-positive patients compared with LGE-negative patients ($p < 0.05$ for all). The LGE-positive patients had lower global longitudinal (GLS) and circumferential (GCS) strains than the LGE-negative group and the healthy controls ($p < 0.05$ for all). The LGE% was independently associated with the Nt-proBNP levels (standardized β = 0.627, $p < 0.001$), beta-blocker treatment (standardized β = -0.372, $p = 0.01$), MWT (standardized β = 0.481, $p = 0.001$) and GCS (standardized β = 0.406, $p = 0.013$). In the receiver operating characteristic (ROC) curve analysis, the combined parameters of Nt-proBNP ≥ 108 pg/mL and MWT ≥ 17.3 mm had good diagnostic performance for LGE, with a specificity of 81.3% and sensitivity of 70.0%.

Conclusions: This study suggests that Nt-proBNP may be a potential biomarker associated with LGE% and, combined with MWT, was useful in detecting myocardial fibrosis in HCM patients with preserved EF. Additionally, LV GCS may be a more sensitive indicator for reflecting the presence of myocardial fibrosis than GLS.

Background

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy and its pathological features manifest as cardiac myocyte hypertrophy, disarray, and fibrosis [1, 2]. Although, myocardial fibrosis is not so much a problem in itself, it is a feature of HCM with important clinical implications such as predisposition to sudden cardiac death (SCD) and progression to advanced disease [3, 4]. Furthermore, myocardial fibrosis may be reversible and has been suggested as a powerful therapeutic target and prognosticator [5, 6]. Extensive late gadolinium enhancement (LGE) imaging on cardiovascular magnetic resonance (CMR) is currently recognized as the gold standard for the identification of left ventricular (LV) focal replacement fibrosis [7]. Data currently suggest that LGE is highly promising in predicting SCD and progression to heart failure in HCM [8, 9]. However, the administration of contrast agents needed for this technology may result in systemic nephrogenic sclerosis [10]. Therefore, identifying the non-invasive biomarkers for the early detection and prediction of myocardial fibrosis could have a role in management and risk stratification in HCM.

Currently, cardiac-specific biomarkers, particularly N-terminal pro b-type natriuretic peptide (Nt-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI), have played a key role in the diagnosis, treatment and risk stratification in the cardiovascular field [11–13]. The two biomarkers are widely used in daily clinical practice due to their easy acquisition, cost-effectiveness, high reproducibility and no contraindications. Although some modest sized studies have been showed a correlation of fibrosis with hs-cTnI and Nt-proBNP [14–16], the prognostic value of both biomarkers in predicting fibrosis in HCM patients was inconsistent and, not systematically evaluated in HCM patients with preserved ejection fraction (EF). Additionally, CMR tissue-tracking technology can evaluate myocardial contractile abnormalities with rapid post-processing for routine cine images [17], which was widely used in various cardiovascular diseases [18–20]. There are some studies showing close correlation between myocardial mechanics and fibrosis in HCM, as well as associations with ventricular arrhythmias [21, 22]. Thus, we speculate that the combination of clinical biomarkers and non-invasive CMR technology may be better utilized to predict myocardial fibrosis and, help clinicians to identify patients with poor prognosis at an early stage.

Our study, therefore, used advanced CMR tissue tracking technology and LGE analysis to explore the correlation between LGE and serum hs-cTnI levels, seurm Nt-proBNP levels, myocardial strains and wall thickness in HCM patients with preserved EF; we further investigated the diagnostic performance of these indexes for the detection of myocardial fibrosis as represented by LGE on CMR.

Methods

Study population

We prospectively recruited 118 consecutive HCM patients and 35 age- and sex-matched controls, who were referred for CMR examination from January 2018 to June 2019. HCM was diagnosed by CMR with the following criteria: unexplained LV wall thickness ≥ 15 mm (or ≥ 13 mm with a clear family history of HCM) in adult patients without any other systemic disease or cardiac diseases that could be responsible for myocardial hypertrophy [1]. The preserved EF was defined as LVEF ≥ 50% by CMR or echocardiography. All HCM patients with evidence of coronary heart disease with significant stenosis ≥ 50% were excluded by computed tomography or invasive coronary angiography. Additionally, patients with evidence of ischemic cardiomyopathy or with a history of invasive cardiac procedure, such as alcohol septal ablation, septal myectomy or heart transplantation, were also excluded. The exclusion criteria for all subjects included renal dysfunction (glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) and any CMR contraindications, such as claustrophobia or inner device implantation. According the above criteria, 19 HCM patients and 2 healthy controls had a LVEF < 50%, 5 patients lacked LGE images because they had renal dysfunction, 4 patients had a history of severe coronary artery disease and 4 patients had a history of cardiac surgery. Thus, 86 HCM patients and 33 healthy controls were eventually enrolled in the present study. This study was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology, and all participants in the study signed informed consent forms autonomously and voluntarily prior to participation.

Laboratory measurements

The biochemical indices included the serum Nt-proBNP, hs-cTnI, creatine kinase (CK), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels, which were obtained for clinical evaluation purposes. Peripheral venous blood samples were collected from all HCM patients at the morning of CMR examination. Blood samples were centrifuged at 3000 rpm for 15 min, and plasma was stored at −80°C for further analysis. An electrochemiluminescent immunoassay assay (Roche Diagnostics, Mannheim, Germany) was performed for measurement of plasma Nt-proBNP levels. The analytical range was 5 to 35000 pg/mL and the normal reference range was ≤ 100 pg/mL. The inter-assay and intra-assay coefficients of variation were < 4.7% and < 5.8%, respectively. Serum levels of hs-cTnI were measured using the Abbott Architect high-sensitivity cTnI assay (Abbott Diagnostics, Abbott Park, USA). The lower limit of detection was 1.2 ng/L; the 99th percentile cutoff value was 26 ng/L; and the coefficient of variation was < 10%. Serum CK, CK-MB, AST and LDH levels were determined using an automatic particle chemiluminescence immunoassay (Abbott Aeroset, Minnesota) with the use of commercial kits (Abbott). The normal reference ranges of the assays were the following: 38 to 174 U/L for CK, < 6.6 ng/mL for CK-MB, 8 to 40 U/L for AST and 109 to 245 U/L for LDH.

CMR examination protocol

All CMR examinations were performed with a 1.5 T system (MAGNETOM Aera, Siemens Healthineers, Erlangen, Germany). The LV long-axis (4-, 3-, 2-chamber) and short -axis (covering all basal to apex segments) cine images were acquired using a balanced steady state free precession (bSSFP) sequence. The parameters were as follows: field of view (FOV): 360 mm × 270 mm, matrix: 256 × 192, repetition time/echo time (TR/TE): 2.9 ms/1.2 ms, flip angle: 80°, and slice thickness: 6 mm. LGE images of the LV long-axis (4-, 3-, 2-chamber) planes and whole LV short-axis slices were performed 10 to 15 minutes after the cubital intravenous administration of a bolus of gadolinium-diethylenetriamine pentaacetic acid (DTPA) (0.2 mmol/kg, Magnevist, Bayer Healthcare, Berlin, Germany) using a phase-sensitive inversion recovery (PSIR) sequence. The parameters were as follows: FOV: 360 mm × 270 mm, matrix: 256 ×192, TR/TE: 12.44 ms/1.19 ms, inversion recovery time: 300 ms; flip angle: 40°, and slice thickness: 8 mm.

CMR image analysis

All CMR image analyses were semi-quantitatively performed using the commercial post-processing software (Cvi42, Circle Cardiovascular imaging, Calgary, AB, Canada).

For the quantification of LV volume and function, we imported all short-axis cines into the software and then manually delineated the LV endocardial and epicardial contours. All cardiac functional parameters were indexed to the body surface area (BSA) in this study. The LVEF, end-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume index (SVI), cardiac index and end-diastolic myocardial mass (MI) were acquired. Additionally, the LV end-diastolic maximum wall thickness (MWT) was defined as the greatest segments of the 16-segment model of the American Heart Association (AHA). For the quantification of LV myocardial strain, we imported all LV long- and short-axis cines into the software.

Then, we manually delineated the LV endocardial and epicardial contours of all the above images in the end diastole stage. Then, the LV 3D global peak systolic longitudinal strain (GLS), circumferential strain (GCS) and radial strain (GRS) were semi-quantitatively calculated using the tissue feature tracking method (Fig. 1).

For the quantification of the extent of LGE, we imported the whole LV short-axis slices of the LGE images into the software and manually delineated the LV endocardial and epicardial contours. A semi-quantitative grey-scale threshold method was used to calculate the extent of LGE. The enhanced myocardium was defined as a signal intensity threshold of > 6 SD above the mean signal intensity of the normal myocardium [23, 24]. The previous studies demonstrated that the 6SD is the most optimal threshold especially for quantitative LGE in patients with HCM, as it is most strongly correlated with histopathology [23], as well as manual measurements [24]. Then, the total LV enhanced volume and mass were calculated, and the extent of LGE was expressed as the percentage of the total myocardial mass (%LGE) (Fig. 2). The HCM patients were divided into two subgroups based on the presence or absence of LGE. All papillary muscles and trabeculae were excluded from the LV myocardium during the LV function, deformation and LGE analyses.

Statistical analysis

The Kolmogorov–Smirnov test was used to check normality. Data are expressed as the mean ± SD or number (percentage) for all continuous and categorical variables. Differences between two groups were assessed using an independent-sample Student's t test or the Mann-Whitney test. Comparisons between three groups were analyzed using one-way ANOVA or the Kruskal-Wallis test, and the Bonferroni correction was selected as the post hoc test when appropriate. The chi-square test or Fisher's exact test was used for the comparison of all categorical variables. Pearson's or Spearman's correlation test was applied for the assessment of the LGE% and all candidate variables, as appropriate. Univariate and multivariate linear regression analyses were utilized to assess the associations between the LGE% and all candidate variables. Receiver operating characteristic (ROC) curve analysis was applied for the detection of the diagnostic performance of the presence of LGE. The highest Youden's index values were used to calculate the optimal cut-off values of the candidate variables. The sensitivity, specificity, optimal cut-off value, positive predictive value (PPV) and negative predictive value (NPV) were calculated and expressed with the corresponding 95% confidence intervals (CI). An intra-class correlation coefficient (ICC) with 95% CI was used for the assessment of the intra- and inter-observer agreement. A two-sided p value < 0.05 was considered statistically significant. Analyses were performed using SPSS Statistics (SPSS, version 21, IBM, Chicago, IL, USA) and MedCalc 16.2.0 (MedCalc Software, Mariakerke, Belgium).

Results

Baseline and biochemical characteristics

Table 1 presents the baseline and biochemical characteristics of the 86 HCM patients and 33 normal controls, as well as the HCM subgroups stratified by the presence of LGE (48 subjects with LGE, 38

subjects without LGE). The LGE-negative patients had a significantly higher heart rate than the controls and LGE positive patients ($p < 0.01$). The serum hs-cTnI and Nt-proBNP levels were significantly higher in LGE-positive patients than in LGE-negative patients ($p < 0.01$ for all) (Fig. 3, A and B). The LGE-positive patients had a significantly higher serum CK-MB levels than the LGE-negative group ($p < 0.05$ for all). There were no significant differences in any other characteristics of the study population, which are listed in Table 1.

Table 1 Demographic and clinical characteristics of the study population

	Controls (n=33)	Total (n=86)	*p* value	LGE negative (n=38)	LGE positive (n=48)	*p'* value
	47.85 ± 10.37	52.81 ± 11.92	0.316	51.71 ± 13.16	53.69 ± 10.90	0.085
	25 (75.76)	70 (81.40)	0.610	32 (84.22)	38 (79.17)	0.668
	168.27 ± 6.00	169.67 ± 6.22	0.637	169.66 ± 6.84	169.71 ± 5.76	0.538
	68.46 ± 8.76	71.79 ± 10.53	0.436	71.76 ± 10.44	71.81 ± 10.71	0.278
	24.17 ± 2.80	24.8 6 ± 2.94	0.746	24.83 ± 2.58	24.88 ± 3.22	0.517
	1.79 ± 0.13	1.85 ± 0.16	0.294	1.85 ± 0.16	1.84 ± 0.17	0.197
eristics, n, %						
pm)	64.39 ± 10.23	69.81 ± 10.83	0.066	71.32 ± 9.71*	68.63 ± 11.61#	**0.009**
	-	25.47 ± 37.61	-	20.73 ± 32.09	29.61 ± 41.82	0.122
	-	34 (39.53)	-	12 (31.58)	22 (45.83)	0.192
ve	-	52 (60.47)	-	26 (68.42)	26 (54.17)	0.192
nal	-	48 (55.81)	-	26 (68.42)	22 (45.83)	-
nal	-	27 (31.40)	-	8 (21.05)	19 (39.58)	-
al	-	11 (12.79)	-	3 (7.89)	7 (14.58)	-
	0 (0)	36 (41.86)	-	16 (42.11)	20 (41.67)	1.000
	0 (0)	12 (13.95)	-	2 (5.56)	10 (20.83)	0.058
	0 (0)	20 (23.26)	-	9 (23.68)	11 (22.92)	1.000
	-	41 (47.67)	-	16 (42.11)	25 (52.08)	0.391

	-	15 (17.44)	-	7 (18.42)	8 (16.67)	1.000
of	0 (0)	0 (0)	-	0 (0)	0 (0)	-
e						
%						
	-	53 (61.6)		23 (60.5)	30 (62.5)	1.000
cker	-	36 (41.86)	-	26 (42.11)	20 (41.67)	0.570
r ARB	-	31 (36.05)	-	14 (36.84)	17 (35.42)	1.000
	-	23 (26.74)	-	6 (15.79)	17 (35.42)	0.051
	-	22 (25.58)	-	6 (38)	16 (48)	0.083
	-	1 (1.16)	-	0 (0)	1 (2.08)	1.000
	-	29.34 ± 21.16		27.52 ± 18.08	30.51 ± 23.07	0.469
	-	207.36 ± 662.00		136.76 ± 83.06	252.61 ± 846.66	0.071
	-	208.03 ± 61.79		212.96 ± 55.27	204.87 ± 66.13	0.378
L)	-	2.30 ± 2.60		1.80 ± 1.72	2.63 ± 3.02	**0.038**
	-	83.89 ± 249.90		43.53 ± 132.04	111.13 ± 303.59	**< 0.001**
/mL)	-	263.67 ± 320.01		170.42 ± 289.14	321.95 ± 328.81	**0.003**

The *p* values reflect the comparison between 2 groups (controls vs. total). The *p'* values reflect the comparison between 3 subgroups (controls vs. LGE (-) vs. LGE (+)) or 2 subgroups (LGE (-) vs. LGE (+)), respectively. * < 0.05 vs. controls. # < 0.05 vs. LGE (-)

LGE late gadolinium enhancement, BMI body mass index, BSA body surface area, LVOTG peak left ventricular outflow tract gradient, NYHA New York heart association, ACE angiotensin-converting enzyme, ARB angiotensin-receptor blocker, AST aspartate aminotransferase, CK creatine kinase, LDH lactate dehydrogenase, CK-MB

creatine kinase-MB, Nt-proBNP N-terminal pro b-type natriuretic peptide, hs-cTnI high-sensitivity cardiac troponin I.

CMR parameters

Table 2 shows the CMR parameters in HCM patients and the healthy controls as well as in the HCM subgroups stratified by the presence of LGE. The LVEF of all HCM patients was more than 50% (range from 50.83% to 77.73%). Among the 48 LGE-positive patients, the mean LGE% was 10.22 ± 6.24%. Based on the LV myocardial systolic strain analysis, all HCM patients had a significantly lower GLS, GCS and GRS than the healthy controls ($p < 0.05$ for all). Additionally, the GLS and GCS were significantly lower in the LGE-positive patients than the LGE-negative group and the healthy controls ($p < 0.05$ for all). However, there were no significant differences in GLS, GCS and GRS between the LGE-negative patients and the healthy controls. The differences in any other LV volume and function parameters are shown in Table 2.

Table 2 CMR parameters of the study population

	Controls (n=33)	Total (n=86)	*p* value	LGE negative (n=38)	LGE positive (n=48)	*p′* value
ıd strains						
	57.41 ± 5.47	65.21 ± 6.25	0.327	66.38 ± 5.78*	64.29 ± 6.56*	**< 0.001**
ı^2)	57.15 ± 9.14	65.52 ± 16.48	**0.017**	59.58 ± 13.48*	70.23 ± 17.23*	**< 0.001**
ı^2)	24.59 ± 5.60	22.99 ± 7.79	0.302	20.15 ± 6.01*	25.23 ± 8.34*#	**0.004**
)	32.56 ± 4.43	42.53 ± 10.72	**< 0.001**	39.43 ± 9.18*	44.99 ± 11.29*	**< 0.001**
ex	2.10 ± 0.38	2.72 ± 0.76	**< 0.001**	2.53 ± 0.69*	2.87 ± 0.78*	**< 0.001**
	42.90 ± 5.94	78.97 ± 30.06	**< 0.001**	64.21 ± 18.71	90.67 ± 40.39*#	**< 0.001**
	9.16 ± 1.13	18.17 ± 4.34	**< 0.001**	16.09 ± 3.47*	19.82 ± 4.27*#	**< 0.001**
	-14.77 ± 2.36	-11.55 ± 3.70	**< 0.001**	-13.43 ± 2.97	-10.11 ± 3.57*#	**< 0.001**
	-20.92 ± 2.54	-20.01 ± 3.58	**0.036**	-21.53 ± 2.85	-18.86 ± 3.67*#	**0.001**
	36.58 ± 8.70	33.25 ± 12.74	**0.030**	35.54 ± 9.10	31.51 ± 14.80	0.055
lume	-	-	-	-	16.71 ± 12.30	-
lass	-	-	-	-	17.55 ± 12.92	-
lass	-	-	-	-	10.22 ± 6.24	-

The p and p' values reflect comparisons between 2 groups (controls. Vs. total) and 3 subgroups (controls. Vs. LGE (-). Vs. LGE (+)), respectively. $^{*} < 0.05$ vs. controls. $^{\#} < 0.05$ vs. LGE (-).

CMR cardiovascular magnetic resonance, LGE late gadolinium enhancement, LV left ventricular EF ejection fraction EDVI end-diastolic volume index ESVI end-systolic volume index SVI stroke volume index MI myocardial mass index MWT maximum wall thickness GLS global longitudinal strain GCS global circumferential strain GRS global radial strain.

Correlations of LGE% with clinical and CMR parameters.

The results of the univariate and multivariate regression analysis of the LGE% and the baseline clinical and CMR characteristics in HCM patients are described in Table 3. The LGE% in HCM patients was inversely associated with the use of beta-blockers and the GCS and was associated with an increased serum Nt-proBNP level and a greater MWT ($p < 0.05$ for all) (Fig. 3, C-F). Furthermore, any candidate variables with $p < 0.3$ and without collinearity on the univariate analysis were chosen for inclusion in the multinomial linear regression analysis using a stepwise algorithm model. The independent determinants of the LGE% were the serum Nt-proBNP level (standardized β = 0.672, $p < 0.001$) and MWT (standardized β = 0.481, $p = 0.001$). The use of beta-blockers (standardized β = -0.372, $p = 0.010$) and GCS (standardized β = 0.406, $p = 0.013$) were also independently correlated with the LGE% (Table 3).

Table 3 Univariate and multivariate regression analysis for LGE (LGE%) and the clinical and CMR indicators in HCM patients

Variables	LGE%			
	Univariate analysis		Multivariate analysis	
	r value	*p* value	Standardized β	*p* value
Age (years)	0.018	0.905		
Male (%)	0.050	0.736		
BMI (kg/m^2)	0.010	0.947		
Heart rate (bpm)	-0.178	0.226		
LVOTG at rest (mmHg)	-0.099	0.550		
Obstructive (%)	0.017	0.911		
NYHA functional (%)	0.046	0.757		
Hypertension (%)	-0.035	0.813		
Diabetes (%)	0.065	0.663		
Hyperlipidemia (%)	-0.182	0.222		
Smoker (%)	-0.128	0.386		
Drinker (%)	0.016	0.913		
Beta-blocker (%)	-0.383	**0.007**	0.372	**0.010**
Ca-channel blocker (%)	0.096	0.516		
ACE inbibitor or ARB (%)	0.024	0.874		
Diuretic (%)	0.239	0.102		
Trimetazidine (%)	-0.051	0.730		
Digoxin (%)	0.153	0.300		
AST (U/L)	-0.279	0.085		
CK (U/L)	0.011	0.946		
LDH (U/L)	0.053	0.749		
CK-MB (ng/mL)	0.190	0.323		
hs-cTnI (ng/mL)	0.160	0.323		
Nt-proBNP (pg/mL)	0.565	**0.001**	0.627	**<0.001**
EF (%)	-0.191	0.194		
EDVI (mL/m^2)	-0.019	0.899		

ESVI (mL/m^2)	0.075	0.613		
SVI (mL/m^2)	-0.118	0.423		
Cardiac index (L/min/m^2)	-0.174	0.237		
MI (g/m^2)	0.017	0.907		
MWT (mm)	0.486	**<0.001**	0.481	**0.001**
GLS (%)	0.163	0.279		
GCS (%)	0.369	**0.012**	0.406	**0.013**
GRS (%)	-0.260	0.081		

LGE late gadolinium enhancement, BMI body mass index, LVOTG peak left ventricular outflow tract gradient, NYHA New York heart association, ACE angiotensin-converting enzyme, ARB angiotensin-receptor blocker, AST aspartate aminotransferase, CK creatine kinase, LDH lactate dehydrogenase, CK-MB creatine kinase-MB, hs-cTnI high-sensitivity cardiac troponin I, Nt-proBNP N-terminal pro b-type natriuretic peptide, LV left ventricular, EF ejection fraction, EDVI end-diastolic volume index, ESVI end-systolic volume index, SVI stroke volume index, MI myocardial mass index, MWT maximum wall thickness, GLS global longitudinal strain, GCS global circumferential strain, GRS global radial strain.

ROC curve analysis

ROC curve analysis was applied to assess the diagnostic performance of MWT, GCS and the serum Nt-proBNP level for the identification of the presence of LGE in HCM patients (Table 4). The ROC curve analysis demonstrated the optimal cut-off values of MWT, GCS, and Nt-proBNP were 17.3 mm ($p < 0.001$), -18.6 ($p = 0.001$) and 108 pg/mL ($p = 0.003$), respectively. Additionally, the combination of MWT ≥ 17.3 mm with Nt-proBNP ≥ 108 pg/mL for the identification of the presence of LGE had a relatively higher area under curve (AUC) (AUC = 0.80), with a sensitivity of 81.25%, a specificity of 70%, a PPV of 77.38% and an NPV of 74.72% (Fig 4).

Table 4 Diagnostic performance of MWT, GCS and Nt-proBNP for identifying the presence of LGE

Variables	AUC	Sensitivity	Specificity	PPV (%)	NPV (%)
MWT ≥ 17.3mm	0.76 (0.66 - 0.86)	70.83 (55.9 - 83.0)	68.42 (51.3 - 82.5)	73.91 (58.86 - 85.73)	64.50 (48.32 - 79.37)
GCS ≥ -18.6	0.72 (0.61 - 0.83)	47.83 (32.9 - 63.1)	88.57 (73.3 - 96.8)	84.09 (65.09 - 95.17)	57.34 (43.75 - 70.17)
Nt-proBNP ≥ 108pg/mL	0.74 (0.60 - 0.86)	71.87 (53.3 - 86.3)	0.80 (56.3 - 94.3)	81.94 (67.04 - 92.08)	69.25 (53.51 - 82.27)
Nt-proBNP+GCS	0.73 (0.59 - 0.87)	53.33 (34.3 - 71.7)	89.47 (66.9 - 98.7)	86.48 (68.90 - 96.19)	60.28 (46.38 - 73.07)
Nt-proBNP+MWT	0.80 (0.67 - 0.92)	81.25 (63.6 - 92.8)	70.0 (45.7 - 88.1)	77.38 (63.41 - 87.96)	74.72 (57.39 - 87.74)

MWT maximum wall thickness, GCS global circumferential strain, Nt-proBNP N-terminal pro b-type natriuretic peptide, LGE late gadolinium enhancement, HCM hypertrophic cardiomyopathy, AUC area under curve, PPV positive predictive value, NPV negative predictive value.

Repeatability analysis

For the repeatability analysis, 20 of the total sample and 15 LGE-positive patients were selected. The ICC with 95% CI was used for assessment of the intra- and inter-observer agreement. The ICC values of the intra-observer agreement for LVEF, GLS, GCS, GRS and the extent of LGE were 0.968, 0.962, 0.947, 0.924 and 0.976, respectively. In addition, the ICC values of the inter-observer agreement for LVEF, GLS, GCS, GRS and the extent of LGE were 0.957, 0.944, 0.928, 0.905 and 0.953, respectively.

Discussion

The present results demonstrated that serum levels of Nt-proBNP and hs-cTnI were significantly higher in LGE-positive HCM patients with preserved EF, and the elevated levels of serum Nt-proBNP were independently associated with the LGE%. The combination of Nt-proBNP ≥ 108 pg/ml and MWT ≥ 17.3 mm had good diagnostic performance for the detection of LGE on CMR. Additionally, GLS and GCS were significantly decreased especially in LGE-positive group, and the impaired GCS was independently correlated with the LGE%. Moreover, the use of beta-blockers was correlated with a lower extent of myocardial fibrosis measured by LGE on CMR.

It is now well established that the serum Nt-proBNP and hs-cTnI levels were elevated in LGE-positive patients than in LGE-negative patients [14, 16, 25, 26]. However, few data are available regarding the two biomarkers' utility for detecting LGE in HCM patients, and the prognostic value of both biomarkers in

predicting fibrosis was inconsistent [14-16]. One study demonstrated that only the hs-cTnI was an independent indicator of the presence of LGE [14]. On the contrary, another study revealed that Nt-proBNP, not hs-cTnI, was strongly correlated with the amount of LGE [15]. And the present study not only showed that the serum levels of Nt-proBNP were correlated with the LGE% in multivariate analyses, but also was useful for the detection of myocardial fibrosis. The above differences in the relationship between the circulating biomarkers and the LGE% may be due to the different study populations and methods of quantifying LGE with CMR. Specifically, in line with the study by Kawasaki et al.[16] our study excluded patients with LVEF < 50%, whereas the other two studies did not [14, 15]. Additionally, previous studies usually used the visual scoring or semiquantitative scoring method [14, 27], and the 2SD thresholding method was used in Kawasaki's study [16]. The current study used a semi-quantitatively grey-scale threshold method (6SD), previously shown to yield improved interobserver variability, reproducibility and precision with regards to LGE, as well as stronger correlations with histopathology in HCM patients [23, 28].

Circulating Nt-proBNP is primarily produced by cardiomyocytes and is released in response to increased myocardial tension, stretching and neurohormonal activation [29]. However, the underlying mechanisms of the associations between elevated levels of Nt-proBNP and myocardial fibrosis in HCM patients are still under investigation. There are multiple possible explanations for the correlation between elevated Nt-proBNP and LGE. Previous research findings implicated that myocardial fibrosis could promote diastolic dysfunction and abnormal microcirculation, leading to ischemia and replacement scarring [30-32]. Additionally, direct Nt-proBNP synthesis by cardiac fibroblasts, as an inhibitory antifibrotic response via the extracellular signal-related kinase pathway has been demonstrated [33]. Thus, there is adequate pathophysiological background to consider investigating the potential of Nt-proBNP as a biomarker reflecting myocardial fibrosis.

Additionally, we also found that the LGE% was independently associated with MWT, which is consistent with the results of several previous studies [14, 27, 34] . As the presence of LGE could be observed especially in areas of ventricular hypertrophy in HCM patients [35], the correlation between MWT and myocardial fibrosis is considered reasonable. Moreover, a level of Nt-proBNP ≥ 108 pg/mL and MWT ≥ 17.3 mm had excellent diagnostic performance for the detection of LGE on CMR. These results suggest that the measurement of Nt-proBNP and MWT could be a non-invasive method of predicting myocardial fibrosis in HCM patients with preserved EF. Our findings are expected to help clinicians to identify patients with poor prognosis at an early stage, especially for patients who cannot complete the LGE examination.

The present study also found that the GLS and GCS were significantly decreased, which was especially true in LGE-positive patients. Although the LVEF was normal or increased in the vast majority of HCM patients, the individual cardiac myocyte contractile and stretching forces were damaged and decreased, resulting in intrinsic dysfunction and myocardial remodeling [36, 37]. Thus, myocardial systolic strains can detect cardiac dysfunction earlier than LVEF, especially in HCM patients with preserved EF. Additionally, we found that myocardial fibrosis was independently correlated with the GCS, while no correlation was observed with GLS or GRS. Some previous studies demonstrated that GLS was

associated with the extent of LGE [38, 39], while Erley et al.[40] found that LGE was correlated with GCS in HCM patients. A possible explanation of the above differences may be the differences in the post-processing software used, the deformation acquisition techniques, study populations, clinical stages and medications in previous studies. The current study showed that the GCS is not only independently associated with LGE%, but also useful for detecting myocardial fibrosis based on ROC curve analysis, therefore suggesting its potential clinical utility for reflecting the presence of LGE.

In the present study, LGE negative patients had higher heart rate compared to both controls and LGE positive patients. Although beta-blocker use was similar in both HCM groups, dosage may have been different possibly explaining observed differences in heart rate. Additionally, the present results showed that the use of beta-blockers was significantly correlated with less myocardial fibrosis as measured by LGE on CMR. Beta-blockers therapy have proved effective in reducing myocardial ischemia and LVOT obstruction, and the current guidelines suggested these drugs as first-line treatment in symptomatic patients with HCM, regardless of whether LV outflow obstruction exists [1, 41]. The advantages of beta-blockers are mediated by sympathetic modulation of myocardial contractility, stiffness and heart rate, which can improve myocardial compliance and increase ventricular diastolic filling time [42, 43]. However, to our knowledge, there are no studies demonstrating that beta-blockers treatment is associated with the amelioration of myocardial fibrosis in HCM patients. Whether beta-blockers therapy has a direct effect on the prevention, improvement or reversal of myocardial fibrosis needs to be further investigated in a longitudinal large-cohort study to determine whether there is a relationship between the duration of beta-blocker therapy, the order of beta-blocker therapy and HCM diagnosis, and the extent of LGE.

Limitations

There are several limitations in the present study. First, the sample size was relatively small. Second, this was a single-centre study, and the HCM subjects were selected with stringent criteria; therefore, some inherent biases were inevitable. Third, although LGE on CMR is limited to identifying diffuse myocardial fibrosis, this technique is widely and frequently used to assess myocardial fibrosis in different types of cardiovascular diseases. The 6SD thresholding method chosen in our study is the optimal method, especially for quantitative LGE in patients with HCM, as it is most strongly correlated with histopathology [23]. However, future large cohort studies with longer follow-up are needed to further confirm the parameters and predictors of the presence of LGE in HCM patients.

Conclusions

In conclusion, our results show that Nt-proBNP is a useful biomarker for detecting LGE and, combined with MWT, has good diagnostic performance for myocardial fibrosis in HCM patients with preserved EF. Additionally, the decreased LV GCS was independently correlated with the LGE%, indicating its potential prognostic value for detecting myocardial fibrosis. These findings suggesting that the combined non-invasive clinical biomarker and imaging technology can be a favorable alternative to LGE for assessing myocardial fibrosis in HCM patients when there were contraindications for contrast agent administration.

List Of Abbreviations

LGE, Late gadolinium enhancement; CMR, Cardiovascular magnetic resonance; HCM, Hypertrophic cardiomyopathy; EF, Ejection fraction; LV, left ventricular; MWT, Maximum wall thickness; hs-cTnI, High-sensitivity cardiac troponin I; Nt-proBNP, N-terminal pro b-type natriuretic peptide; GLS, Global longitudinal strain; GCS, Global circumferential strain; GRS, Global radial strain; ROC, Receiver operating characteristic; SCD, Sudden cardiac death; CK, Creatine kinase; CK-MB, Creatine kinase-MB; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase; bSSFP, Balanced steady state free precession; FOV, Field of view; TR, Repetition time; TE, Echo time; DTPA, Gadolinium-diethylenetriamine pentaacetic acid; PSIR, Phase-sensitive inversion recovery; BSA, Body surface area; EDVI, End-diastolic volume index; ESVI, End-systolic volume index; SVI, Stroke volume index; MI, myocardial mass; AHA, American Heart Association; PPV, positive predictive value; NPV, negative predictive value; CI, Confidence intervals; ICC, Intra-class correlation coefficient; AUC, Area under curve; LVOTG, Peak left ventricular outflow tract gradient; NYHA, New York heart association; ACE, Angiotensin-converting enzyme; ARB, Angiotensin-receptor blocker;

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was obtained from all the participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

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Authors’ contributions

HSS, YC, YML and JL were responsible for the study concept, design and drafting the article. YML, JL, YKC XYZ and XYH were responsible for the data collection, statistical analysis and data interpretation. JG GZS and TTH were responsible for CMR image analysis. All the authors critically revised the manuscript and gave final approval of the manuscript to be published.

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References

1. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al: 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-79.
2. Marian AJ, Braunwald E. Hypertrophic Cardiomyopathy. Circ Res. 2017;121(7):749-70.
3. Briasoulis A, Mallikethi-Reddy S, Palla M, Alesh I, Afonso L. Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis. Heart. 2015;101(17):1406-11.
4. Maron MS, Chan RH, Kapur NK, Jaffe IZ, McGraw AP, Kerur R, et al. Effect of Spironolactone on Myocardial Fibrosis and Other Clinical Variables in Patients with Hypertrophic Cardiomyopathy. Am J Med. 2018;131(7):837-41.
5. Diez J, Querejeta R, Lopez B, Gonzalez A, Larman M, Martinez Ubago JL. Losartandependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation. 2002;105(21):2512-17.
6. Izawa H, Murohara T, Nagata K, Isobe S, Asano H, Amano T, et al: Mineralocorticoid receptor antagonism ameliorates left ventricular diastolic dysfunction and myocardial fibrosis in mildly symptomatic patients with idiopathic dilated cardiomyopathy: a pilot study. Circulation. 2005; 112(19):2940-45.
7. Pennell DJ. Cardiovascular magnetic resonance. Circulation. 2010;121(5):692-705.
8. Mentias A, Raeisi-Giglou P, Smedira NG, Feng K, Sato K, Wazni O, et al. Late Gadolinium Enhancement in Patients with Hypertrophic Cardiomyopathy and Preserved Systolic Function. J Am Coll Cardiol. 2018;72(8):857-70.
9. Freitas P, Ferreira AM, Arteaga-Fernandez E, de Oliveira Antunes M, Mesquita J, Abecasis J, et al. The amount of late gadolinium enhancement outperforms current guideline-recommended criteria in the identification of patients with hypertrophic cardiomyopathy at risk of sudden cardiac death. J Cardiovasc Magn Reson. 2019;21(1):50.
10. Thomsen HS, Morcos SK, Almen T, Bellin MF, Bertolotto M, Bongartz G, et al. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee

guidelines. Eur Radiol. 2013;23(2):307-18.

11. Zelt JGE, Liu PP, Erthal F, deKemp RA, Wells G, O'Meara E, et al. N-Terminal Pro B-Type Natriuretic Peptide and High-Sensitivity Cardiac Troponin T Levels Are Related to the Extent of Hibernating Myocardium in Patients With Ischemic Heart Failure. Can J Cardiol. 2017;33(11):1478-88.
12. Geske JB, McKie PM, Ommen SR, Sorajja P. B-type natriuretic peptide and survival in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61(24):2456-60.
13. Kubo T, Kitaoka H, Yamanaka S, Hirota T, Baba Y, Hayashi K, et al. Significance of high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;62(14):1252-59.
14. Zhang C, Liu R, Yuan J, Cui J, Hu F, Yang W, et al. Predictive Values of N-Terminal Pro-B-Type Natriuretic Peptide and Cardiac Troponin I for Myocardial Fibrosis in Hypertrophic Obstructive Cardiomyopathy. PLoS One. 2016;11(1):e0146572.
15. Gawor M, Spiewak M, Kubik A, Wrobel A, Lutynska A, Marczak M, et al. Circulating biomarkers of hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy assessed by cardiac magnetic resonance. Biomarkers. 2018;23(7):676-82.
16. Kawasaki T, Sakai C, Harimoto K, Yamano M, Miki S, Kamitani T. Usefulness of High-Sensitivity Cardiac Troponin T and Brain Natriuretic Peptide as Biomarkers of Myocardial Fibrosis in Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2013;112(6):867-72.
17. Claus P, Omar AMS, Pedrizzetti G, Sengupta PP, Nagel E. Tissue Tracking Technology for Assessing Cardiac Mechanics: Principles, Normal Values, and Clinical Applications. JACC Cardiovasc Imaging. 2015;8(12):1444-60.
18. Vigneault DM, Yang E, Jensen PJ, Tee MW, Farhad H, Chu L, et al. Left Ventricular Strain Is Abnormal in Preclinical and Overt Hypertrophic Cardiomyopathy: Cardiac MR Feature Tracking. Radiology. 2019, 290(3):640-48.
19. Buss SJ, Breuninger K, Lehrke S, Voss A, Galuschky C, Lossnitzer D, et al. Assessment of myocardial deformation with cardiac magnetic resonance strain imaging improves risk stratification in patients with dilated cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2015;16(3):307-15.
20. Heermann P, Hedderich DM, Paul M, S Schülke C, Kroeger JR, Baeßler B, et al. Biventricular myocardial strain analysis in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) using cardiovascular magnetic resonance feature tracking. J Cardiovasc Magn Reson. 2014;16(1):75.
21. Haland TF, Almaas VM, Hasselberg NE, Saberniak J, Leren IS, Hopp E, et al. Strain echocardiography is related to fibrosis and ventricular arrhythmias in hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2016;17(6):613-21.
22. Xu HY, Chen J, Yang ZG, Li R, Shi K, Zhang Q, et al. Early marker of regional left ventricular deformation in patients with hypertrophic cardiomyopathy evaluated by MRI tissue tracking: The effects of myocardial hypertrophy and fibrosis. J Magn Reson Imaging. 2017;46(5):1368-76.
23. Moravsky G, Ofek E, Rakowski H, Butany J, Williams L, Ralph-Edwards A, et al. Myocardial Fibrosis in Hypertrophic Cardiomyopathy. JACC: Cardiovasc Imaging. 2013; 6(5):587-96.

24. Harrigan CJ, Peters DC, Gibson CM, Maron BJ, Manning WJ, Maron MS, et al. Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast- enhanced cardiovascular MR imaging. Radiology. 2011;258(1):128-33.
25. Moreno V, Hernandez-Romero D, Vilchez JA, Garcia-Honrubia A, Cambronero F, Casas T, et al. Serum levels of high-sensitivity troponin T: a novel marker for cardiac remodeling in hypertrophic cardiomyopathy. J Card Fail. 2010;16(12):950-56.
26. Paya E, Marin F, Gonzalez J, Gimeno JR, Feliu E, Romero A, et al. Variables associated with contrast-enhanced cardiovascular magnetic resonance in hypertrophic cardiomyopathy: clinical implications. J Card Fail 2008;14(5):414-419.
27. Zhou Y, Yuan J, Wang Y, Qiao S. Predictive Values of Apelin for Myocardial Fibrosis in Hypertrophic Cardiomyopathy. International Heart Journal. 2019; 60(3):648-55.
28. Mahrholdt H, Wagner A, Holly TA, Elliott MD, Bonow RO, Kim RJ, et al. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. Circulation. 2002;106(18):2322-7.
29. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail. 2004;6(3):257-60.
30. Hasegawa K, Fujiwara H, Doyama K, Miyamae M, Fujiwara T, Suga S, et al. Ventricular expression of brain natriuretic peptide in hypertrophic cardiomyopathy. Circulation. 1993; 88(2):372-80.
31. Tesic M, Seferovic J, Trifunovic D, Djordjevic-Dikic A, Giga V, Jovanovic I, et al. N-terminal pro-brain natriuretic peptide is related with coronary flow velocity reserve and diastolic dysfunction in patients with asymmetric hypertrophic cardiomyopathy. J Cardiol. 2017; 70(4):323-28.
32. Petersen SE, Jerosch-Herold M, Hudsmith LE, Robson MD, Francis JM, Doll HA, et al. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. Circulation. 2007; 115(18):2418-25.
33. Kapoun AM, Liang F, O'Young G, Damm DL, Quon D, White RT, et al. B-type natriuretic peptide exerts broad functional opposition to transforming growth factor-beta in primary human cardiac fibroblasts: fibrosis, myofibroblast conversion, proliferation, and inflammation. Circ Res. 2004;94(4):453-61.
34. Hinojar R, Fernandez-Golfin C, Gonzalez-Gomez A, Rincon LM, Plaza-Martin M, Casas E, et al. Prognostic implications of global myocardial mechanics in hypertrophic cardiomyopathy by cardiovascular magnetic resonance feature tracking. Relations to left ventricular hypertrophy and fibrosis. Int J Cardiol. 2017;249:467-72.
35. Makavos G, Kappaairis C, Tselegkidi ME, Karamitsos T, Rigopoulos AG, Noutsias M, et al. Hypertrophic cardiomyopathy: an updated review on diagnosis, prognosis, and treatment. Heart Fail Rev. 2019; 24(4):439-59.
36. Pouleur H, Rousseau MF, van Eyll C, Brasseur LA, Charlier AA. Force-velocity-length relations in hypertrophic cardiomyopathy: evidence of normal or depressed myocardial contractility. Am J Cardiol. 1983;52(7):813-7.

37. Ho CY, López B, Coelho-Filho OR, Lakdawala NK, Cirino AL, Jarolim P, et al. Myocardial Fibrosis as an Early Manifestation of Hypertrophic Cardiomyopathy. N Engl J Med. 2010;363(6):552-63.
38. Murtagh G, Laffin LJ, Patel KV, Patel AV, Bonham CA, Yu Z, et al. Improved detection of myocardial damage in sarcoidosis using longitudinal strain in patients with preserved left ventricular ejection fraction. Echocardiography. 2016; 33(9):1344-52.
39. Romano S, Judd RM, Kim RJ, Kim HW, Klem I, Heitner JF, et al. Feature-Tracking Global Longitudinal Strain Predicts Death in a Multicenter Population of Patients With Ischemic and Nonischemic Dilated Cardiomyopathy Incremental to Ejection Fraction and Late Gadolinium Enhancement. JACC Cardiovasc Imaging. 2018;11(10):1419-29.
40. Erley J, Genovese D, Tapaskar N, Alvi N, Rashedi N, Besser SA, et al. Echocardiography and cardiovascular magnetic resonance based evaluation of myocardial strain and relationship with late gadolinium enhancement. J Cardiovasc Magn Reson. 2019; 21(1):46.
41. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: Executive Summary. Circulation. 2011;124(24):2761-96.
42. Alvares RF, Goodwin JF. Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs. Br Heart J.1982;48(3):204-12.
43. Spoladore R, Maron MS, D'Amato R, Camici PG, Olivotto I. Pharmacological treatment options for hypertrophic cardiomyopathy: high time for evidence. Eur Heart J. 2012; 33(14):1724-33.

Figures

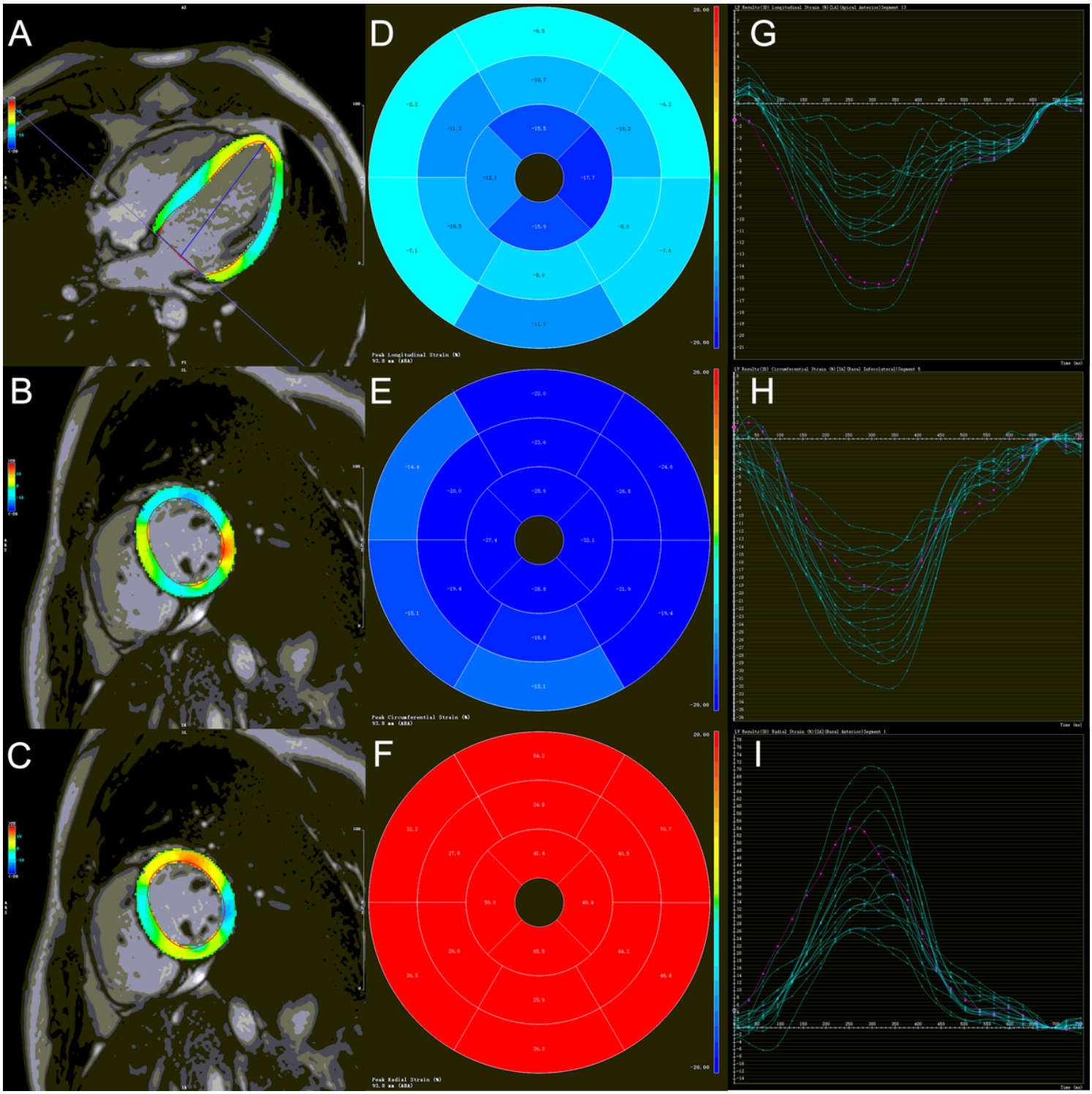

Figure 1

Example of left ventricular myocardium peak systolic strain analysis in a healthy volunteer. The left shows the colored tissue-tracking maps of longitudinal (A), circumferential (B), and radial (C) strain. In the middle is the 16-segment model of the longitudinal (D), circumferential (E), and radial (F) values in a cardiac cycle. On the right are the strain–time curves of the longitudinal (G), circumferential (H), and radial (I) values in a cardiac cycle.

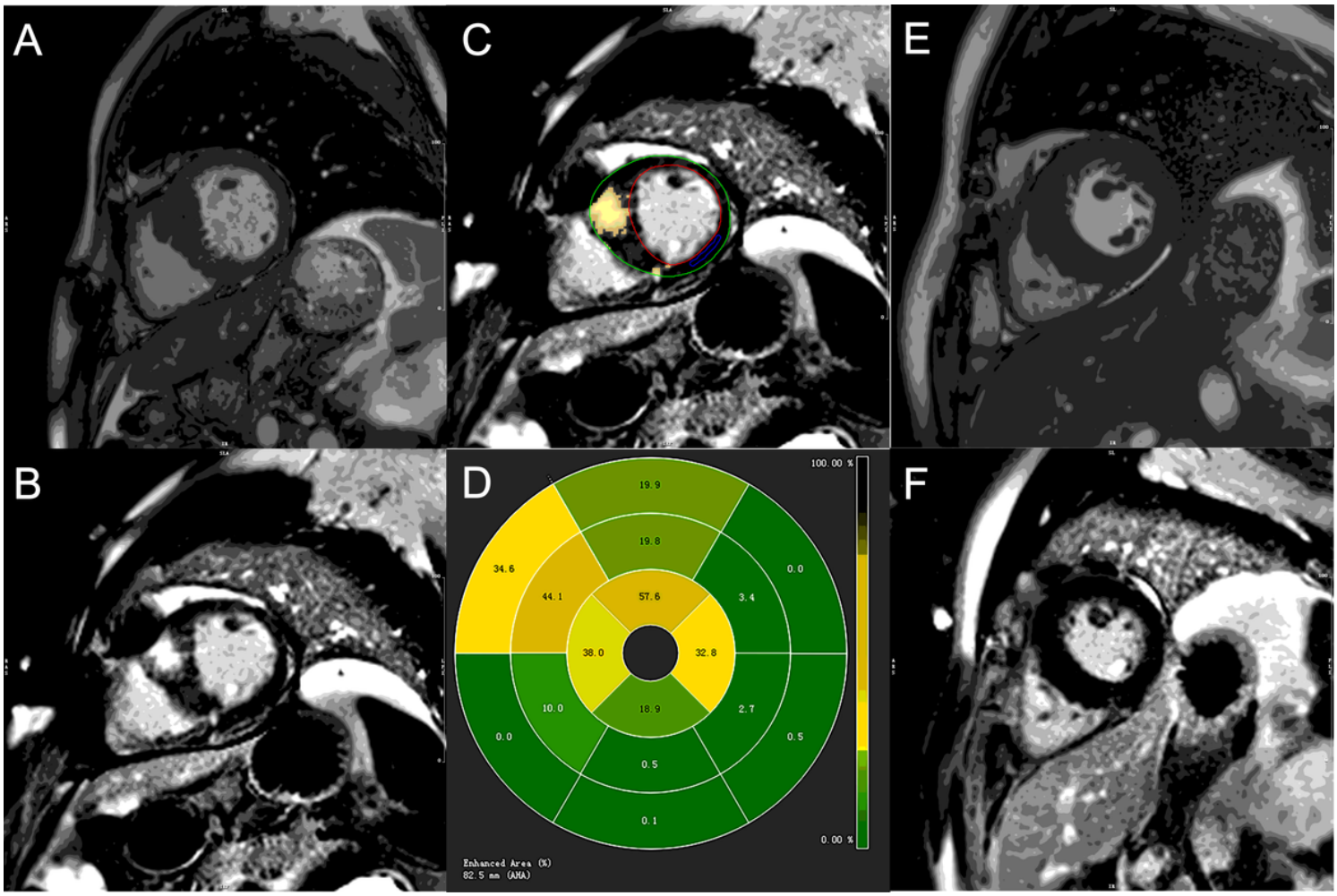

Figure 2

Examples of hypertrophic cardiomyopathy patients with and without LGE. On the left are the short-axis cine (A) and LGE images (B) in a 46-year-old man. (C) Same image showing quantification of LGE using the 6SD thresholding method. (D) A representative 16-segment model of the LGE% in this patient. On the right are the short-axis cine (E) and LGE images (F) in a 46-year-old man without LGE. LGE late gadolinium enhancement.

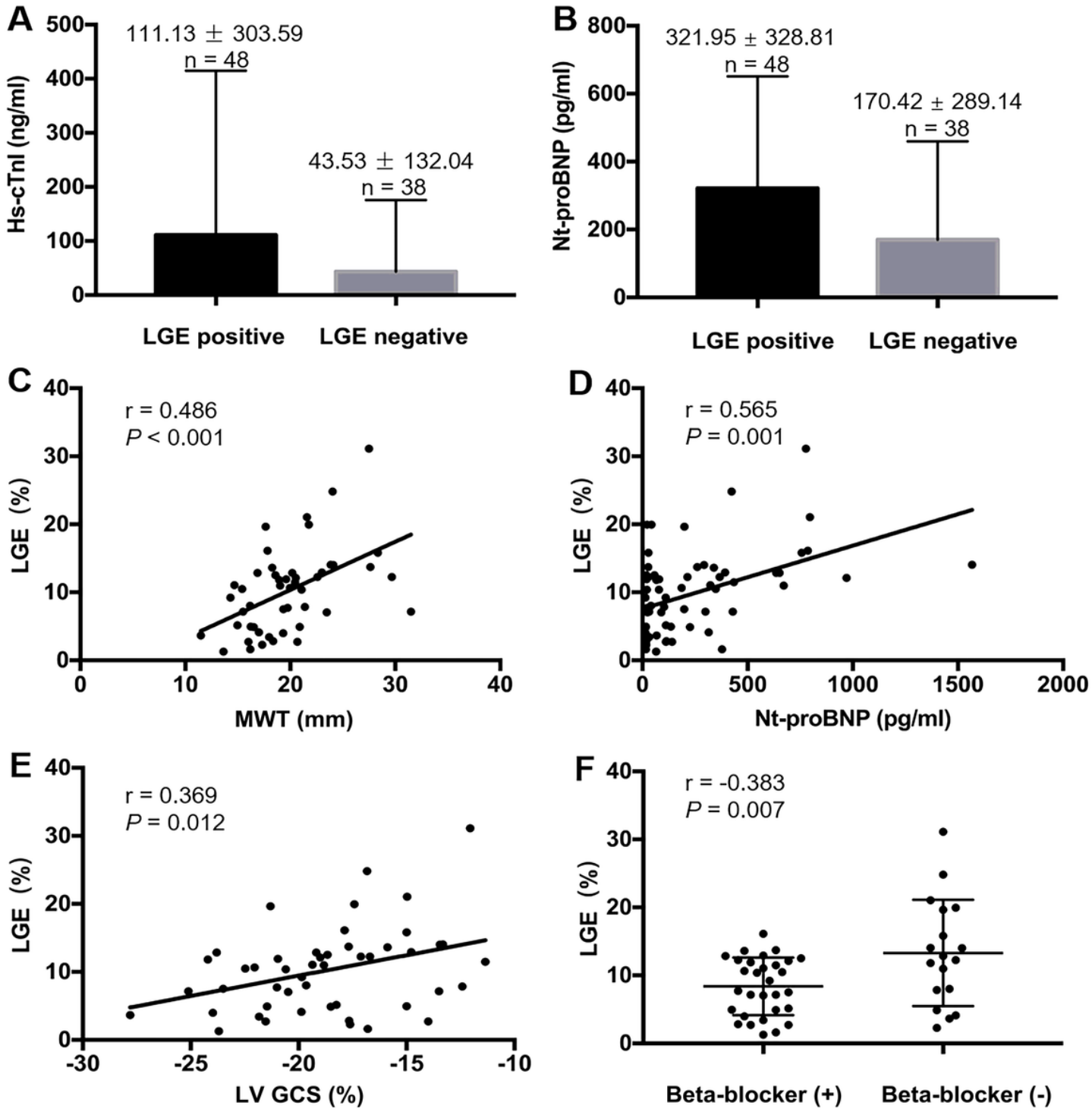

Figure 3

Comparison of the mean serum hs-cTnI (A) and Nt-proBNP (B) levels between LGE-positive and LGE-negative patients. Correlations between the LGE% and the MWT (C), Nt-proBNP (D), GCS (E) and beta-blocker treatment (F) in HCM patients. hs-cTnI high-sensitivity cardiac troponin I, Nt-proBNP N-terminal pro B-type natriuretic peptide, LGE late gadolinium enhancement, MWT maximum wall thickness, GCS global circumferential strain.

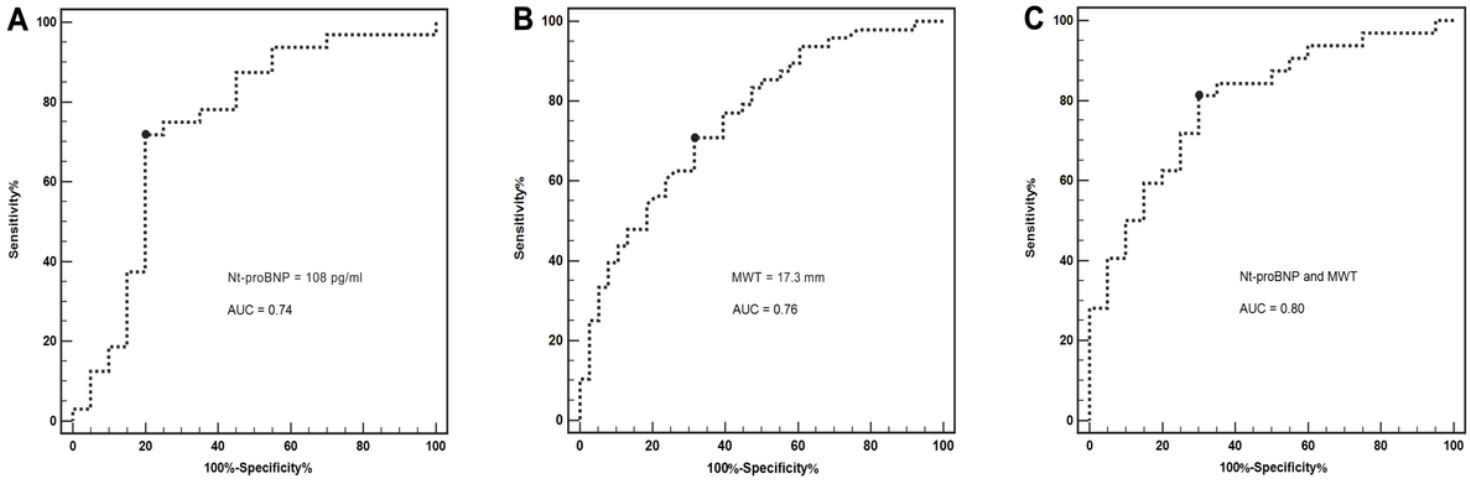

Figure 4

ROC curve analysis of the serum Nt-proBNP levels, MWT and the serum Nt-proBNP level + MWT for the identification of the presence of LGE in HCM patients. AUC area under curve, ROC receiver operating characteristic curve analysis, LGE late gadolinium enhancement, HCM hypertrophic cardiomyopathy, MWT Maximum wall thickness, Nt-proBNP N-terminal pro B-type natriuretic peptide.