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The additional impact of metabolic syndrome on left ventricular deformation and myocardial energetic efficiency impairment in ischemia with nonobstructive coronary arteries patients

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Background Ischemia with nonobstructive coronary arteries (INOCA) has high morbidity, mortality, and poor quality of life. Metabolic syndrome (MetS) is a complex of multiple cardiac metabolic risk factors, significantly increasing the risk of major adverse cardiovascular events in INOCA patients. The study aimed to investigate the aggravating effect of MetS on left ventricular (LV) deformation and function impairment in INOCA patients.

Materials and methods This study collected 104 INOCA patients (INOCA [MetS−]: $n=56$; INOCA [MetS+]: $n=48$) and 41 sex- and age-matched controls. LV function, indexed myocardial energetic efficiency (MEEI), and LV global peak strains (including radial, circumferential, and longitudinal directions) were measured among the three groups. The independent factors of reduced MEEI and impaired LV function and strain parameters for all INOCA patients were assessed using multivariable linear regression analyses.

Results In contrast to the INOCA (MetS-) group, the indexed LV stroke volume (LVSVI) (49.57 ± 11.58 mL/m^2 vs. 42.58 ± 12.23 mL/m^2, $p=0.007$), MEEI [0.85(0.70–1.03) ml/s/g vs. 0.75(0.54–0.91) ml/s/g, $p=0.045$] and LV global longitudinal peak strain (GLPS) (− 13.26 ± 2.86% vs. -10.95 ± 3.93%, $p=0.001$) reduced in the INOCA (MetS+) group. Compared with the controls, LV GLPS decreased in the INOCA (MetS-) group (− 15.14 ± 2.83% vs. −13.26 ± 2.86%, $p=0.017$). MetS was negatively associated with LVSVI, MEEI, and LV GLPS (all $p<0.05$). After multivariable adjustment, MetS was found to be an independent factor of decreased LVSVI (β = −0.231, $p=0.012$), MEEI (β = −0.262, $p=0.009$), and LV GLPS (β = −0.266, $p=0.002$) in INOCA patients. Using calcium channel blockers medication (β = 0.320, $p=0.001$) and hypertension (β = −0.298, $p=0.002$) were also independently associated with impaired MEEI.

Conclusions MetS aggravated LV deformation and function impairment in patients with INOCA. MetS was found to be an independent factor of impaired MEEI and LV GLPS, the further decrease of MEEI and LV GLPS in INOCA patients

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caused by MetS might involve the synergistic injury mechanism. Early diagnosis and treatment of MetS in patients with INOCA are important.

Keywords Metabolic syndrome, Ischemia with nonobstructive coronary arteries, Myocardial energetic efficiency, Myocardial strain

Introduction

Coronary artery disease (CAD) is one of the most prevalent cardiovascular diseases, widely acknowledged globally [1]. With increasing awareness of CAD, clinicians are more frequently encountering patients with cardiovascular symptoms who do not exhibit 50% or greater stenosis in coronary computed tomography angiography (CCTA) or coronary angiography (CAG), which is termed ischemia with nonobstructive coronary arteries (INOCA) [2]. INOCA is associated with high morbidity, mortality, and poor quality of life, increasingly considered to be an important factor of major adverse cardiovascular events (MACE) [3–5]. Several studies have highlighted that INOCA is linked to an increased risk of acute coronary syndrome, heart failure with preserved ejection fraction, and stroke, and INOCA increases the risk of MACE by 1.5–1.8 times [6, 7]. Besides, INOCA frequently coexists with various metabolic-related risk factors, including hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, obesity and smoking [8]. Metabolic syndrome (MetS) is a complex of syndrome composed of these risk factors. A prior study has shown that MetS significantly increased the risk of MACE in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) [9]. Recently, the impact of MetS on INOCA patients has rarely been studied. Therefore, it is of great significance to investigate how MetS additive effect of the left ventricular (LV) deformation impairment on INOCA.

Cardiac magnetic resonance (CMR) feature tracking can detect subtle cardiac morphological and functional changes early, which has become an important tool for quantifying myocardial impairment and identifying subclinical myocardial changes [10]. Myocardial energetic efficiency (MEE), which refers to the heart's ability to convert chemical energy from oxidative metabolism into mechanical work, is a key indicator of cardiac function [11]. The impaired MEE has emerged as an independent factor of adverse cardiovascular outcomes [12]. Previous studies have validated a simple non-invasive method for estimating myocardial MEE based on the determination of stroke work (SW) and myocardial oxygen consumption (MVO_2) [13, 14]. CAD associated with limited oxygen supply often leads to myocardial ischemia which induces the reduction of MEE [11] and this coronary artery abnormality leading to myocardial ischemia also exists in INOCA patients. The decrease of MEE may also be observed in INCOA patients and indexed MEE (MEEI) has been demonstrated to correlate with MetS [13]. Up to now, the additive impact of MetS on MEEI and LV myocardial strain in INOCA patients remained unclear and there were a few studies using CMR feature tracking to evaluate additive effect. Therefore, this study aimed to investigate the combined impact of MetS on MEEI and LV myocardial strain in INOCA patients by CMR feature tracking, and to explore the independent factors associated with decreased MEEI and LV strain.

Methods

Study population

In the study, a cohort of patients with chest pain or myocardial ischemia or suspected CAD who underwent CMR examination were retrospectively recruited (from January 2012 to August 2023) and were found to have INOCA which was defined as < 50% luminal diameter stenosis in an epicardial coronary artery on CCTA or CAG [3]. The exclusion criteria included: (1) obstructive CAD, that is, at least one major coronary artery stenosis ≥ 50%; (2) previous operation history of coronary artery revascularization or myocardial infarction (MI); (3) congenital heart diseases; (4) primary cardiomyopathy; (5) severe cardiac arrhythmia or valvular heart disease; (6) malignancy or other severe medical illnesses with short survival time and (7) CMR image inadequate or poor image quality. Following these criteria, 104 patients with INOCA were included in this study. The diagnosis of MetS was based on a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention (2009) [15]. The presence of any 3 of 5 risk factors was defined as MetS: (1) elevated waist circumference (specific definitions based on different populations and countries); (2) elevated triglycerides [≥ 150 mg/dL (1.7 mmol/L)] or drug treatment for this lipid abnormality; (3) reduced high-density lipoprotein cholesterol[< 40 mg/dL (1.0 mmol/L) in males; < 50 mg/dL (1.3 mmol/L) in females] or drug treatment for this lipid abnormality; (4) elevated blood pressure (systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg) or treatment of previously diagnosed HTN; and (5) elevated fasting glucose [> 100 mg/dL (5.6 mmol/L)] or previously diagnosed type 2 diabetes mellitus (T2DM). Body mass index (BMI) was used instead of waist circumference for patients without waist circumference measurement and BMI > 25 kg/m^2 was considered as exceeding the waist circumference threshold MetS [16]. Adhering to whether there was coexisting MetS, patients were further divided into two groups: INOCA

with MetS [INOCA (MetS+), $n=48$] and INOCA without MetS [INOCA (MetS−), $n=56$]. In addition, we recruited age- and sex-matched controls who underwent CMR examination. The exclusion criteria were as follows: (1) T2DM; (2) HTN; (3) hyperlipidemia; (4) BMI ≥ 25 kg/m^2; (5) known cardiovascular disease; (6) malignancy or other severe medical illnesses with short survival time and (7) abnormalities detected by CMR (abnormal ventricular motion, perfusion defect, decreased ejection fraction, valvular stenosis, etc.). Finally, a total of 41 controls were included in this study. The study protocol was approved by our hospital Biomedical Research Ethics Committee. Written informed consent was waived due to the retrospective nature of the study.

Baseline clinical characteristics (BMI, blood pressure, heart rate, etc.), cardiovascular risk factors, laboratory indices and the data of medication using were collected in detail. The interval time between CMR scan and laboratory examination of all subjects was no more than 2 weeks. T2DM was diagnosed by the American Diabetes Association guidelines [17]. BMI was computed as weight (kg) /height^2 (m^2) and obesity was defined as BMI ≥ 25 kg/m^2 [18]. The HTN was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg at rest or on antihypertensive treatments [19]. Current or previous smoking of at least one cigarette per day for at least 1 year was defined as smoking [20].

CMR protocol

CMR imaging was performed using a 3.0 T whole-body magnetic resonance scanner (Tim Trio or MAGNETOM Skyra, Siemens Medical Solutions, Erlangen, Germany). Cine images were obtained with a retrospectively gated balanced steady-state free-precession (b-SSFP) sequence, acquired using a retrospective vector ECG gating technique at the end of expiratory breath holding, and twenty-five frames were reconstructed per breath-hold acquisition. Cine images included the whole LV from the base to the apex in the short-axis slices, as well as the four- and two-chamber in the long-axis views. The following scanning parameters were used: temporal resolution 39.34 or 42 ms, repetition time (TR) 2.81 or 3.4 ms, echo time (TE) 1.22 or 1.3 ms, flip angle 38° or 50°, slice thickness 8 mm, field of view (FOV) 250 × 300 mm^2 or 340 × 285 mm^2, and matrix 256 × 166 or 208 × 139. Late gadolinium enhancement(LGE)images were acquired in the corresponding slice position as the cine imaging 10–15 min after contrast injection. The images were obtained using a phase-sensitive inversion recovery sequence with the following parameters: temporal time 300 ms, TE 1.44 ms, flip angle 40°, slice thickness 8 mm, FOV 275 × 400 mm^2, and matrix size = 256 × 184.

CMR data analysis

All CMR imaging data were analyzed using a semi-automated software (Cvi42; Circle Cardiovascular Imaging, Inc., Calgary, Canada). The LV endocardial and epicardial traces were delineated manually or semiautomatically in serial short-axis slices during the end-diastolic and end-systolic phases. Papillary muscles were considered as part of the ventricular cavity, and epicardial fat was excluded. The LV functional parameters including LV mass (LVM) at end-diastole, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV stroke volume (LVSV), and LV ejection fraction (LVEF) automatically calculated. LVEDV, LVESV, LVSV, and LVM indexed for body surface area (BSA) according to the Mosteller formula and respectively represented as LVEDVI, LVESVI, LVSVI, and LVMI [21].

To analyze LV myocardial strains, we put the short-axis, two- and four-chamber long-axis views into the feature tracking module. The LV global myocardial strains including the global radial peak strain (GRPS), global circumferential peak strain (GCPS), and global longitudinal peak strain (GLPS) were estimated automatically by the software. The LV GCPS and GLPS are negative during systole because the myocardium is shortened, while the LV GRPS is positive due to myocardial thickening during systolic phase (Fig. 1). LGE was defined as the area of signal intensity five standard deviations above the mean intensity of the normal myocardium on the LGE short axis images. Two radiologists categorized delayed enhancement into 5 categories: (1) None: in which there were no areas of LGE; (2) Subendocardial: in which there were LGE is limited to subendocardial; (3) Midmyocardium: in which there were LGE is limited to Midmyocardium; (4) Subepicardial: in which there were LGE is limited to Subepicardial; (5) Transmural: in which there was a whole layer, of LGE extending from the endocardium to the epicardium [22].

MEE measurement

The MEE is defined as the ratio between the external systolic work, and the amount of total energy produced for each contraction [14]. MEE was calculated using the following formula: $MEE = SW/MVO_2 \approx (SBP \times SV)/(SBP \times HR) = SV \times HR$ [23]. HR was expressed in seconds (HR/60). Due to MEE is highly related to LVM, MEE was normalized for the LVM (i.e. indexed MEE, MEEI, ml/s/g), which was an estimate of energetic expenditure per unit of myocardial mass in 1 s.

Statistical analysis

All statistical analyses were performed using SPSS (version 25.0, IBM SPSS Inc., Armonk, New York, USA) and GraphPad Prism (version 9.5, GraphPad Software Inc., San Diego, CA, USA). Continuous variables were

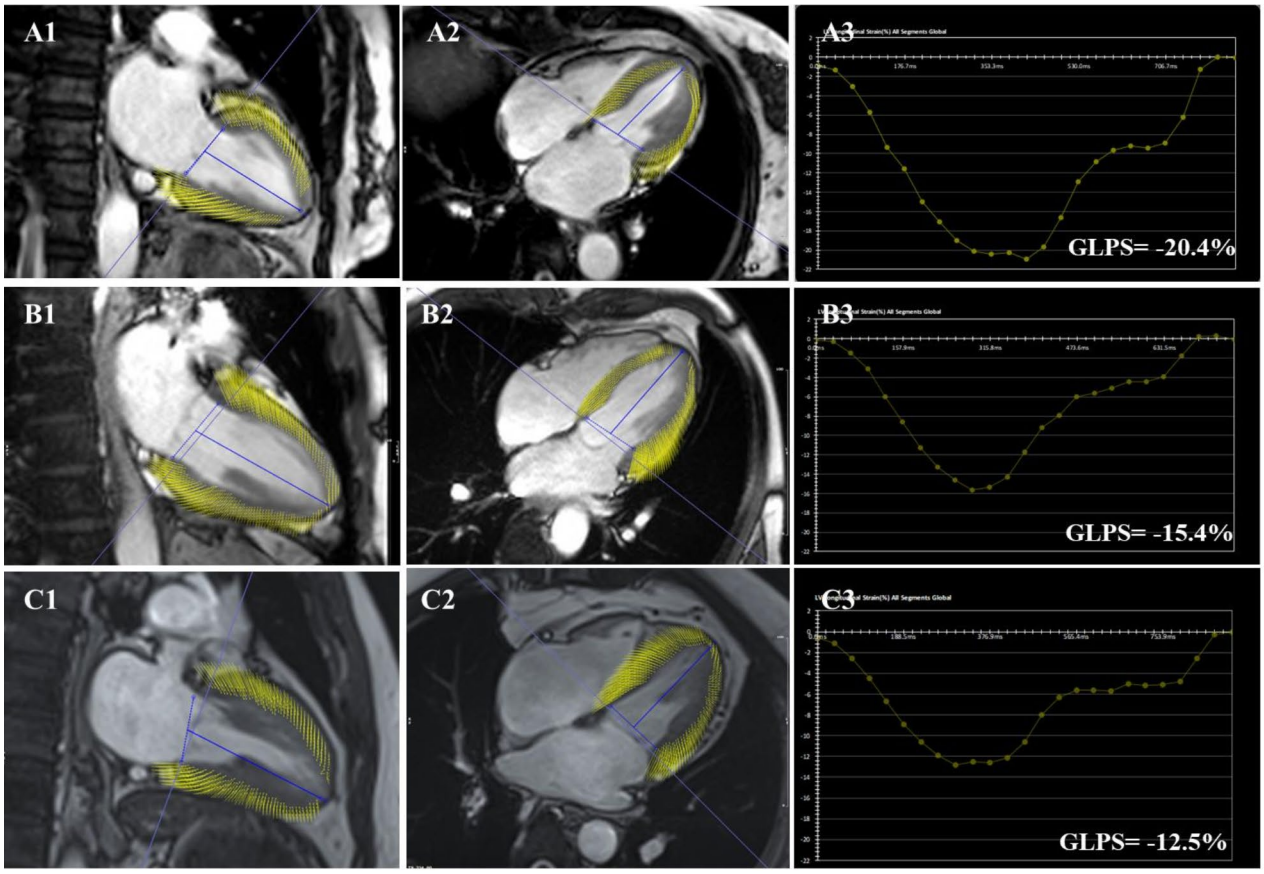

Fig. 1 The representative CMR imaging LV pseudo color images of long-axis four-and two-chamber cine images at the end-systole and the GLPS curves in the control, INOCA (MetS−) patient, and INOCA (MetS+) patient. A1–A3 a control subject, female, 60 years, B1–B3 an INOCA (MetS−) patient, male, 46 years, C1–C3 an INOCA (MetS+) patient, male, 52 years. CMR: cardiac magnetic resonance, LV: left ventricle; GLPS: global longitudinal peak strain; INOCA: ischemia with nonobstructive coronary arteries; MetS: metabolic syndrome

assessed for normality distribution by the Kolmogorov–Smirnov test and the homogeneity of variance was evaluated using the Levene's test. Continuous variables were expressed as means ± standard deviations (SD) or as medians and interquartile ranges (IQR). Categorical data were presented as numbers (percentages).The Student's t test or Mann-Whitney U test was used to compare the continuous variables between the two groups. One-way analysis of variance (one-way ANOVA) was used to compare variables the INOCA with MetS group, INOCA without MetS group, and controls, and Bonferroni's hoc post-test or Kruskal-Wallis rank test was performed. Binary variables were analyzed using the chi-square test or Fisher's exact test. The variables selected for univariable analysis were mainly significant statistical differences or trends between group analyses and also included factors that have been clearly reported in previous literature to have an impact. Then, stepwise multivariable analysis was used to select variables that were not collinear in univariable analysis and had a p-value < 0.1. For all analyses, a p-value of < 0.05 was considered statistically significant.

Intra- and inter-observer reproducibility

Intra- and inter-observer reproducibility for the MRI parameters was analyzed using the intraclass correlation coefficients (ICCs). To assess the intra-observer variability in LV functional and global strain parameters, 40 randomly selected subjects (30 INOCA patients and 10 controls) were measured twice by one observer (C.Y.M) with an interval of one month. The inter-observer variability was evaluated by another independent double-blinded skilled observer (Y.G.) who measured the same subjects.

Results

Demographic and clinical characteristics

The baseline demographic and clinical characteristics of the study cohort are presented in Table 1. In total, we included 104 INOCA patients [INOCA (MetS−): $n = 56$, 66.1% males, 61 ± 11 years; INOCA (MetS+): $n = 48$, 66.7% males, 59 ± 12 years] and 41 controls (73.2% males, 58 ± 9 years). From the controls to the INOCA (MetS-) group to the INOCA (MetS+) group, the BMI increased (all $p < 0.001$). Compared with the INOCA (MetS-) group,

Table 1 Baseline characteristics of the study cohort

	Controls($n=41$)	INOCA (MetS−)($n=56$)	INOCA (MetS+) ($n=48$)	*P* value
Baseline characteristics				
Age (y)	58 ± 9	61 ± 11	59 ± 12	0.415
Male (n, %)	30(73.2%)	37(66.1%)	32(66.7%)	0.727
BSA(m^2)	1.67 ± 0.10	1.71 ± 0.15	1.87 ± 0.16 *	< 0.001
BMI(kg/m^2)	22.12 ± 1.70	23.94 ± 2.62 *	26.40 ± 2.46 *#	< 0.001
Heart rate(bpm)	74 ± 11	68 ± 12	74 ± 12 #	0.024
SBP(mmHg)	119 ± 10	126 ± 16 *	127 ± 16 *	0.040
DBP(mmHg)	73 ± 9	77 ± 9	79 ± 15	0.094
Chest pain CCS classification (n, %)		INOCA (MetS−)(n = 46)	INOCA (MetS+) (n = 38)	
I/ II/ III/ IV	-	18(39.1%)/16 (34.8%)/ 5(10.9%)/ 7(15.2%)	10(26.3%)/17(44.7%)/ 5 (13.2%)/6(15.8%)	0.649
Cardiovascular risk factors (n, %)				
T2DM	0(0%)	1(1.8%)	19(39.6%) *#	< 0.001
HTN	0(0%)	19(33.9%) *	32(66.7%) *#	< 0.001
Obesity	0(0%)	18(32.1%) *	40 (83.3%) *#	< 0.001
Smoking	-	22(39.3%)	18(38.3%)	0.918
Coronary characteristics (n, %)				
Normal vessels	-	25(44.6%)	14(29.2%)	0.104
Vessel with any stenosis < 50%	-	31(55.4%)	34(70.8%)	0.104
Laboratory parameters				
TG (mmol/l)	-	1.46 (0.96–1.93)	2.36(1.76–3.44) #	< 0.001
TC (mmol/l)	-	3.95(3.35–4.61)	4.19(3.47–5.16)	0.404
HDL (mmol/l)	-	1.34(1.09–1.48)	0.97(0.84–1.13) #	< 0.001
LDL (mmol/l)	-	2.11(1.72–2.74)	2.38(1.65–3.32)	0.314
HbA1c (%)	-	5.8(5.6–6.1)	6.2(5.7–6.9)	0.139
Glucose (mmol/l)	-	3.83(2.61–5.26)	7.59(4.82–13.21) #	< 0.001
Triglyceride index	-	5.26(4.96–5.75)	6.12(5.55–7.12) #	< 0.001
cTn-T(ng/l)	-	8.50(6.50-15.63)	9.65(7.13–21.48)	0.481
CK-MB(ng/ml)	-	1.68(1.01–2.43)	1.54(1.09–2.28)	0.938
Myoglobin (ng/ml)	-	24.99(21.00-36.77)	26.13(21.00-38.26)	0.776
NT-proBNP (pg/ml)	-	140.00(49.50-332.50)	112.50(41.75-541.75)	0.964
eGFR (ml/min/1.73 m^2)	-	89.44(84.34–95.75)	86.89(85.70-94.27)	0.186
Creatinine(umol/l)	-	77.00(64.50–87.00)	78.00(65.25–91.75)	0.426
Medication therapy (n, %)				
Insulin	-	1 (3.8%)	6(12.5%) #	0.036
SGLT2 inhibitors	-	0(0%)	3(6.3%)	0.095
Biguanides	-	0(0%)	7(14.6%) #	0.003
ACEI/ARB	-	16 (28.6%)	26(54.2%) #	0.008
Beta-blocker	-	21(37.5%)	24(50.0%)	0.200
CCB	-	9(16.1%)	22(45.8%) #	0.001
Statins	-	44(78.6%)	42(87.5%)	0.230
Anti-thrombotic agents	-	38(67.9%)	42(87.5%) #	0.018

Data are presented as the mean ± SD, median (Q1–Q3) or number (percentage)

INOCA: ischemia with nonobstructive coronary arteries; MetS: metabolic syndrome; BSA: body surface area; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CCS: Canadian Cardiovascular Society; T2DM: type 2 diabetes mellitus; HTN: hypertension; TG: triglycerides; TC: triglyceride; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; cTnT: cardiac troponin T; CK-MB: creatine kinase-MB; NT-proBNP: amino-terminal pro-B-type natriuretic peptide; eGFR: estimated glomerular filtration rate; SGLT2: sodium-dependent glucose transporters 2; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blockers

* P less than 0.05vs. the controls group

#P less than 0.05 vs. the INOCA (MetS−) group

the INOCA (MetS+) group had higher levels of BSA, HR, triglycerides, glucose, and triglyceride index (all $p < 0.05$). The level of high-density lipoprotein decreased from the INOCA (MetS-) group to the INOCA (MetS+) group. More patients in the INOCA (MetS+) group existed T2DM, HTN, and obesity than in the INOCA (MetS-) group (all $p < 0.001$). While, there was no statistically significant difference in smoking between INOCA patients

with and without MetS. In the INOCA (MetS+) group, the proportion of patients with coronary stenosis (stenosis < 50%) [31(55.4%) vs. 34(70.8%)] was similar to that in the INOCA (MetS-) group, and there was no statistical difference between the two groups. In addition, more patients in the INOCA (MetS+) group used insulin, Biguanides, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), and anti-thrombotic agents (all $p < 0.05$).

Comparison of LV CMR parameters among controls and INOCA patients with and without MetS

The LV CMR parameters are shown in Table 2. Compared with the controls and the INOCA (MetS-) group, the LVSVI [INOCA (MetS-) vs. INOCA (MetS+): 49.57 ± 11.58 mL/m^2 vs. 42.58 ± 12.23 mL/m^2, $p = 0.007$] and MEEI [INOCA (MetS-) vs. INOCA (MetS+): 0.85(0.70–1.03) ml/s/g vs. 0.75(0.54–0.91) ml/s/g, $p = 0.045$] reduced in the INOCA (MetS+) group (all $p < 0.05$). INOCA patients with or without MetS exhibited an increased LVMI and decreased LVGFI compared with the controls (all $p < 0.05$). The MEEI showed a downward trend from the controls to the INOCA (MetS-) group [0.96(0.81–1.08) ml/s/g vs. 0.85(0.70–1.03) ml/s/g, $p = 0.304$]. However, the LVSVI and MEEI were no statistically significant differences between the controls and the INOCA (MetS-) group.

The LV GLPS reduced from controls to the INOCA (MetS-) group to the INOCA (MetS+) group (all $p < 0.05$). In contrast to the INOCA (MetS-) group, LV GLPS decreased significantly in the INOCA (MetS+) group (− 13.26 ± 2.86% vs. −10.95 ± 3.93%, $p = 0.001$). INOCA patients with or without MetS exhibited a decreased LV GRPS compared with the controls (both $p < 0.05$). In addition, the INOCA patients with MetS had significantly lower LV GCPS than the controls (− 20.35 ± 2.42% vs. −17.82 ± 6.21%, $p = 0.024$). Compared with the INOCA (MetS-) group, the LV GRPS (30.61 ± 9.31% vs. 28.98 ± 12.63%) and GCPS (− 18.87 ± 3.71% vs. −17.82 ± 6.21%) showed downwards trend in the INOCA (MetS+) group, whereas there was no statistically significant difference between the two groups (all $p > 0.05$) (Fig. 2).

In total, contrast-enhanced imaging performed on 98 INOCA patients [INOCA (MetS-): $n = 54$; INOCA (MetS+): $n = 44$] to evaluate LGE pattern. 22 patients with INOCA had LGE, of which 5 patients had LGE type of subendocardial, 6 patients with midmyocardium LGE, 1 patient with subepicardial LGE, and 10 patients with transmural LGE in our study. There were no statistically significant differences between the INOCA (MetS-) group and the INOCA (MetS+) group.

Table 2 LV CMR parameters among INOCA patients with and without MetS and controls

	Controls(n=41)	INOCA (MetS−) (n=56)	INOCA (MetS+) (n=48)	P value
Cardiac function parameters				
LVEDVI(mL/m^2)	74.68(63.79-85.80)	79.52(66.63-97.82)	75.88(62.60-88.21)	0.258
LVESVI(mL/m^2)	25.49(20.49-30.42)	29.14(21.71-39.34)	26.91(21.66-37.82)	0.121
LVSVI(mL/m^2)	49.62 ± 10.27	49.57 ± 11.58	4258±12.23 *#	0.003
LVEF (%)	64.90(62.68-70.01)	61.64(47.23-68.85)	62.96(47.23-68.85)	0.040
LVMI (g/m^2)	41.93(37.52-48.78)	51.76(41.88-58.04) *	50.05(39.58-60.70) *	0.001
MEEI (ml/s/g)	0.96(0.81-1.08)	0.85(0.70-1.03)	0.75(0.54-0.91) *#	0.001
Strain parameters				
GRPS (%)	38.50 ± 7.85	30.61±9.31*	2898±12.63 *	<0.001
GCPS (%)	−20.35 ± 2.42	−18.87±3.71	−17.82± 6.21 *	0.030
GLPS (%)	−15.14 ± 2.83	−13.26±2.86*	−10.95± 3.93 *#	<0.001

* P less than 0.05vs. the controls group

#P less than 0.05 vs. the INOCA (MetS−) group

Data are presented as the mean ± SD, median (Q1–Q3)

CMR: cardiac magnetic resonance; INOCA: ischemia with nonobstructive coronary arteries; MetS: metabolic syndrome; LVEDVI: indexed left ventricular end-diastolic volume; LVESVI: indexed left ventricular end-systolic volume; LVSVI: indexed left ventricular stroke volume; LVEF: left ventricular ejection fraction; LVMI: indexed left ventricular mass; LVGFI: left ventricular global function index; MEEI: indexed myocardial energetic efficiency; GRPS: global radial peak strain; GCPS: global circumferential peak strain; GLPS: global longitudinal peak strain

Univariable linear regression analyses of LVSVI, MEEI and LV GLPS in INOCA patients

As shown in Table 3, the univariable analyses revealed that MetS was negatively associated with LVSVI (β =−0.284, $p = 0.003$), MEEI (β = −0.255, $p = 0.009$), and LV GLPS (β = −0.324, $p = 0.001$). Estimated glomerular filtration rate (eGFR), amino-terminal pro-B-type natriuretic peptide (NT-proBNP), using ACEI/ARB medication and HTN were associated with LVSVI and MEEI (all $p < 0.05$). Age and smoking had a positive correlation with the LVSVI (both $p < 0.05$). Besides, in LV GLPS, Gender (male) (β = −0.272, $p = 0.005$), NT-proBNP (β = −0.311, $p = 0.001$), using ACEI/ARB medication (β = −0.301, $p = 0.002$) and using insulin medication (β = −0.265, $p = 0.007$) also had a negative correlation. MEEI (β = 0.385, $p < 0.001$) had a positive correlation with the LV GLPS (Fig. 3).

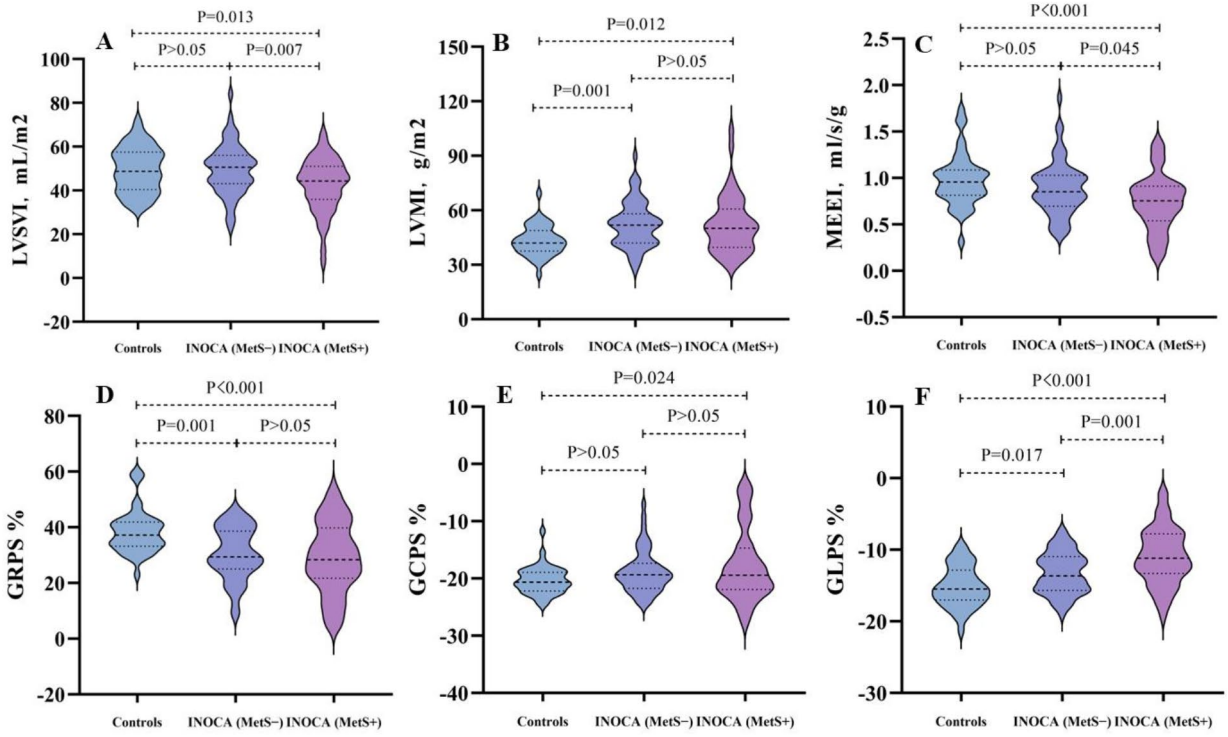

Fig. 2 Comparison of the LV function, MEEI, and global strain among the three groups. LVSVI: indexed left ventricular stroke volume; LVMI: indexed left ventricular mass; MEEI: indexed myocardial energetic efficiency; GRPS: global radial peak strain; GCPS: global circumferential peak strain; GLPS: global longitudinal peak strain

Association between clinical risk factors and impaired LVSVI, MEEI and LV GLPS in INOCA patients

After multivariable adjustment for covariates among INOCA patients, MetS was found to be an independent factor of decreased LVSVI (β = −0.231, $p = 0.012$), MEEI (β = −0.262, $p = 0.009$), and LV GLPS (β = −0.266, $p = 0.002$). In addition, using ACEI/ARB medication was independently associated with impaired LV GLPS (β = −0.174, $p = 0.043$). Using CCB medication was independently associated with MEEI (β = 0.320, $p = 0.001$). In LV GLPS, gender (male) (β = −0.367, $p < 0.001$) and NT-proBNP (β = −0.373, $p < 0.001$) were also independent factors. HTN was found to be an independent factor of decreased MEEI (β = −0.298, $p = 0.002$). Multivariable linear regression analyses were shown in Table 3.

Intra- and inter-observer variabilities

The detailed results of ICCs are shown in Table 4. There was significantly high intra- and inter-observer agreement of LV CMR parameters. The coefficient of variation of intra-observer variability for LVEDV, LVEF, LVM, and LV GLPS were 0.927–0.979, 0.885–0.967, 0.878–0.964, and 0.911–0.974 respectively. The ICCs for inter-observer variability of those parameters were 0.932–0.981, 0.921–0.977, 0.876–0.964 and 0.864–0.960 respectively.

Discussion

Our study assessed the additive effect of MetS on LV function, MEEI, and myocardial strain in INOCA patients using CMR feature tracking. The principal findings were as follows: (1) INOCA patients exhibited impaired LV myocardial strain, particularly in the longitudinal direction, and with MetS aggravated damage of LV GLPS. (2) Both LVSVI and MEEI were significantly decreased in the INOCA patients with MetS compared to those without MetS. (3) MetS was independently associated with impaired MEEI and LV GLPS, the further decrease of MEEI and LV GLPS in INOCA patients with MetS might have co-existing mechanisms. (4) There was a higher proportion of HTN and the treatment of CCB in INOCA patients with MetS, and HTN and CCB were independently associated with impaired MEEI. Therefore, MetS is recommended for early intervention in INOCA patients to prevent further LV damage.

The additive impact of LV longitudinal myocardial impairment in INOCA patients with MetS

INOCA is increasingly recognized in clinically practice as a condition that can lead to poor prognosis despite the absence of coronary artery occlusion [6]. Coronary microvasculature (especially small arteries) is an important part of coronary vascular resistance, and

Table 3 Univariable and multivariable linear regression analysis of impaired LV function, MEEI, and LV strain in INOCA patients

	GLPS				MEEI				LVSVI			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value
MetS	−0.324	0.001	−0.266	0.002	−0.255	0.009	−0.262	0.009	−0.284	0.003	−0.231	0.012
Male(n)	−0.272	0.005	−0.367	<0.001	−0.155	0.116			0.080	0.422		
Age (y)	0.140	0.158			−0.040	0.687			0.246	0.012	−0.155	0.127
Smoking	−0.075	0.453			−0.025	0.802			0.210	0.033	0.160	0.075
HTN	−0.034	0.737			−0.305	0.002	−0.298	0.002	−0.224	0.022	−0.100	0.301
Obesity	0.007	0.945			−0.045	0.653			−0.081	0.415		
TG (mmol/l)	−0.120	0.224			0.030	0.760			0.091	0.358		
HDL (mmol/l)	0.264	0.007	0.062	0.534	0.159	0.107			0.098	0.321		
HbA1c (%)	−0.167	0.091	0.070	0.445	−0.186	0.059	−0.052	0.605	−0.193	0.050	−0.119	0.233
eGFR (ml/min/1.73 m^2)	0.105	0.290			0.211	0.032	0.130	0.157	0.352	<0.001	0.360	<0.001
NT-proBNP*(pg/mL)	−0.311	0.001	−0.373	<0.001	−0.237	0.015	−0.134	0.150	−0.277	0.004	−0.168	0.078
ACEI/ARB	−0.301	0.002	−0.174	0.043	−0.293	0.003	−0.118	0.257	−0.229	0.019	−0.145	0.120
Insulin	−0.265	0.007	−0.091	0.299	−0.184	0.062	−0.122	0.180	−0.195	0.047	−0.136	0.139
Biguanides	0.020	0.840			−0.144	0.145			−0.210	0.032	−0.171	0.068
CCB	0.097	0.328			0.163	0.099	0.320	0.001	0.017	0.867		
Anti-thrombotic agents	0.107	0.278			0.025	0.802			−0.198	0.044	−0.066	0.483

βis the adjusted regression coefficient

* NT-proBNP was log-transformed before being included in the regression analysis

Abbreviations as listed in Tables 1 and 2

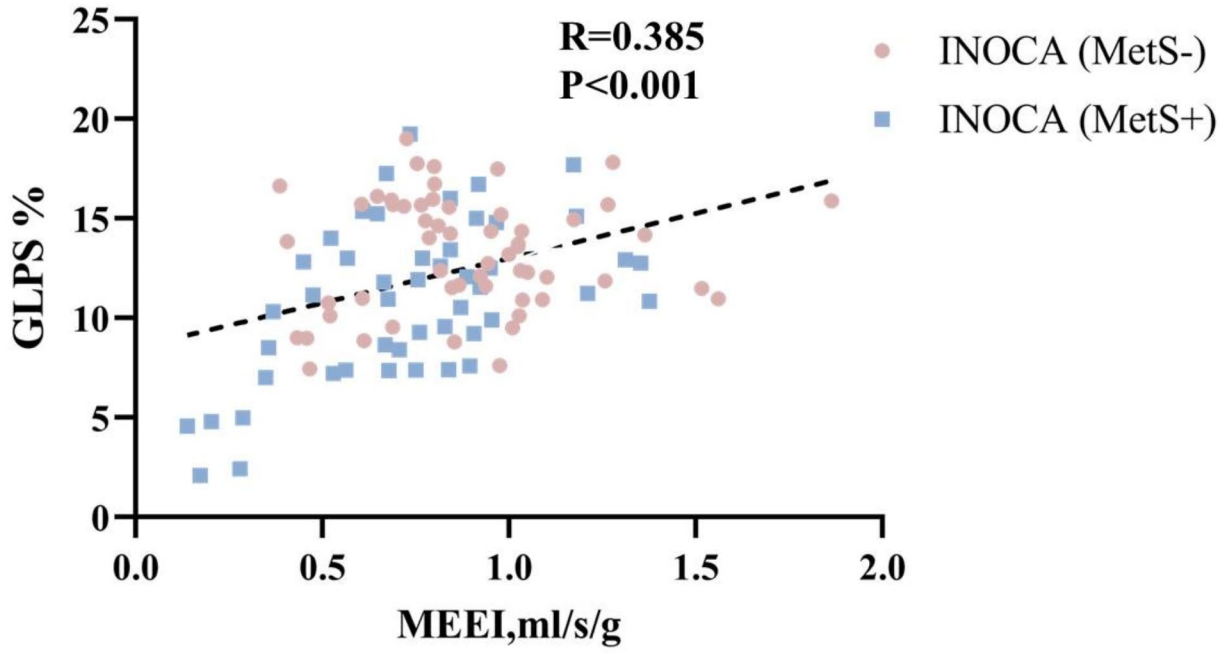

Fig. 3 The scatter plot of the association of GLPS with MEEI. MEEI: indexed myocardial energetic efficiency; GLPS: global longitudinal peak strain; MetS: metabolic syndrome

Table 4 Intra- and inter-observer variabilities of LV CMR parameters

	Intra-observer (n = 40)		Inter- observer (n = 40)	
	ICC	95% CI	ICC	95% CI
Cardiac function parameters				
LVEDV (ml)	0.961	0.927-0.979	0.964	0.932-0.981
LVESV (ml)	0.987	0.976-0.993	0.982	0.966-0.990
LVM (g)	0.934	0.878-0.964	0.932	0.876-0.964
LVEF (%)	0.938	0.885-0.967	0.958	0.921-0.977
Strain parameters				
GRPS (%)	0.958	0.923-0.978	0.919	0.850-0.957
GCPS (%)	0.957	0.920-0.977	0.942	0.893-0.969
GLPS (%)	0.952	0.911-0.974	0.926	0.864-0.960

Abbreviations as listed in Tables 1 and 2

microvascular structural disorders or vasodilation dysfunction can lead to INOCA [24]. According to current studies, the mechanism of myocardial injury in INOCA patients may be caused by coronary microvascular dysfunction (CMD), coronary vasospasm or both [8, 25]. A previous study of INOCA patients using echocardiography has shown LV GLPS decrease [26]. Our study also showed that LV GLPS was impaired in INOCA patients. A short-term follow-up study has explored the prognostic implications of MetS and its components on clinical outcomes in MINOCA patients and found that the risk of MACE in MINOCA patients with MetS was 2.13 times higher than that in patients without MetS [9]. For INOCA patients without MI, we found that MetS can also cause significant LV longitudinal strain damage, suggesting that this damage may occur earlier. It is not clear that the mechanism by which MetS led to further myocardial strain damage in INOCA patients. Recent studies have confirmed that DM promoted endothelial impairment and CMD through various mechanisms to aggravate INOCA, including increased oxidative stress, inflammation, and activation of the renin-angiotensin-aldosterone system [27]. Additionally, DM-related endothelial dysfunction also exacerbated other risk factors of INOCA (such as HTN, obesity, and dyslipidemia) and interacted with them to further aggravate CMD [28]. In our study, we also observed a significant increase in the proportion of HTN, obesity and T2DM in INOCA patients with MetS. In summary, we speculate that MetS, as a combination of the above risk factors, may also be associated with impaired endothelial function and aggravated CMD in the mechanism of further myocardial impairment in INOCA patients.

Besides, the impairment of LV GLPS was obvious in INOCA patients with MetS. Longitudinal myocardial strain was often associated with subendocardial fibers. Subendocardial fibers are most vulnerable to the adverse effects of CMD [29]. Diffuse subendocardial ischemia in INOCA patients was also considered to be caused by CMD [26]. Early attention has been paid to subendocardial ischemia in CAD patients in clinical, and we also

observed similar changes in INOCA patients. Therefore, subendocardial myocardial ischemia in INOCA patients is also worthy of attention.

Association of MetS with LVSVI and MEEI in INOCA patients

MEE has recently become an important indicator for providing information about myocardial structure, function, and oxygen consumption, which was widely used in the various prediction of MACE [12, 30]. Comparative analysis of multiple studies have shown that low LVSVI and MEEI were associated with heart failure (HF) event risk, and MEEI seemed stronger [30]. Our study found that the MEEI was reduced in INOCA patients compared to controls. In addition, both MEEI and LVSVI were significantly reduced in patients with INOCA and MetS, even in those with preserved LVEF, indicating that MEEI and LVSVI were more sensitive than LVEF in detecting superimposed LV function impairment in INOCA patients with MetS, especially MEEI. Previous studies have confirmed that impaired MEE was associated with a variety of cardiovascular diseases and metabolic factors, including ischemic cardiomyopathy, MI, HTN, DM, and MetS, and the injury mechanism was related to metabolic and hemodynamic changes, such as insulin resistance, concentric LV geometry, LV diastolic and discrete systolic dysfunction [30–33]. MEEI was independently associated with LV GLPS in individuals with MetS [13]. A study on the evaluation of cardiac function in DM patients after treatment has shown that the changes of MEEI and LV GLPS were consistent [34]. In summary, MEEI can early identify LV function impairment in INOCA patients with MetS. The management of MetS is of great significance for patients with INOCA. Early diagnosis and intervention for MetS may delay the progression of LV function impairment in INOCA patients. MEEI is relatively simple in calculation and can be obtained by non-invasive examinations such as echocardiography or CMR, which may be recommended as a useful and sensitive monitoring indicator for these patients.

Prior studies have also demonstrated that impaired MEEI in patient with MetS was primarily related to insulin resistance [13, 33]. Under the condition of insulin resistance, the myocardium reduces glucose intake, resulting in the transfer of metabolic substrates from glucose to free fatty acid (FFA) oxidation [14]. On the other hand, insulin resistance is associated with endothelial dysfunction [35]. Endothelial dysfunction has been considered as one of the pathophysiological mechanisms of impaired MEEI in patients with HF and HTN [36]. HTN is one of the important components of MetS and myocardial injury caused by MetS is also associated with insulin resistance. We speculate that the impairment of MEEI in INOCA patients with MetS may also be related to the aggravation of endothelial dysfunction. The mechanism of further reduction of MEEI and LV GLPS in INOCA patients caused by MetS may be consistent.

The independent association of HTN and medication with impaired LV deformation and function in INOCA patients

This study found that about half of INOCA patients existed HTN, and the proportion of HTN was higher in INOCA patients with MetS. Besides, HTN was independently associated with impaired MEEI in INOCA patients. The previous studies have shown that HTN was more common in INOCA patients than diabetes and HTN was associated with impaired CMD [8, 37]. This is consistent with our research. The mainly drugs for the treatment of HTN such as CCB and ACEI/ARB [38], which were independent factors of impaired MEEI and LV GLPS in INOCA patients in our study. Our study also found that the proportion of INOCA patients with MetS receiving CCB and ACEI/ARB treatment increased. This may be related to the higher proportion of HTN in INOCA patients with MetS. Additionally, CCB has been shown to improve symptoms in patients with CMD [39]. In INOCA management, the guideline also recommended the use of CCB as a drug treatment [8]. ACEI/ARB improved CMD and endothelial dysfunction in female patients with INOCA [40].

Based on our previous findings that demonstrated the additive effect of LV deformation and function impairment caused by MetS in patients with obstructive CAD [16], we further found that MetS still had a superimposed import on LV deformation and function impairment in INOCA patients even when the degree of coronary artery stenosis was mild and LVEF was preserved. Therefore, early monitoring and treatment of MetS hold significant clinical value for these patients, regardless of the presence or absence of obstructive coronary artery stenosis.

Limitations

Our study has several limitations. First, BMI was used as a substitute for waist circumference in patients who didn't have this measurement, which was accurate and convenient. Previous studies had confirmed the feasibility of this alternative [41]. Second, as a single-center study, our study had its inherent limitations, including the lack of prospective sample size calculation, bias in patient selection and data collection, and unmeasured confounding factors in the control group. Third, the clinical manifestations of INOCA can be categorized into microvascular angina and vasospasm angina, which are attributed to CMD and coronary vasospasm, respectively [3]. However, the auxiliary examination data of patients in this study are limited, which makes it difficult to classify INOCA to explore the additive effect of MetS. In the future, performing animal studies can be used to understand the effect of MetS on LV function and deformation

impairment in patients with various types of INOCA. Fourth, the correlation between a single component of MetS and LV deformation and MEEI has not been included in the study. We will pursue further research to assess this correlation in the future. Finally, we did not evaluate the stress echocardiography, coronary flow reserve, fractional flow reserve and index of microvascular resistance in the study. Further prospective and multicenter studies are necessary to confirm and expand upon our findings.

Conclusions

MetS aggravated LV deformation and MEEI impairment in INOCA patient, and was independently associated with impaired LVSVI, MEEI, and LV GLPS. The further decrease of MEEI and LV GLPS in INOCA patients caused by MetS might involve the synergistic injury mechanism. MEEI is relatively simple in calculation and early identify LV function impairment in INOCA patients with MetS, which is worthy of clinical attention. Early diagnosis and treatment of MetS in INOCA patients is of great significance.

Abbreviations

INOCA	Ischemia with nonobstructive coronary arteries
MetS	Metabolic syndrome
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CAG	Coronary angiography
MACE	Adverse cardiovascular events
DM	Diabetes mellitus
HTN	Hypertension
MINOCA	Myocardial infarction with non-obstructive coronary arteries
CMR	Cardiac magnetic resonance
LV	Left ventricular
MEE	Myocardial energetic efficiency
MEEI	Indexed myocardial energetic efficiency
SW	Stroke work
MVO_2	Myocardial oxygen consumption
MI	Myocardial infarction
T2DM	Type 2 diabetes mellitus
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
LVEDVI	Indexed left ventricular end-diastolic volume
LVESVI	Indexed left ventricular end-systolic volume
LVSVI	Indexed left ventricular stroke volume
LVEF	Indexed left ventricular ejection fraction
LVMI	Indexed left ventricular mass
BSA	Body surface area
LVGFI	Left ventricular global function index
HR	Heart rate
GRPS	Global radial peak strain
GCPS	Global circumferential peak strain
GLPS	Global longitudinal peak strain
LGE	Late gadolinium enhancement
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
CCB	Calcium channel blockers
NT-proBNP	Amino-terminal pro-B-type natriuretic peptide
CMD	Coronary microvascular dysfunction

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Author contributions
CYM, YG and ZGY designed the study. CYM interpreted the data and wrote the manuscript. CYM and YG analyzed the data and gave advice on data presentation. YNJ and LTS were responsible for collecting and sorting statistical data. HYX and RX participated in editing and review of the manuscript. XL and YKG supervised the overall study and reviewed the manuscript. YL and ZGY are the guarantor of this work and had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Biomedical Research Ethics Committee of our hospital. Informed consent was waived due to the retrospective nature of the research. The patient-sensitive data were protected with full confidentiality.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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