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ORIGINAL RESEARCH

Myocardial Abnormalities Across the AHA/ACC Stages of Heart Failure in Patients With Diabetes

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ABSTRACT

BACKGROUND Cardiac magnetic resonance imaging (CMR) could serve as a robust tool for comprehensive evaluation of early changes across heart failure (HF) stages classified by the American Heart Association/American College of Cardiology guideline in diabetes mellitus (DM).

OBJECTIVES The authors aimed to explore phenotypic imaging features characterizing DM participants at different HF stages by CMR.

METHODS DM participants with preserved ejection fraction who underwent CMR examination between January 2020 and December 2021 were evaluated. Left ventricular strain analysis and myocardial fibrosis was evaluated by CMR.

RESULTS A total of four hundred seventy-five DM participants at different HF stages (mean age 56 ± 12 years; 326 men) and 78 healthy control subjects were evaluated. Significantly decreased absolute strain values with rising HF stage were identified in DM. In addition, early diastolic strain rates were significantly lower in stage B and C HF than in stage A HF and control subjects. Myocardial extracellular volume increased with advancing HF stage in DM (stage A, 27.0% ± 2.9%; stage B, 29.1% ± 3.5%; stage C, 30.5% ± 4.1%; $P < 0.05$). In multivariable logistic regression analysis, early diastolic longitudinal strain rate (OR: 2.184; 95% CI: 1.378-3.461; $P < 0.001$) was a significant contributor that independently distinguished DM participants at stage A from control subjects, with an area under the receiver-operating characteristic curve of 0.726. For global longitudinal strain and extracellular volume, each 1% increase was associated with 1.333 and 1.300 times adjusted odds of diagnosis of stage B HF (both $P < 0.05$).

CONCLUSIONS Subclinical dysfunction and myocardial fibrosis derived from CMR were progressively remarkable with advancing HF stage in DM. Comprehensive CMR provided sensitive tools for better delineation of DM patients with pre-HF and at risk for HF. (JACC Asia. 2024;4:940-952) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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

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Diabetes mellitus (DM) is a common metabolic condition, which is a contributor for development of cardiovascular disease at a 2- to 4-fold higher risk.[1] Heart failure (HF) is one of the most common cardiovascular manifestations in DM patients. DM with HF with reduced ejection fraction has been well investigated, and the diabetic phenotype in heart failure with preserved ejection fraction (HFpEF) has received increasing attention in terms of clinical characteristics and outcomes in recent years.[2-4] DM was associated with more HF signs and symptoms, left ventricular (LV) remodeling, and poorer prognosis compared with those patients without DM, regardless of HF phenotype.[5,6]

According to the definitions of stage A/B HF updated in the American Heart Association (AHA)/American College of Cardiology (ACC) guideline, asymptomatic patients with risk factors including DM are considered to be at-risk for HF or have stage A HF, and those with abnormal biomarkers or structural or functional abnormality have developed pre-HF (stage B HF) that have a higher-risk profile for HF.[7] With increasing attention to the development of HF, asymptomatic DM patients at risk of progression to symptomatic HF were also considered to be an important entity.[8] Evaluating DM individuals with asymptomatic HF provides an opportunity to initiate effective management strategy that may prevent or delay the transition to overt HF. New treatment strategies, such as sodium-glucose cotransporter-2 inhibitors recommended as high-level evidence in the guidelines, have been confirmed to improve outcomes in HFpEF.[9,10] It was associated with both structural and functional cardiac improvements, as well as reverse remodeling of myocardial tissue indicated by CMR-derived extracellular volume (ECV) in DM and HF patients.[11,12]

Detecting early stage of HF in DM patients can be challenging because of its asymptomatic nature and likely with preserved ejection fraction. It was reported that more than one-half of DM patients without known HF should be reclassified as pre-HF based on natriuretic peptide screening.[13] The latest European Society of Cardiology guidelines for management of DM heightened the utmost importance of screening all patients with DM for HF, including by noninvasive cardiac imaging assessment.[1] Transthoracic echocardiography for assessment of diastolic function and subclinical abnormalities has been studied in stage A/B HF, but it is highly dependent on operator experience and imaging quality.[14] By contrast, CMR outperforms echocardiography in terms of its typically high anatomic resolution and good image quality; thus, it may appear to be a well-suited imaging technique for comprehensive assessments in DM. Patients with DM had prevalent higher LV mass, systolic and diastolic dysfunction, and interstitial fibrosis in accordance with potential pathophysiological mechanisms.[15-17] The multiparametric capabilities of CMR to assess cardiac subtle dysfunction and tissue characterization permit assessment of longitudinal changes of cardiac abnormalities across HF stages in DM patients,[18,19] especially for precise assessments in early stage of HF.

A complete assessment of myocardial function, anatomy, and underlying tissue characterization to accurately phenotype DM patients in early stage of HF will provide crucial information for therapeutic management. Therefore, we aimed to explore phenotypic imaging features characterizing DM patients across HF stages by CMR, and provide information for identification of the early stages of HF in DM patients.

ABBREVIATIONS AND ACRONYMS

DM = diabetes mellitus

ECV = extracellular volume fraction

GCS = global circumferential strain

GLS = global longitudinal strain

GRS = global radial strain

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LA = left atrial

LGE = late gadolinium enhancement

LV = left ventricular

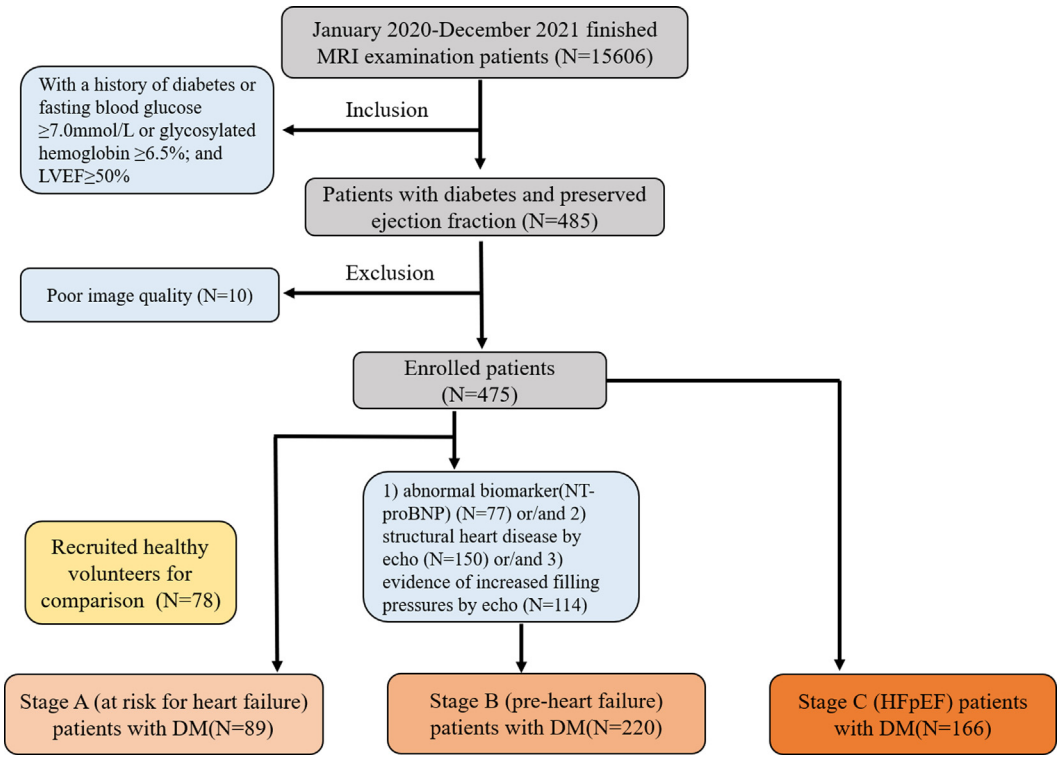
LVEF = left ventricular ejection fraction

ROC = receiver-operating characteristic

METHODS

STUDY POPULATION. From January 2020 to December 2021, DM participants with preserved left ventricular ejection fraction (LVEF) who underwent CMR examination were consecutively screened for inclusion in the study (**Figure 1**). In this prospective study, the following inclusion criteria had to be fulfilled: diagnosis of DM (a history of diabetes or fasting blood glucose ≥7.0 mmol/L or glycosylated hemoglobin ≥6.5%) and LVEF ≥50%. The exclusion criteria were: constrictive pericarditis, severe arrhythmia, heart tumor, primary cardiomyopathy, myocardial amyloidosis, acute coronary syndrome in the previous 30 days, and moderate or severe valvular heart disease. Stage A (at risk for heart failure) and stage B (pre-HF) patients were consecutively recruited at our center according to 2022 AHA/ACC guideline for HF,[8] while stage C (symptomatic HFpEF) also referred to European Society of Cardiology guidelines.[20] HFpEF participants were recruited as part of a prospective, cohort study conducted at our center (NCT04603404). Detailed information on the recruitment across HF stages is shown in the Supplemental Methods. In addition, 78 healthy volunteers were recruited for comparison. Participant data including demographics, medical history, and blood sample analysis were obtained from the electronic medical records database or inquiry. This study

FIGURE 1 Flow Diagram of the Study Population



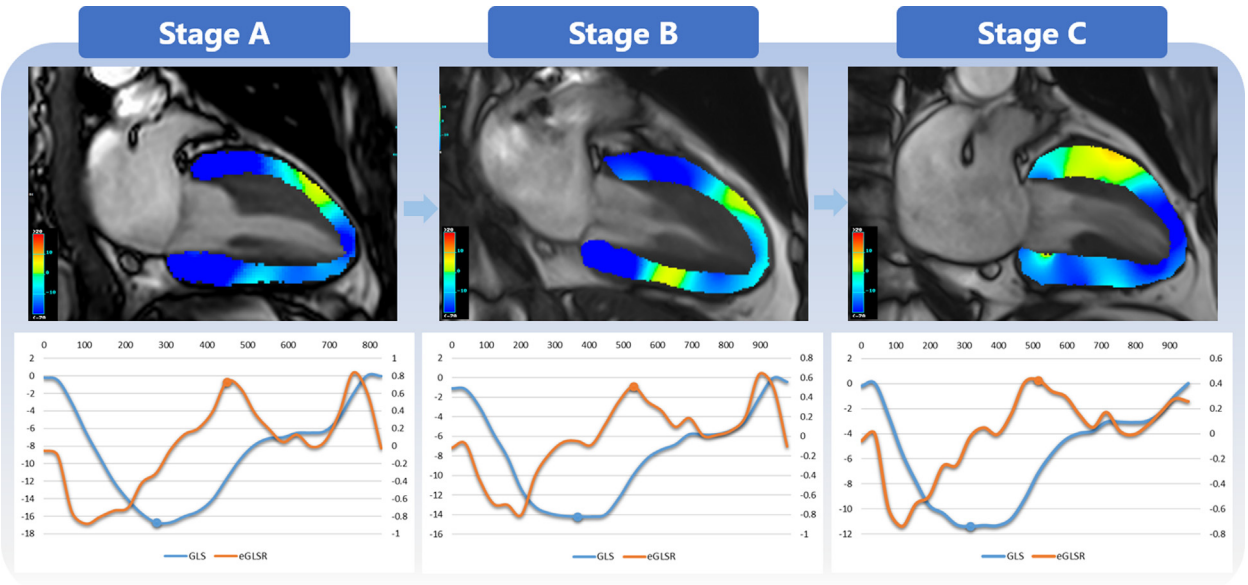
A total of 475 diabetes mellitus (DM) participants with left ventricular ejection fraction (LVEF) were enrolled for analysis, including 89 at stage A, 220 at stage B, and 166 at stage C (heart failure with preserved ejection fraction [HFpEF]). A group of 78 healthy volunteers were recruited for comparison. MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-brain natriuretic peptide.

was approved by Fuwai hospital ethics committee (approval number 2020-1382), and written informed consent was obtained from all study participants.

CMR PROTOCOL AND IMAGE ANALYSIS. All subjects underwent CMR examination using 3-T scanners (MAGNETOM Skyra, Siemens Healthcare, or Ingenia, Philips Healthcare) during sinus rhythm with retrospective electrocardiogram gating. Cardiac 2-, 3-, and 4-chamber and short-axis view cine images were acquired using a standard breath-held steady-state free precession cine sequence. Contrast-enhanced CMR and T_1 mapping examination were also performed in some participants for further evaluation. All CMR analyses were performed with commercially processing software packages fully blinded to echocardiography results and clinical data. Global longitudinal strain (GLS), systolic global longitudinal strain rate (sGLSR) and early diastolic global longitudinal strain rate (eGLSR) were derived from 2-, 3-, and 4-chamber views of the cine magnetic resonance (MR) images; global circumferential strain (GCS), global radial strain (GRS), systolic GCS/GRS rate (sGCSR, sGRSR), and early diastolic GCS/GRS rate (eGCSR, eGRSR) were derived from a stack of short-axis views covering the whole LV. Strain analysis was performed as in Figure 2. All strain and strain parameters were compared by absolute value, and the lower values meant worse cardiac function. Details on CMR protocol and analysis, including strain analysis, late gadolinium enhancement (LGE), and ECV assessment, and echocardiography protocol are shown in the Supplemental Methods.

STATISTICAL ANALYSIS. Variables are presented as percentage for categorical data and mean ± SD or median (Q1, Q3) for continuous variables, as appropriate. Normality was tested using the Shapiro-Wilk test. Clinical and CMR variables were compared across stages using 1-way analysis of variance or Kruskal-Wallis tests for continuous variables depending on the distribution, and using the chi-square test for categorical variables, followed by post hoc tests. The Pearson's correlation analysis was used to determine correlations between continuous imaging variables and shown as a heatmap. Receiver-

FIGURE 2 **Left Ventricular Longitudinal Strain and Strain Rate Analysis**



Representative cardiac magnetic resonance studies of left ventricular longitudinal strain and strain rate images and curves from stage A/B/C heart failure in diabetes mellitus participants. Top row shows strain measurements in 2-chamber view, and bottom row shows strain curves of global longitudinal strain and strain rate. eGLSR = early diastolic global longitudinal strain rate; GLS = global longitudinal strain.

operating characteristic (ROC) curves were used to identify parameters that best differentiated stage A HF from control subjects and stage B from stage A HF. Logistic regression analysis was performed to determine independent contributors of stage B vs stage A and stage A vs control subjects in DM participants. Covariates with a P value <0.50 in univariable analysis were chosen for subsequent multivariable analysis for identifying independent factors. In addition, the combined accuracy of the imaging variables to differentiate participants was tested by the area under the curve (AUC). Analysis of covariance was used to evaluate differences of CMR parameters after adjusting for age and sex. Sensitivity analysis of comparisons among groups in subjects without ischemic late gadolinium enhancement (LGE) patterns was also performed. In addition, comparisons were conducted among groups with or without the presence of other comorbidities, as well as between subjects with normal and abnormal biomarkers in stage B HF. Intraobserver and interobserver variability of strain parameters were assessed in 30 randomly chosen participants at least 4 weeks apart (by W.Y. and L.Z., with over 2 years of experience in cardiovascular CMR). Two-sided $P < 0.05$ was considered indicative of statistically significant difference. All analyses were performed using IBM SPSS Statistics for Windows, version 21.0, MedCalc Statistical Software, version 19.6.4, and OriginPro 2021, version 9.8.

RESULTS

PARTICIPANT CHARACTERISTICS. In total, 475 DM participants were enrolled in the study, including 89 at stage A, 220 at stage B, and 166 at stage C (HFpEF). A group of healthy volunteers were recruited for comparison (n = 78). Participant characteristics are detailed in **Table 1**. DM participants in stage C HF were older than the other groups ($P < 0.05$). Stage B and C HF participants had a higher prevalence of hypertension, obesity, and coronary heart disease than in stage A. All HF stages of DM participants showed significantly higher hypersensitive C-reactive protein level than control subjects. There were also differences in estimated glomerular filtration rate and N-terminal pro-brain natriuretic peptide level with worsening HF stages (all $P < 0.05$ for post hoc tests) (Supplemental Figure 1).

MR STRUCTURE AND FUNCTION CHARACTERISTICS. CMR data are shown in **Table 2** and **Figure 3**. Overall, worse LV systolic function and more severe LV remodeling were observed with rising HF stage in DM participants, particularly in stage C. LVEF decreased

TABLE 1 Baseline Characteristics

	Normal Control (n = 78)	Stage A (n = 89)	Stage B (n = 220)	Stage C (n = 166)	*P* Value
Age, y	50.1 ± 7.4	53.7 ± 11.5	55.0 ± 12.5[a]	59.7 ± 12.2[a,b,c]	<0.001
Female	39 (50.0)	34 (38.2)	60 (27.3)[a]	55 (33.1)	0.003
Body mass index, kg/m^2	23.6 ± 2.9	25.3 ± 3.0[a]	27.3 ± 3.6[a,b]	27.3 ± 4.0[a,b]	<0.001
Systolic blood pressure, mm Hg	120.3 ± 10.2	131.5 ± 18.3[a]	136.3 ± 16.9[a]	135.1 ± 19.6[a]	<0.001
Diastolic blood pressure, mm Hg	75.8 ± 9.4	78.0 ± 14.0	79.8 ± 11.0[a]	77.9 ± 14.2	0.033
Hypertension	/	38 (42.7)	154 (70.0)[b]	144 (86.7)[b,c]	<0.001
Obesity	/	21 (23.6)	90 (40.9)[b]	68 (41.0)[b]	0.010
Prevalent CHD	/	7 (7.9)	57 (25.9)[b]	45 (27.1)[b]	0.001
Prior MI	/	0 (0)	19 (8.6)[b]	16 (9.6)[b]	0.012
PCI/CABG intervention	/	0 (0)	29 (13.2)[b]	10 (6.0)	<0.001
Smokers	6 (7.7)	17 (19.1)	71 (32.3)[a]	70 (42.2)[a,b]	<0.001
Fast plasma glucose, mmol/L	5.29 ± 0.44	7.80 ± 3.11[a]	7.74 ± 2.86[a]	7.36 ± 2.86[a]	<0.001
HbA1C, %	5.44 ± 0.32	7.02 ± 1.18[a]	7.28 ± 1.35[a]	7.10 ± 1.29[a]	<0.001
HDL-C, mmol/L	1.60 ± 0.39	1.23 ± 0.34[a]	1.07 ± 0.25[a,b]	1.15 ± 0.41[a]	<0.001
Triglycerides, mmol/L	1.33 ± 0.86	1.94 ± 1.55	2.11 ± 1.86[a]	1.90 ± 1.93	0.025
eGFR, mL/min/1.73 m^2	107.4 ± 11.5	92.1 ± 16.4[a]	82.4 ± 19.7[a,b]	71.9 ± 20.6[a,b,c]	<0.001
hsCRP, mg/L	0.43 (0.18-1.11)	1.09 (0.37-2.15)[a]	1.04 (0.47-2.72)[a]	1.19 (0.50-2.99)[a]	<0.001
NT-proBNP, pg/mL	/	56.6 (20.3-84.4)	98.9 (46.7-251.5)[b]	592.4 (255.3-1,113.0)[b,c]	<0.001
Medication use					
ACEI/ARB	/	25 (28.1)	129 (58.6)[b]	111 (66.9)[b]	<0.001
β-blocker	/	37 (41.6)	155 (70.5)[b]	127 (76.5)[b]	<0.001
Statin	/	39 (43.8)	118 (53.6)	98 (59.0)	0.067
Aspirin	/	20 (22.5)	74 (33.6)	58 (34.9)	0.098
Diuretic	/	8 (9.0)	65 (29.5)[b]	112 (67.5)[b,c]	<0.001
Antidiabetic medication	/	59 (69.4)	173 (80.8)	130 (82.3)	0.045
Insulin	/	16 (18.8)	32 (15.0)	23 (154.6)	0.647
Biguanides	/	37 (43.5)	111 (51.9)	51 (32.3)[c]	0.001
Sulfonylureas	/	9 (10.6)	26 (12.1)	9 (5.7)	0.107
α-glucosidase inhibitor	/	16 (18.8)	58 (27.1)	41 (25.9)	0.318
SGLT2 inhibitor	/	13 (15.3)	48 (22.4)	63 (39.9)[b,c]	<0.001
Others	/	8 (9.4)	30 (14.0)	18 (11.4)	0.505

Values are mean ± SD, n (%), or median (Q1-Q3). [a]$P < 0.05$ vs control subjects. [b]$P < 0.05$ vs participants with stage A HF. [c]$P < 0.05$ vs participants with stage B HF using post hoc Bonferroni analysis.

ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CABG = coronary artery bypass graft; CHD = coronary heart disease; eGFR = estimated glomerular filtration rate; HbA1C = glycosylated hemoglobin; HDL-C = high-density lipoprotein-cholesterol; hsCRP = hypersensitive C-reactive protein; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCI = percutaneous coronary intervention; SGLT2 = sodium-glucose cotransporter-2.

with worsening HF stage ($P < 0.001$), but there were no significant differences between stages A and B HF (61.7% ± 5.9% vs 60.2% ± 6.4%; $P > 0.05$). Index left atrial (LA) volume, LV end-diastole volume, and LV mass increased with worsening HF in DM, and differed significantly between groups (all $P < 0.05$ for post hoc tests). In comparison with control subjects, participants in stage A HF had lower LV end-diastole volume index. Neither LVEF nor LV remodeling (LA volume and LV mass index) differed between stage A HF and control subjects.

MR STRAIN MEASUREMENTS. Through comparing strain parameter among groups, worse LV function were reported with significantly decreased absolute GLS, GCS, and GRS values with progressive HF severity (stage A > B > C; all $P < 0.05$) (Figure 3). The mean GLS across HF stages was −16.4% ± 2.5%, −13.8% ± 3.1%, and −11.6% ± 3.3%, respectively. Compared with control subjects, DM participants in stage A HF had significantly worse GLS (−16.4% ± 2.5% vs −17.7% ± 1.7%; $P < 0.05$), but comparable GCS and GRS. Regarding strain rates, HFpEF group had lower systolic strain rate value than the other 3 groups (all $P < 0.05$). DM participants with pre-HF also had significant lower sGLSR when compared with stage A HF and control subjects. For assessment of diastolic function, eGLSR, eGCSR, and eGRSR were significantly lower in both pre-HF and HFpEF than in stage A HF and control subjects (all $P < 0.05$). But pre-HF and HFpEF participants with DM had comparable early diastolic strain rates. Comparing participants in stage A HF to control

TABLE 2 Image Variables Among 4 Groups Including Control and Stage A/B/C HF

	Normal Control (n = 78)	Stage A (n = 89)	Stage B (n = 220)	Stage C (n = 166)	*P* Value
Echocardiographic data					
LVEF, %	/	65.0 ± 4.8	63.3 ± 6.7[a]	59.2 ± 7.4[a,b]	<0.001
E/E' ratio	/	8.6 ± 2.0	10.3 ± 3.1[a]	12.4 ± 3.9[a,b]	<0.001
LAVi, mL/m^2	/	23.4 ± 5.4	30.1 ± 9.3[a]	39.9 ± 18.3[a,b]	<0.001
LV mass index, g/m^2	/	80.7 ± 18.5	103.0 ± 26.4[a]	114.6 ± 34.9[a,b]	<0.001
CMR function					
Heart rate, beats/min	68 ± 10	70 ± 12	69 ± 12	69 ± 15	0.880
LVEF, %	62.2 ± 4.9	61.7 ± 5.9	60.2 ± 6.4[c]	57.9 ± 7.8[a,b,c]	<0.001
Cardiac index, L/min/m^2	3.11 ± 0.56	2.92 ± 0.51	3.04 ± 0.70	3.23 ± 0.86[a]	0.003
LAVi, mL/m^2	33.0 ± 8.0	31.3 ± 7.4	39.6 ± 14.7[a,c]	51.1 ± 25.7[a,b,c]	<0.001
LVEDV index, mL/m^2	73.9 ± 11.8	69.0 ± 10.8[c]	74.8 ± 16.5[a]	84.6 ± 26.0[a,b,c]	<0.001
LVESV index, mL/m^2	28.1 ± 6.4	26.6 ± 7.0	30.2 ± 9.7	36.8 ± 16.0[a,b,c]	<0.001
LV mass index, g/m^2	43.6 ± 7.6	46.4 ± 8.6	60.6 ± 15.8[a,c]	66.0 ± 20.5[a,b,c]	<0.001
RVEF, %	53.7 ± 4.3	54.6 ± 6.8	55.9 ± 9.1[c]	51.5 ± 10.4[a,b]	<0.001
Strain analysis					
GLS, %	−17.7 ± 1.7	−16.4 ± 2.5[c]	−13.8 ± 3.1[a,c]	−11.6 ± 3.3[a,b,c]	<0.001
GCS, %	−19.2 ± 1.9	−19.0 ± 2.6	−17.1 ± 2.9[a,c]	−14.3 ± 4.1[a,b,c]	<0.001
GRS, %	34.1 ± 5.6	33.8 ± 7.9	29.3 ± 7.5[a,c]	23.5 ± 9.9[a,b,c]	<0.001
sGLSR, per s	−0.91 ± 0.15	−0.89 ± 0.18	−0.78 ± 0.18[a,c]	−0.65 ± 0.17[a,b,c]	<0.001
sGCSR, per s	−0.99 ± 0.18	−1.01 ± 0.21	−0.97 ± 0.24	−0.78 ± 0.20[a,b,c]	<0.001
sGRSR, per s	1.74 ± 0.43	1.82 ± 0.55	1.61 ± 0.51[a]	1.21 ± 0.46[a,b,c]	<0.001
eGLSR, per s	0.81 ± 0.17	0.66 ± 0.19[c]	0.54 ± 0.23[a,c]	0.51 ± 0.22[a,c]	<0.001
eGCSR, per s	0.89 ± 0.18	0.73 ± 0.19[c]	0.62 ± 0.22[a,c]	0.56 ± 0.23[a,c]	<0.001
eGRSR, per s	−1.71 ± 0.42	−1.52 ± 0.50	−1.19 ± 0.43[a,c]	−0.99 ± 0.49[a,b,c]	<0.001
Tissue characterization					
Presence of LGE	/	/	50 (22.7)	42 (25.3)	0.975
LGE mass, g	/	0.00 (0.00-0.00)	0.00 (0.00-2.85)[a]	0.00 (0.00-3.50)[a]	<0.001
LGE percentage (% of mass)	/	0.00 (0.00-0.00)	0.00 (0.00-2.52)[a]	0.00 (0.00-2.86)[a]	<0.001
Native T1 (ms)	1,212.8 ± 38.4	1,205.9 ± 84.0	1,229.9 ± 78.9	1,265.5 ± 96.7[a,b,c]	<0.001
ECV, %	26.4 ± 2.1	27.0 ± 2.9	29.1 ± 3.5[a,c]	30.5 ± 4.1[a,b,c]	<0.001

Values are mean ± SD or median (Q1-Q3). [a]$P < 0.05$ vs participants with stage A HF. [b]$P < 0.05$ vs participants with stage B HF using post hoc Bonferroni analysis. [c]$P < 0.05$ vs control subjects.

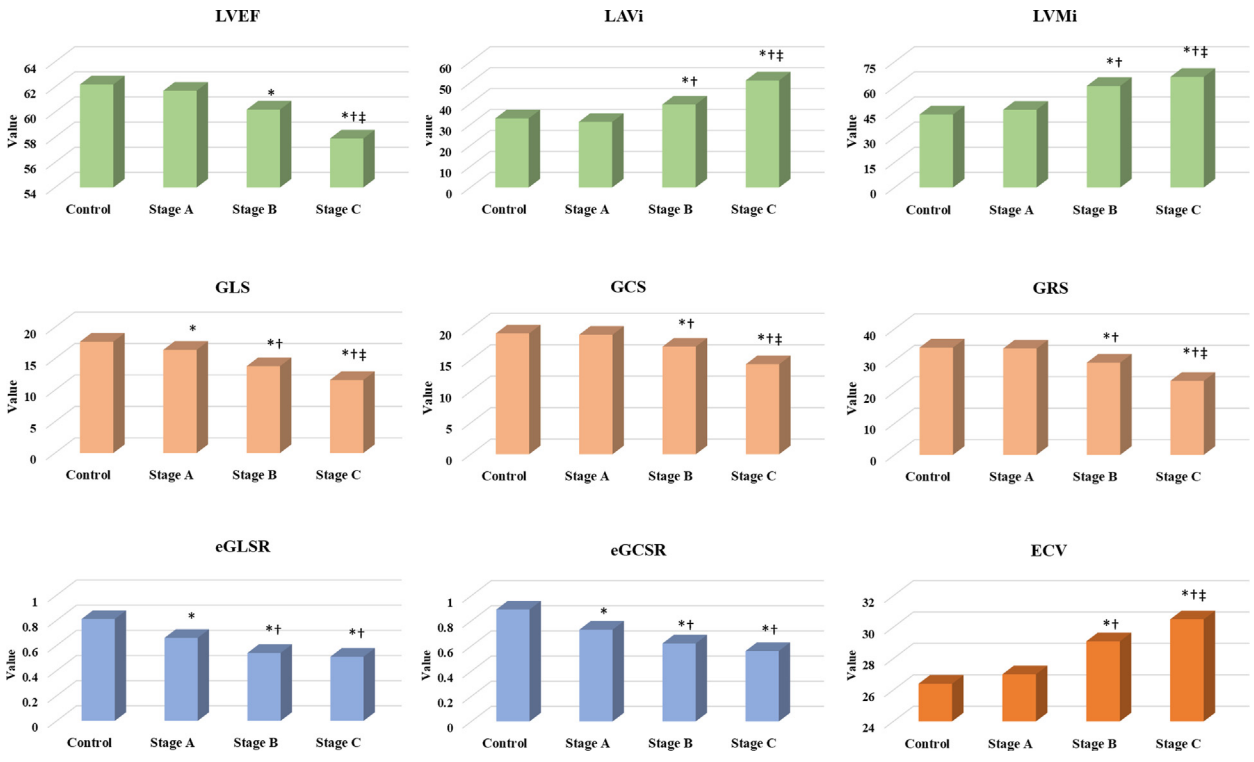
ECV = extracellular volume fraction; eGCSR = global early diastolic circumferential strain rate; eGLSR = global early diastolic longitudinal strain rate; eGRSR = global early diastolic radial strain rate; GCS = global circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; LAV = left atrial maximum volume; LGE = late gadolinium enhancement; LV= left ventricular; LVEDV = left ventricular end-diastole volume; LVEF =left ventricular ejection fraction; LVESV = left ventricular end-systole volume; RVEF = right ventricular ejection fraction; sGCSR = global systolic circumferential strain rate; sGLSR = global systolic longitudinal strain rate; sGRSR = global systolic radial strain rate.

subjects revealed no differences in systolic strain rates, but diastolic dysfunction shown by worse eGLSR (0.66 ± 0.19/s vs 0.81 ± 0.17/s; $P < 0.05$) and eGCSR (0.73 ± 0.19/s vs 0.89 ± 0.18/s; $P < 0.05$) was identified. Of note, using the mean and 1 SD of GLS and eGLSR in the control group as the cutoff value for severity stratifications, the differences between the distribution of impaired GLS and eGLSR were notable across HF stages (**Figure 4**). Higher prevalence of severely impaired GLS than eGLSR was evident in stage C HF, while in stage A HF the prevalence of severely impaired eGLSR was higher than that of GLS.

Sensitivity analyses excluding participants with ischemic LGE and covariance analysis after adjusting for age and sex yielded similar results for strain analysis measurements (Supplemental Tables 1 and 2).

MYOCARDIAL TISSUE CHARACTERIZATION. Of the DM participants, 316 completed contrast-enhanced CMR examination. In total, 33.9% (50 of 152) pre-HF and 33.1% (42 of 127) HFpEF participants presented with positive LGE. There was no significant difference in quantitative LGE between pre-HF and HFpEF group. Furthermore, pre- and post-T_1 mapping examinations were completed in 278 DM participants (stage A n = 31, stage B n = 138, stage C n = 109) and 48 control subjects. HFpEF group had significant higher native T_1 value than the other groups. For evaluation of myocardial interstitial fibrosis, ECV was higher in more severe patients across HF stages (stage

FIGURE 3 Comparison of CMR Characteristics Among 4 Groups

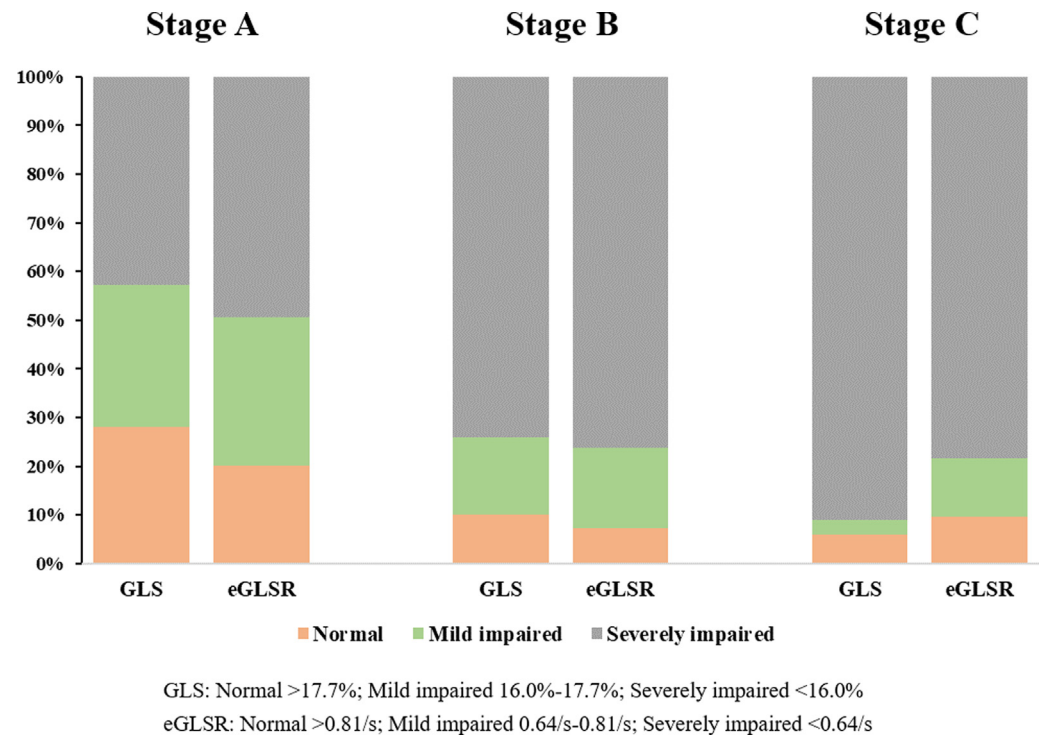


Strain parameters were expressed as absolute values, and the lower values meant worse cardiac function. Among groups of control subjects and stage A/B/C heart failure, left atrial maximum volume index (LAVi) and left ventricular mass index (LVMi) increased with worsening heart failure in diabetes mellitus (top row). Absolute GLS, global circumferential strain (GCS) and global radial strain (GRS) values significantly decreased with progressive HF severity (Middle row). For diastolic strain rates, eGLSR and early diastolic global circumferential strain rate (eGCSR) were significant lower in both pre-heart failure and heart failure with preserved ejection fraction than in stage A heart failure and control subjects. extracellular volume fraction (ECV) was also higher in more severe patients across HF stages (Bottom row). Abbreviations as in **Figures 1 and 2**.

A, 27.0% ± 2.9%; stage B, 29.1% ± 3.5%; stage C, 30.5% ± 4.1%; all $P < 0.05$ for post hoc tests). After excluding participants with ischemic LGE, similar results were shown for tissue characterization, particularly for ECV (Supplemental Table 2).

IDENTIFICATION FOR PRE-HF AND PARTICIPANTS AT RISK FOR HF. The ROC analysis for differentiation stage A HF from control group and stage B from stage A HF were shown in **Figure 5** and Supplemental Table 3. And the ROC data about comparing stage C with stage A/B were shown in Supplemental Table 3 and Supplemental Figure 2. Among CMR parameters, eGLSR and eGCSR showed the best performance for discriminating participants at risk for HF from control subjects, followed by GLS (AUC 0.726 for both eGLSR and eGCSR, AUC 0.674 for GLS; all $P < 0.001$). For differentiating participants in stage B from A HF, LA volume index, LV mass index, and GLS showed better diagnostic ability than other CMR parameters (AUC 0.691 for LA volume index, AUC 0.791 for LV mass index, AUC 0.730 for GLS; all $P < 0.001$). In multivariable logistic regression analysis with significant CMR variables between groups, the association between eGLSR and diagnosis of stage A HF was independent of other parameters (OR: 2.184; 95% CI; 1.378-3.461; $P = 0.001$), and the cutoff value of eGLSR was 0.623/s from ROC analysis. In addition, GLS (OR: 1.333; 95% CI: 1.042-1.706; $P = 0.022$) and ECV (OR: 1.300; 95% CI: 1.063-1.590; $P = 0.011$) were identified as independent contributors that distinguished stage B from A HF (**Table 3**). The results of sensitivity analysis using polytomous logistic regression analysis are shown in Supplemental Table 4. For GLS and ECV, the cutoff values were −14.6% (sensitivity, 59.8%; specificity, 75.3%) and 26.48% (sensitivity, 81.2%; specificity, 51.6%), respectively. The combined of estimated glomerular filtration rate, LV end-diastole volume index, and eGLSR for distinguishing stage A

FIGURE 4 Distribution of GLS and eGLSR Across Heart Failure Stages



The severity of impaired GLS and eGLSR was stratified by mean and 1 × SD in the healthy group (−17.7% ± 1.7% for GLS and 0.81 ± 0.17/s for eGLSR). In stage A heart failure, impaired eGLSR was more notable while the impairment of GLS was more severe in more advanced stages. It is suggested that the eGLSR at stage A could be a more sensitive assessment of functional impairment, whereas GLS was superior to eGLSR in assessing myocardial dysfunction at stage C. Abbreviations as in Figure 2.

from control subjects had an AUC of 0.843, and the AUC was 0.844 for distinguishing stage B from A by estimated glomerular filtration rate, LV mass index, GLS, and ECV (both $P < 0.05$) (Figure 5).

CORRELATES OF MR PARAMETERS. Heatmap shows the relationship among CMR parameters and echocardiography parameters in all enrolled participants (Supplemental Figure 3). There were significant correlations between some strain variables and echocardiography diastolic function parameters (r = −0.30 to 0.36; $P < 0.05$). ECV has significant correlations with the conventional MR parameters (r = −0.12 to 0.27; $P < 0.05$) and strain parameters (for GLS, r = 0.291; $P < 0.001$ and for eGLSR, r = −0.188; $P = 0.001$).

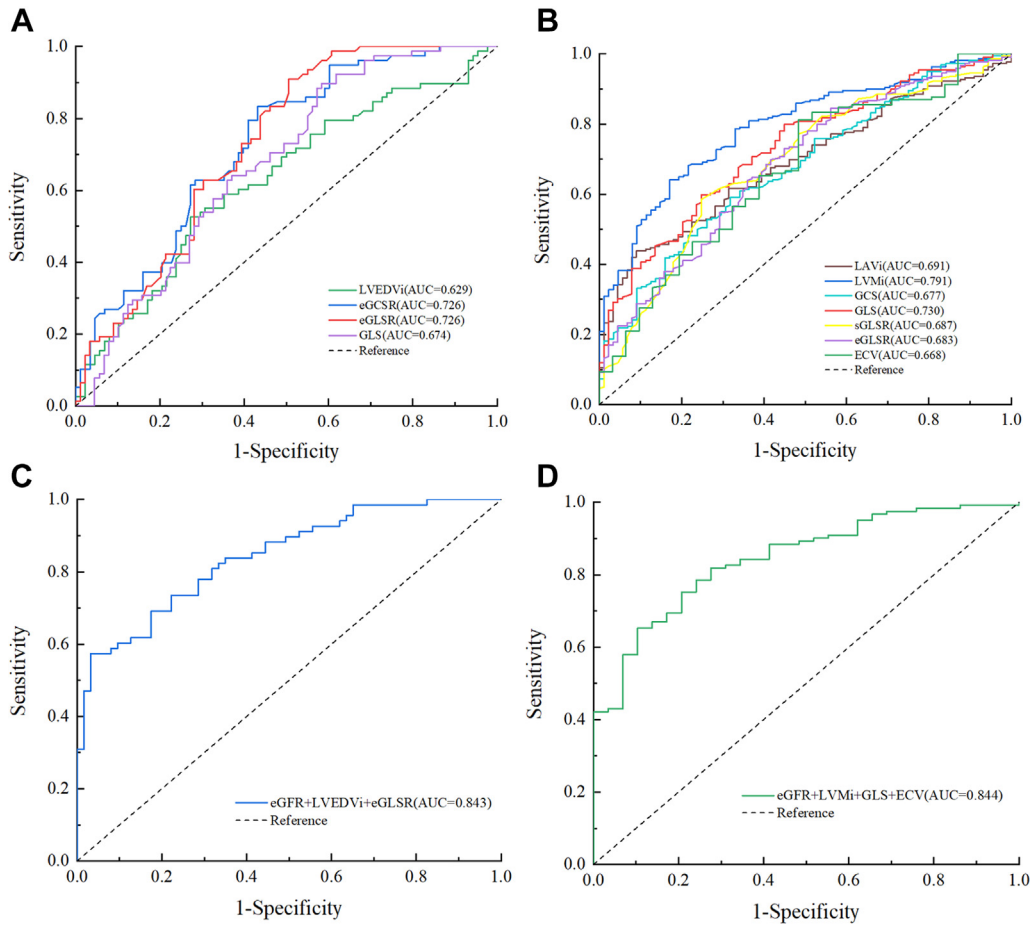
SUBGROUP ANALYSIS AND REPRODUCIBILITY. In DM participants at stage B HF, the presence of abnormal biomarkers was significantly associated with LA enlargement and impaired LV function detected by GLS, sGLSR, and eGLSR (Supplemental Table 5). Considering the effect of other comorbidities, we compared the CMR variables among groups with or without the presence of hypertension and obesity, and the results are shown in Supplemental Table 6.

Intraobserver and interobserver variability of strain parameters are shown in Supplemental Table 7. All of the strain measurements showed excellent reproducibility, with intraclass correlation coefficient ranging from 0.894 to 0.981. Bland-Altman plots for the measurements are shown in Supplemental Figures 4 and 5.

DISCUSSION

The present study provided several key findings in terms of MR features in DM patients across AHA/ACC HF stages, which are summarized in **Central Illustration**. The disease severity and pathogenesis varied at different HF stages associated DM, and CMR could describe the characteristics of different HF stages by distinctive parameters with optimal performance. First, strain parameters derived from CMR feature tracking decreased with rising HF stage in DM

FIGURE 5 Receiver-Operating Characteristic Curves for Identifying Patients With Stage A/B HF



Top row shows cardiac magnetic resonance-derived left ventricular parameters for differentiation stage A from normal control (A) and stage B from stage A (B). Bottom row shows receiver-operating characteristic curves using combined parameters obtained from logistic regression analysis, and they show greater AUC than a single parameter, with an AUC of 0.843 for distinguishing stage A from control subjects (C) and an AUC of 0.844 for distinguishing stage B from A (D). eGFR = estimated glomerular filtration rate; LVEDVi = left ventricular end-diastole volume index; sGLSR = systolic global longitudinal strain rate; other abbreviations as in Figure 3.

participants, in which early diastolic strain rates showed more remarkable differences in the early HF stage whereas GLS decreased more significantly in advanced HF stage. Then, independent GLS and early diastolic strain rate had sufficient accuracy for screening to identify individuals with stages A and B HF, respectively. In addition, progressive HF stage in DM was associated with a higher degree of myocardial fibrosis assessed by CMR T_1 mapping, which was also independently associated with diagnosis of stage B HF. With precise tissue characterization and sensitive parameters for identification of cardiac dysfunction, CMR provide incremental imaging profiles for phenotyping early stage of HF in DM patients. Integrating CMR in the routine clinical work-up will offer crucial information for implementation of early treatment to avoid future adverse cardiac events in DM patients with early stage of HF.

Recognition of HF in DM is challenging because of subjectivity of symptoms or under-reporting of laboratory results, especially when a large proportion of subjects are featured by preserved ejection fraction providing limited diagnostic information.[13,21] In addition, the updated AHA/ACC guideline was shown to reclassify approximately 20% older adults without prevalent HF to stage B, which is helpful in identifying subjects at higher HF risk.[22] Given that DM is an important risk factor for HF,[2,23] it is of utmost importance to explore sensitive tools to characterize subclinical dysfunction and tissue composition

TABLE 3 Logistic Regression Analysis for Identifying DM Patients With Stage A and B HF

	Control Subjects vs Stage A		Stage A vs Stage B	
	Univariable OR (95% CI) *P* Value	Multivariable OR (95% CI) *P* Value	Univariable OR (95% CI) *P* Value	Multivariable OR (95% CI) *P* Value
Age	1.038 (1.005-1.072) **0.024**	0.879 (0.810-0.954) **0.002**	1.009 (0.989-1.030) 0.375	
Sex	0.618 (0.334-1.145) 0.126		0.607 (0.360-1.021) 0.060	
Body mass index, kg/m^2	1.212 (1.086-1.352) **0.001**	–	1.188 (1.097-1.287) **<0.001**	–
SGLT2 inhibitor[a]	/		1.601 (0.818-3.137) 0.170	–
Ischemic LGE[a]	/		/	–
Hypertension	/		3.132 (1.881-5.212) **<0.001**	–
Smokers	5.013 (1.826-13.765) **0.002**	4.313 (1.007-18.485) **0.049**	2.172 (1.127-4.183) **0.020**	–
eGFR, mL/min/1.73 m^2	0.924 (0.894-0.954) **<0.001**	0.900 (0.853-0.950) **<0.001**	0.972 (0.956-0.988) **0.001**	0.948 (0.914-0.983) **0.004**
LAVi, mL/m^2	0.970 (0.932-1.010) 0.142		1.073 (1.044-1.104) **<0.001**	–
LV mass index, g/m^2	1.045 (1.005-1.086) **0.026**	–	1.107 (1.075-1.140) **<0.001**	1.072 (1.014-1.134) **0.015**
LVEDV index, mL/m^2	0.962 (0.935-0.989) **0.007**	0.945 (0.893-1.000) **0.049**	1.027 (1.009-1.046) **0.003**	–
GLS, %[b]	1.333 (1.141-1.558) **<0.001**	–	1.379 (1.240-1.534) **<0.001**	1.333 (1.042-1.706) **0.022**
GRS, %	1.006 (0.962-1.051) 0.807		1.078 (1.042-1.115) <0.001	
GCS, %	1.046 (0.914-1.197) 0.516		1.284 (1.161-1.419) <0.001	
sGRSR, per 0.1/s	0.969 (0.910-1.031) 0.320		1.077 (1.028-1.128) 0.002	
sGLSR, per 0.1/s[b]	1.064 (0.887-1.275) 0.506		1.392 (1.205-1.607) **<0.001**	–
eGLSR, per 0.1/s[b]	1.604 (1.310-1.963) **<0.001**	2.184 (1.378-3.461) **0.001**	1.285 (1.128-1.464) **<0.001**	–
eGRSR, per 0.1/s	1.092 (1.020-1.169) **0.011**	–	1.162 (1.097-1.231) <0.001	
eGCSR, per 0.1/s	1.606 (1.322-1.950) **<0.001**	–	1.241 (1.105-1.394) <0.001	
ECV, %	1.101 (0.912-1.330) 0.316		1.238 (1.074-1.426) **0.003**	1.300 (1.063-1.590) **0.011**

Covariates with a *P* value of <0.50 in univariable analysis were chosen for subsequent multivariable analysis for identifying patients with stage A HF from control subjects and identify patients with stage B from stage A HF. Bold indicate statistical significance. [a]To adjust for potential effect, SGLT2 inhibitors and ischemic LGE were included as covariates when identifying patients with stage B from stage A HF. [b]For strain and strain rates, we selected the strongest predictor to enter the multivariable analysis for identifying patients with stage B from stage A HF.

Abbreviations as in Table 1 and 2.

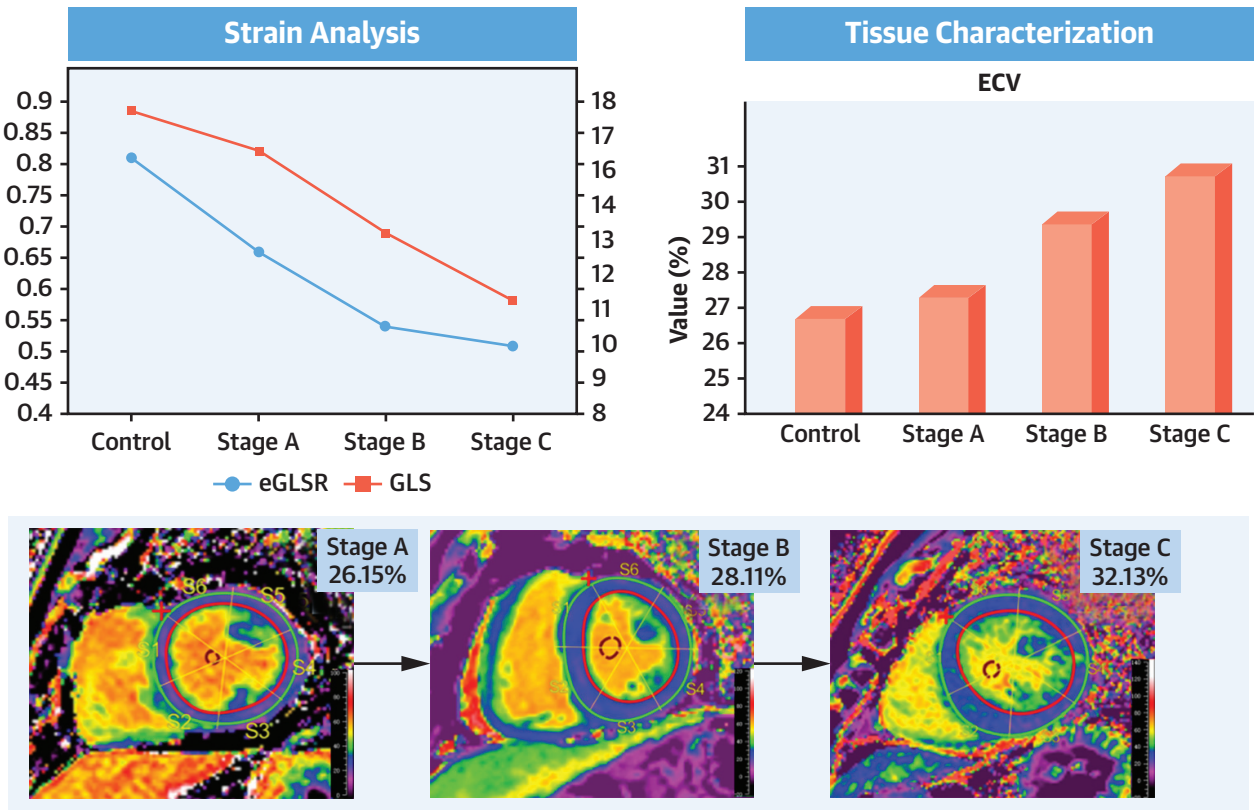
associated with DM in early stages of HF including HFpEF and stage A/B HF.

HF is a progressive condition, and there is a need to understand the characteristic changes in different stages. In preclinical stage A/B subjects, noninvasive cardiac imaging such as echocardiography offered tools for evaluation of functional and structural abnormalities and prediction of HF progression.[14] In asymptomatic elderly patients with DM, subclinical systolic dysfunction was revealed by GLS.[16] HFpEF with DM displayed more evidence of echocardiographic abnormalities including greater LV mass and LA area compared with those without DM.[5,24] Echocardiographic phenotypes of asymptomatic DM patients were also exhibited, which highlighted the prognostic value of LV remodeling and subclinical systolic dysfunction in DM by cluster analysis.[25]

However, limited data are available on cardiac features of DM patients across HF stages assessed by CMR. DM is one of underlying comorbid conditions related to HFpEF phenotype, and the association of DM with impaired systolic strains and high level of fibrosis was reported in HFpEF, highlighting the potential role of cardiac CMR.[2-4] With more attention shifting on the earlier stages of HF, that is asymptomatic HF, CMR could serve as a robust tool for

CENTRAL ILLUSTRATION **Characteristic Magnetic Resonance Features in Development of Heart Failure With Preserved Ejection Fraction in Diabetes Mellitus Patients**

	Normal Control	Stage A	Stage B	Stage C
LVEF	–	–	↓	↓↓
Strain (GLS)	–	↓	↓↓	↓↓↓
Early diastolic strain rate	–	↓	↓↓	↓↓
ECV	–	↑/–	↑↑	↑↑↑



Yang W, et al. JACC Asia. 2024;4(12):940–952.

The top row shows the characteristic changes of CMR features including strain analysis and myocardial fibrosis assessed by T_1 mapping. The middle row demonstrated the distinct change trends in GLS, eGLSR, and ECV among 4 groups. The bottom row shows representative short-axis ECV images in DM participants with different stages of heart failure. DM = diabetes mellitus; ECV = extracellular volume fraction; eGLSR = global early-diastolic global longitudinal strain rate; GLS = global longitudinal strain; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction.

comprehensive evaluation of early and longitudinal changes in DM. Our study demonstrated that GLS decreased with the rising HF stage in DM, which corroborated with a previous study showing its diagnostic and prognostic value and thus incorporating impaired GLS into the definition of stage B HF.[26] Of note, requirements for accuracy of diastolic strain rates are more demanding in the stage A HF to detect subtle dysfunction, whereas GLS is more demanding in the stage B HF. That is, diastolic dysfunction reflected by strain rates presented earlier before stage B HF. In STZ-induced diabetic pigs, it has been confirmed that the early decrease in LV diastolic function was consistent with the corresponding degree of myocardial microstructure.[27] In addition, Liu et al[28] also found that peak diastolic strain rates were

significantly lower in DM patients than healthy subjects. Furthermore, early diastolic strain rate showed independent prognostic value for HF patients with preserved ejection fraction.[29] The distinction of stage B from A HF through a more targeted parameter is intended to identify the patients at highest risk for progression to next stage of HF.

Myocardial fibrosis is an important pathological change in the progression of DM, and has been confirmed in preclinical studies.[15] The availability of CMR T_1 mapping techniques permits noninvasive assessment of interstitial fibrosis in the progression of HF related to DM. A meta-analysis including 32 studies showed DM is associated with higher degree of myocardial fibrosis assessed by histology and ECV.[30] Although Storz et al[31] also reported myocardial tissue characterization by CMR, the diffuse fibrosis appears to be less relevant in DM patients with preserved LVEF, showing lower ECV than healthy control subjects. By contrast, another study showed that DM patients had significantly higher ECV, demonstrating that myocardial fibrosis occurs in the early stage of diabetes.[28] Although without obvious numerical differences in the early-stage HF in our study, an increase in ECV in diabetic patients has been found in previous study to be associated with a higher risk of death or HF hospitalization.[32] Increased fibrosis across HF stages in DM patients in our study highlights the great importance of T_1 mapping by CMR, and it needs to be further investigated for clinical practice in early-stage HF.

STUDY LIMITATIONS. First, the study enrolled participants were from a single center, and it is uncertain whether these findings can be generalized to other studies. Relatively small samples in stage A HF, especially T_1 mapping performed in a limited sample size, made some differences and associations undetectable. A large-scale prospective study is planned to further confirm the results. Second, not all participants had contrast-enhanced CMR and T_1 mapping examinations for further evaluation because the sequence was not available or because of unwillingness of the participant. Given consecutive enrollment in this study, we avoid selection bias to the greatest extent, including for performing enhanced examinations. In addition, the numerical differences in ECV values between stages may appear modest, but the statistical significance indicates that these changes are meaningful. Further investigation is warranted regarding the potential clinical applications of ECV in early-stage HF. Finally, although image characteristics and phenotypes at different stages were exhibited in this study, these findings warrant additional investigation into whether the imaging features show prognostic value for identification of patients with higher risk.

CONCLUSIONS

This study shed light on CMR characteristics in DM participants across HF early stages. With the advancing AHA/ACC HF stage in DM, progressively impaired subclinical systolic and diastolic dysfunction and myocardial fibrosis derived from CMR were detected. Furthermore, CMR provided sensitive tools for independently distinguishing DM patients with pre-HF and at risk for HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: With multiparametric capabilities to assess subtle dysfunction and tissue characterization, CMR could better describe the characteristics of different HF stages by distinctive parameters with optimal performance. In this study, with the advancing HF stage in diabetes, progressively impaired subclinical dysfunction and increased degree of myocardial fibrosis were detected by strain analysis and T_1 mapping from CMR. Furthermore, early diastolic strain rates showed more remarkable differences in the early HF stage whereas GLS decreased more significantly in advanced HF stage.

TRANSLATIONAL OUTLOOK: HF is one of the most common cardiovascular manifestations in diabetes patients. According to the definitions of HF stage updated in the AHA/ACC guideline, asymptomatic HF (pre-HF and at-risk for HF) at risk of progression to symptomatic HF has received increasing attention. Future investigation is warranted to show whether the CMR features have prognostic value for identification of diabetes patients with higher risk.

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KEY WORDS cardiac magnetic resonance, diabetes mellitus, heart failure, strain analysis, tissue characterization

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.