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ORIGINAL RESEARCH

Multiparametric Cardiac Magnetic Resonance Imaging to Discriminate Endomyocardial Biopsy-Proven Chronic Myocarditis From Healed Myocarditis

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ABSTRACT

BACKGROUND Detecting ongoing inflammation in myocarditis patients has prognostic relevance, but there are limited data on the detection of chronic myocarditis and its differentiation from healed myocarditis.

OBJECTIVES This study sought to assess the performance of cardiac magnetic resonance (CMR) for the detection of ongoing inflammation and the discrimination of chronic myocarditis from healed myocarditis.

METHODS Consecutive patients with persistent symptoms (>30 days) suggestive of myocarditis were prospectively enrolled from a single tertiary center. All patients underwent a multiparametric 1.5-T CMR protocol including biventricular strain, T_1/T_2 mapping, and late gadolinium enhancement (LGE). Endomyocardial biopsy was chosen for the reference standard diagnosis.

RESULTS Among 452 consecutive patients, 103 (median age: 50 years; 66 men) had evaluable CMR and cardiopathologic reference diagnosis: 53 (51%) with chronic lymphocytic myocarditis and 50 (49%) with healed myocarditis. T_2 mapping as a single parameter showed the best accuracy in detecting chronic myocarditis, if abnormal in ≥3 segments (92%; 95% CI: 85-97), and provided the best discrimination from healed myocarditis, as defined by the area under the receiver-operating characteristic curve (0.87 [95% CI: 0.79-0.93]; $P < 0.001$), followed by radial peak systolic strain rate of the left ventricle (0.86) and the right ventricle (0.84); T_1 mapping (0.64), extracellular volume fraction (0.62), and LGE (0.57). Specificity increased when T_2 mapping was combined with elevation of either troponin or C-reactive protein.

CONCLUSIONS A multiparametric CMR protocol allows detection of ongoing myocardial inflammation and discrimination of chronic myocarditis from healed myocarditis, with segmental T_2 mapping and biventricular strain analysis showing higher diagnostic accuracy compared with T_1 mapping, extracellular volume fraction, and LGE. The use of biomarkers (troponin or C-reactive protein) may improve specificity. (JACC Cardiovasc Imaging 2024;■:■-■)

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ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CRP = C-reactive protein

ECV = extracellular volume fraction

GRS = global radial strain

ICC = intraclass correlation coefficient

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RV = right ventricular

RVEF = right ventricular ejection fraction

SAX = short-axis

SSR_{radial} = radial systolic strain rate

Cardiac magnetic resonance (CMR) is an established method for the noninvasive diagnosis of myocarditis because of its multiparametric myocardial tissue characterization ability.[1-6] Recently, CMR follow-up scans at 3 months in acute myocarditis patients have been suggested to identify ongoing inflammation.[7] It is impossible for clinicians to discriminate chronic myocarditis from healed myocarditis based only on clinical symptoms, electrocardiography, laboratory parameters, and echocardiography findings. However, such differentiation has important clinical implications because ongoing myocardial inflammation (chronic myocarditis) would require more intense care and monitoring in addition to general supportive therapy as well as physical rest and abstinence from competitive sports to support the myocardial healing process.[7-9]

Therefore, separating these 2 entities is of paramount importance for the treating physician, and CMR might have important diagnostic value because of its distinctive noninvasive myocardial tissue characterization ability. T_1 mapping, which indicates diffuse myocardial abnormalities, ie, fibrosis or inflammation, has been demonstrated to detect inflammation in patients with acute myocarditis.[10] However, for biopsy-proven chronic myocarditis, data about inflammatory or fibrotic processes displayed noninvasively by a multiparametric CMR protocol are scarce.

We hypothesized that CMR tissue characterization parameters differ between chronic myocarditis with ongoing myocardial inflammation and healed myocarditis without myocardial inflammation. In particular, T_2 mapping, with elevated values indicating myocardial edema, may be an adequate tool to differentiate both myocarditis stages.[11,12] Additionally, assessment of myocardial biventricular strain as a functional parameter seems to be of high predictive value in patients with myocarditis[7,13] and is a reproducible method[14]; however its value as a diagnostic marker in patients with different stages of myocarditis is unknown. To date, there is a lack of prospective studies in which a multiparametric CMR protocol is used in a head-to-head comparison of biopsy-proven chronic myocarditis and healed myocarditis. Therefore, the aim of our study was to assess the performance of CMR for the following: 1) the detection of ongoing inflammation; and 2) the discrimination of chronic myocarditis from healed myocarditis in patients with endomyocardial biopsy-proven myocarditis with persistent symptoms.

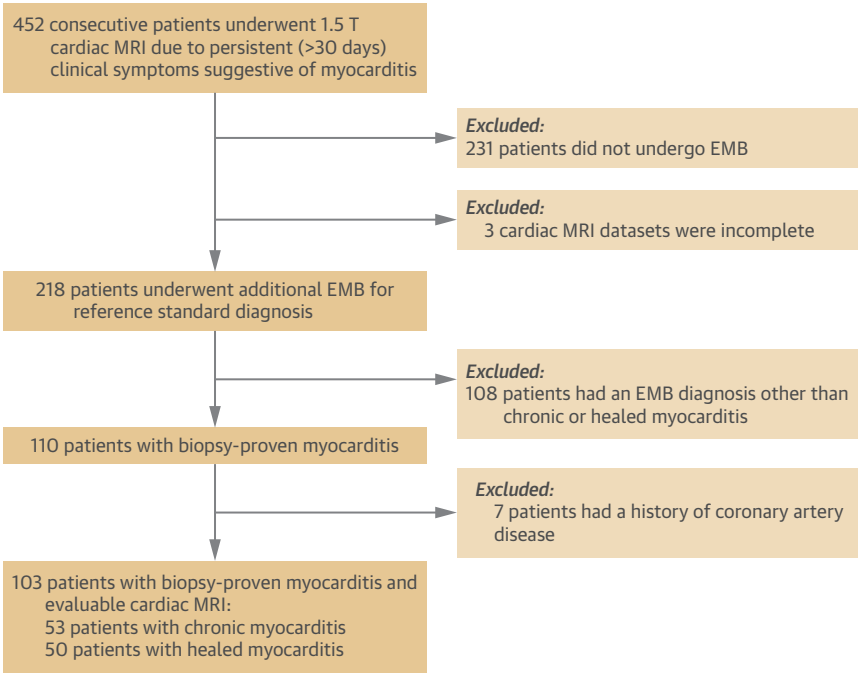
METHODS

PATIENTS. Patients were enrolled in this single-center prospective study (Tübingen University Hospital, Tübingen, Germany) between January 2020 and May 2023. Consecutive patients referred for CMR because of persistent (>30 days)[15] clinical symptoms or signs suggestive of myocarditis were included. Patients underwent both endomyocardial biopsy for the reference standard diagnosis and a multiparametric 1.5-T CMR protocol. Patients with incomplete CMR data, a cardiopathologic diagnosis other than chronic or healed myocarditis, or a history of coronary artery disease (CAD) were excluded. Symptoms (including NYHA functional class), cardiovascular risk profiles (including arterial hypertension, diabetes, dyslipidemia, smoking, and a family history of CAD), and laboratory values (including troponin, N-terminal pro-B-type natriuretic peptide [NT-proBNP] and C-reactive protein [CRP]) were recorded. Twenty healthy control individuals served as an in-house control group to establish a local reference range for mapping values specific to the scanner used in our study. Some patients participated in a previous study.[16] The Institutional Review Board approved the study, and all patients gave written informed consent.

CMR PROTOCOL. CMR examinations were performed on a 1.5-T scanner (MAGNETOM Aera, Siemens Healthcare). The CMR protocol comprised morphologic analysis, functional assessment including biventricular 3-dimensional (3D) strain, mapping (T_1, extracellular volume fraction [ECV], T_2), and late gadolinium enhancement (LGE) imaging. For functional assessment, steady-state free precession CINE loops in long-axis and short-axis (SAX) orientations were performed. For T_2 mapping, a T_2-prepared steady-state free precession sequence in 3 SAX sections (basal, midventricular, apical) was used. T_1 mapping was performed precontrast and 15 to 20 minutes postcontrast using a 5(3)3 Modified Look-Locker Inversion recovery sequence in 3 SAX sections (basal, midventricular, apical). LGE imaging was performed using a 2-dimensional inversion recovery gradient recovery echo sequence 10 minutes after intravenous administration of 0.15 mmol Gadovist (Bayer Healthcare) (gadobutrol) per kilogram of body weight. Detailed CMR sequence parameters are provided in the Supplemental Methods.

CMR ANALYSIS. CMR analysis was conducted in consensus by a resident (J.M.B., 6 years of CMR

FIGURE 1 Study Cohort



Flowchart displaying reasons patients were excluded from the study. EMB = endomyocardial biopsy; MRI = magnetic resonance imaging.

experience) and a senior radiologist (P.K., 13 years of CMR experience). To assess intrareader and interreader reliability, a second reading of CMR parameters was performed by the senior radiologist (P.K.) and a third reading by a senior cardiac imaging specialist (S.G., 22 years of CMR experience). Analysis was performed using dedicated software (cvi42 version 5.13, Circle Cardiovascular Imaging) according to the Society for Cardiovascular Magnetic Resonance recommendations.[17,18] Readers were blinded to the results of clinical data or endomyocardial biopsy. Functional assessment was performed in a stack of SAX sections with semiautomated contouring of the endocardial and epicardial borders. Biventricular 3D strain analysis was performed using postprocessing CMR feature tracking after a 3D construction of both ventricles combining the different 2-dimensional planes, detailed in Supplemental Methods. LGE was assessed by localization (anterior, inferior, septal, lateral; 17-segment model of the American Heart Association[19]), distribution (linear, patchy), and pattern (subepicardial, midwall).[20] Semiquantitative evaluation of the LGE fraction of the left ventricular (LV) myocardial mass was conducted with a threshold of ≥5 SD above the remote myocardium.[17] T_1, T_2, and ECV values were evaluated by a global and segmental approach according to the adapted 16-segment American Heart Association model. For descriptive statistics, T_1 and T_2 relaxation times of >2 SD above the mean of the control group were considered elevated (T_1 >1,053 ms; T_2 >51 ms); for ECV, values above 30% were considered definitely elevated.[21-23]

ENDOMYOCARDIAL BIOPSY. All patients underwent endomyocardial biopsy in accordance with current European Society of Cardiology diagnostic guidelines.[24] At least 5 right ventricular (RV) samples were taken, followed by a comprehensive cardiopathologic work-up including histology, immunohistology for the detection of immune cells, and molecular pathology for the detection of viral genomes (Supplemental Methods).

HISTOPATHOLOGIC DEFINITION OF CHRONIC LYMPHOCYTIC MYOCARDITIS VS HEALED MYOCARDITIS. Each diagnosis of chronic and healed myocarditis was made independently by 2 experienced cardiopathologists (K.K., >25 years of experience; T.M., >5 years of experience) and were based on the following histopathologic criteria:[24]

TABLE 1 Patient Characteristics

	Chronic Myocarditis (n = 53)	Healed Myocarditis (n = 50)	*P* Value
Age, y	47 ± 13	48 ± 17	0.698
Age range, y	18-77	18-79	
Women	21/53 (40)	16/50 (32)	0.538
Men	32/53 (60)	34/50 (68)	0.538
BMI, kg/m^2	25 (22-29)	26 (24-31)	0.912
Rhythm disorders	16/53 (30)	12/50 (24)	0.514
Symptoms			
Dyspnea	37/53 (70)	27/50 (54)	0.109
Fatigue	29/53 (55)	14/50 (28)	0.009
Chest pain	16/53 (30)	11/50 (22)	0.378
Palpitations	10/53 (19)	13/50 (26)	0.479
Peripheral edema	8/53 (15)	7/50 (14)	1.000
Fever	4/53 (8)	–	–
Syncope	3/53 (6)	4/50 (8)	0.710
NYHA functional class			
I	16/53 (30)	23/50 (46)	0.109
II	14/53 (26)	16/50 (32)	0.665
III	13/53 (25)	10/50 (20)	0.641
IV	10/53 (19)	1/50 (2)	0.008
Cardiovascular risk factors			
Arterial hypertension	15/53 (28)	13/50 (26)	0.828
Diabetes	5/53 (9)	5/50 (10)	1.000
Dyslipidemia	6/53 (11)	7/50 (14)	0.771
Smoking	12/53 (23)	10/50 (20)	0.813
Family history of CAD	6/53 (11)	9/50 (18)	0.408
Endomyocardial biopsy findings			
Presence of viral genomes	25/53 (47)	–	–
HHV6	10/53 (19)	–	–
PVB19	9/53 (17)	–	–
EBV	4/53 (8)	–	–
HSV 1 and 2	1/53 (2)	–	–
HHV 7	1/53 (2)	–	–
Blood testing			
Troponin, ng/L, all values	77 (21-518)	10 (0-29)	<0.001
Troponin, ng/L, only if elevated >57 ng/L	287 (163-3,083)	60 (58-63)	0.005
Troponin elevated >57 ng/L	27/53 (51)	3/50 (6)	<0.001
NT-proBNP, ng/L	583 (202-2,674)	232 (51-940)	0.002
NT-proBNP elevated >300 ng/L	35/53 (66)	15/50 (30)	<0.001
CRP, mg/dL	0.8 (0.1-4.3)	0.1 (0.0-0.3)	<0.001
CRP elevated >0.5 mg/dL	29/53 (55)	–	–

Values n/total (%), mean ± SD, or median (Q1-Q3), unless noted otherwise.

BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; EBV = Epstein-Barr virus; HHV6 = human herpesvirus type 6; HHV7 = human herpesvirus type 7; HSV 1 and 2 = herpes simplex virus types 1 and 2; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PVB19 = parvovirus B19.

- Chronic lymphocytic myocarditis: no myocyte necrosis, ≥14 infiltrating leukocytes/mm^2, and focal and/or diffuse fibrosis.
- Healed myocarditis: no myocyte necrosis, <14 infiltrating leukocytes/mm^2, focal and/or diffuse fibrosis.

STATISTICAL ANALYSIS. A statistical power analysis was performed for patient enrollment size estimation with an equal (1:1) enrollment ratio, alpha of 0.05, power of 0.85, and anticipated T_2 mean of 63 ms and 60 ms with a 4.5-ms variance of mean for patients with chronic myocarditis and patients with healed myocarditis, respectively, based on previous results of the MyoRacer (Magnetic Resonance Imaging in Myocarditis) Trial.[25] The calculated number of patients to be enrolled was n = 40 per group—ie, n = 80 in total. The normality of the data was tested using the Kolmogorov-Smirnov test. Continuous data are presented as the mean ± SD or median (Q1-Q3). Categorical data are presented as the frequency (percentage). Continuous data were compared using the 2-tailed unpaired Student's *t-test* or the Mann-Whitney *U* test; for categorical CMR data, the Fisher exact test was performed (JMP version 16.2, SAS Institute Inc). Intraclass correlation coefficients (ICCs) based on single measures ($k = 2$) for absolute agreement was used to assess the intrareader and interreader reliability in the measurements of LGE, T_1, ECV, and T_2. ICC coefficients of >0.9 indicate excellent reliability, 0.75 to 0.9 show good reliability, and 0.5 to 0.75 represent moderate reliability. Receiver-operating characteristic curves were generated to compare the area under the curve (AUC)—including CIs—of LGE (percentage of LV mass) and mapping parameters in patients with chronic and healed myocarditis by applying the method of DeLong et al[26] (MedCalc version 18, MedCalc Software Ltd). Youden's *J* index was used to calculate the optimal probability AUC cutoff values. A value of $P < 0.05$ was considered to indicate a significant difference.

RESULTS

PATIENT CHARACTERISTICS. Overall, 452 consecutive patients underwent CMR because of clinically suspected myocarditis and were prospectively evaluated (Figure 1). Patients without an endomyocardial biopsy (n = 231) or incomplete CMR data sets (n = 3) were excluded; 108 patients were excluded because of a cardiopathologic diagnosis other than chronic or healed myocarditis; and 7 patients were excluded because of a history of CAD. Thus, the final data set consisted of 53 patients with chronic lymphocytic myocarditis and 50 patients with healed myocarditis (median age: 50 years; Q1-Q3: 36-57; 66 men and 37 women). All patients had persistent (>30 days) clinical symptoms suggestive of myocarditis with a median time interval of 4 months from initial symptom onset. An endomyocardial biopsy was performed within a median of 2 days (Q1-Q3: 0-7 days) of CMR. At the time of diagnostic work-up, the most common

symptom was dyspnea in 37 of 53 (70%) patients with chronic myocarditis and 27 of 50 (54%) patients with healed myocarditis ($P = 0.109$) (Table 1). Specifically, 10 of 53 (19%) patients with chronic myocarditis experienced dyspnea at rest (NYHA functional class IV) vs 1 of 50 (2%) of the healed myocarditis group ($P = 0.008$). Viral genomes and elevated CRP as an inflammatory marker were exclusively detected in patients with chronic myocarditis. Troponin was elevated in 27 of 53 (51%) patients in the chronic group vs 3 of 50 (6%) patients in the healed group ($P < 0.001$). NT-proBNP was elevated in 35 of 53 (66%) patients in the chronic group vs 15 of 50 (30%) patients in the healed group ($P < 0.001$).

CMR FINDINGS: FUNCTION. Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) were not different between groups ($LVEF_{chronic}$: 45% [Q1-Q3: 30-55] vs $LVEF_{healed}$: 49% [Q1-Q3: 30-57]; $P = 0.537$; $RVEF_{chronic}$: 38% ± 15% vs $RVEF_{healed}$: 42% ± 14%; $P = 0.212$) (Table 2, Figure 2). Biventricular peak global radial strain (GRS) and radial systolic strain rate (SSR_{radial}) were lower in the chronic myocarditis group than in the healed myocarditis group (LV-GRS: 14% ± 8% vs 24% ± 9%; $P < 0.001$; RV-GRS: 13% ± 7% vs 21% ± 10%; $P < 0.001$; LV-SSR_{radial}: 0.9 [Q1-Q3: 0.5-1.3] vs 1.9 [Q1-Q3: 1.3-3.1]; $P < 0.001$; RV-SSR_{radial}: 0.6 [Q1-Q3: 0.4-1.1] vs 1.8 [Q1-Q3: 1.1-2.9]; $P < 0.001$).

CMR FINDINGS: TISSUE CHARACTERIZATION. LGE was present in 36 of 53 (68%) patients with chronic myocarditis vs 30 of 50 (60%) patients with healed myocarditis ($P = 0.420$) (Table 3). LGE had an extent of 4% ± 2% of the LV myocardial mass in patients with chronic myocarditis vs 3% ± 2% in patients with healed myocarditis ($P = 0.049$). Septal LGE location was the most common in chronic myocarditis (n = 21 of 53; 40%). Global native T_1 values had a median of 1,057 ms (Q1-Q3: 1,046-1,062 ms) in patients with chronic myocarditis and a median of 1,048 ms (Q1-Q3: 1,042-1,056 ms) in patients with healed myocarditis ($P = 0.016$). T_1 values were definitely elevated (>1,053 ms) in 33 of 53 (62%) patients with chronic myocarditis vs in 19 of 50 (38%) patients with healed myocarditis ($P = 0.018$). The median number of elevated T_1 segments was 8 (Q1-Q3: 4-10) in patients with chronic myocarditis and 6 (Q1-Q3: 4-8) in patients with healed myocarditis ($P = 0.037$). Global ECV was 31% ± 3% in patients with chronic myocarditis and 30% ± 2% in patients with healed myocarditis ($P = 0.025$). Global ECV was elevated (>30%) in 36 of 53 (68%) patients with chronic myocarditis vs in 32 of 50 (64%) patients with healed myocarditis ($P = 0.684$). Global T_2 mapping values were elevated (>51 ms) in 46 of 53 (87%) patients with chronic myocarditis with a median of 54 ms (Q1-Q3: 53-55 ms) vs in 17 of 50 (34%) patients with healed myocarditis with a median of 49 ms (Q1-Q3: 48-51 ms) ($P < 0.001$ for the comparison of frequency; $P < 0.001$ for the comparison of median T_2 values). T_2 elevation in ≥3 segments occurred in 51 of 53 (96%) patients with chronic myocarditis vs in 6 of 50 (12%) patients with healed myocarditis ($P < 0.001$). In chronic myocarditis, a median of 10 segments (Q1-

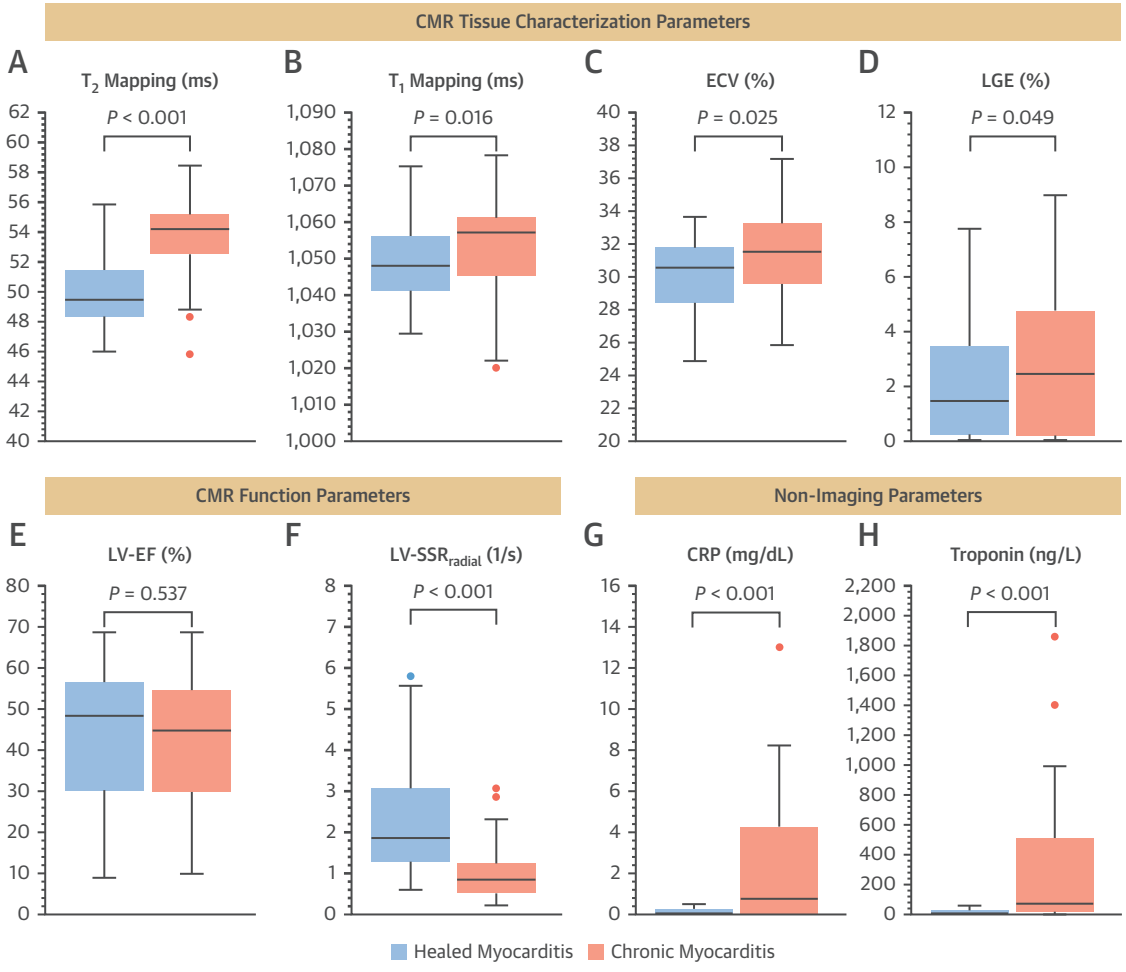
TABLE 2 Morphology, Biventricular Volumetry, and Strain in Patients With Chronic Myocarditis and Healed Myocarditis

	Chronic Myocarditis (n = 53)	Healed Myocarditis (n = 50)	*P* Value
Morphology			
Interventricular septum, mm	9 (8-10)	9 (8-10)	0.897
Pericardial effusion > 5 mm	7/53 (13)	–	–
Left ventricle			
Volumetry			
EF, %	45 (30-55)	49 (30-57)	0.537
SV, mL	76 ± 30	69 ± 24	0.169
Indexed SV, mL/m^2	39 ± 14	34 ± 12	0.104
EDV, mL	183 (154-247)	163 (137-197)	0.034
Indexed EDV, mL/m^2	93 (76-124)	79 (69-95)	0.004
ESV, mL	88 (71-176)	87 (59-122)	0.159
Indexed ESV, mL/m^2	50 (35-78)	43 (31-59)	0.073
Global peak strain, %			
GRS	14 ± 8	24 ± 9	<0.001
GCS	-14 ± 6	-17 ± 8	0.009
GLS	-11 ± 8	-20 ± 10	<0.001
Peak systolic strain rate, s^{-1}			
Radial	0.9 (0.5 to 1.3)	1.9 (1.3 to 3.1)	<0.001
Circumferential	-0.9 (-0.6 to -1.2)	-1.3 (-0.8 to -2.3)	0.002
Longitudinal	-0.8 (-0.5 to -1.4)	-1.6 (-0.8 to -2.9)	<0.001
Right ventricle			
Volumetry			
EF, %	38 ± 15	42 ± 14	0.212
SV, mL	63 ± 24	64 ± 23	0.884
Indexed SV, mL/m^2	32 ± 12	32 ± 11	0.856
EDV, mL	173 (136-200)	156 (133-181)	0.151
Indexed EDV, mL/m^2	88 (70-108)	77 (66-92)	0.036
ESV, mL	114 ± 56	96 ± 39	0.063
Indexed ESV, mL/m^2	57 ± 25	47 ± 19	0.035
Global peak strain, %			
GRS	13 ± 7	21 ± 10	<0.001
GCS	-13 ± 6	-16 ± 7	0.054
GLS	-15 ± 6	-20 ± 9	0.002
Peak systolic strain rate, s^{-1}			
Radial	0.6 (0.4 to 1.1)	1.8 (1.1 to 2.9)	<0.001
Circumferential	-0.9 (-0.6 to -1.4)	-1.2 (-0.8 to -1.8)	0.004
Longitudinal	-1.1 (-0.7 to -1.4)	-1.7 (-1.0 to -2.6)	<0.001

Values are n (%) mean ± SD, or median (Q1-Q3), unless noted otherwise. Indexed data are normalized to body surface area.

EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; GCS = global circumferential strain; GLS = global longitudinal strain; GRS = global radial strain; SV = stroke volume.

FIGURE 2 **Distribution of Imaging and Nonimaging Parameters**



Boxplots show the distribution of (A to D) CMR tissue characterization parameters, (E,F) CMR function parameters, and (G,H) nonimaging parameters. CMR = cardiac magnetic resonance; CRP = C-reactive protein; ECV = extracellular volume fraction; EF = ejection fraction; LGE = late gadolinium enhancement; LV = left ventricular; RV = right ventricular; SSR_{radial} = radial systolic strain rate.

Q3: 8-11 segments) per patient had elevated T_2 vs a median of 2 segments (Q1-Q3: 0-2 segments) per patient with healed myocarditis ($P < 0.001$). The frequency of T_2-elevated segments is displayed in Figure 3.

REPRODUCIBILITY. Excellent intrareader and interreader ICCs were observed for the measurement of LGE (0.93 and 0.92, respectively), T_1 (0.94 and 0.91), ECV (0.94 and 0.91), and T_2 (0.95 and 0.94). Typical CMR findings characterizing myocardial tissue in chronic and healed myocarditis are illustrated in Figure 4.

DIFFERENTIATION OF CHRONIC VS HEALED MYOCARDITIS. To discriminate chronic from healed myocarditis, T_2 mapping demonstrated the highest AUC (AUC: 0.87 [95% CI: 0.79-0.93]; $P < 0.001$), followed by peak SSR_{radial} of the LV (AUC: 0.86 [95% CI: 0.77-0.92]; $P < 0.001$) and the RV (AUC: 0.84 [95% CI: 0.75-0.90]; $P < 0.001$) (Figure 5). T_1 mapping (AUC: 0.64), ECV (AUC: 0.62), and LGE (AUC: 0.57) had lower diagnostic value as defined by AUCs when compared with T_2: $P < 0.001$ for AUC_{T2} vs AUC_{T1}; $P < 0.001$ for AUC_{T2} vs AUC_{ECV}, and $P < 0.001$ for AUC_{T2} vs AUC_{LGE}. Youden's index revealed the following cutoffs indicating chronic myocarditis: >52.4 ms for T_2 mapping, ≤1.27 for LV-SSR_{radial}, and ≤0.82 for RV-SSR_{radial}.

DIAGNOSTIC PERFORMANCE. The diagnostic accuracy statistics of different CMR parameters and their combinations are summarized in Table 4 and Supplemental Table 1. The highest sensitivity

detecting chronic myocarditis was obtained by T_2 mapping if increased in ≥1 segment (52 of 53, 98%; 95% CI: 90-99). The highest diagnostic accuracy was provided by T_2 mapping if abnormal in ≥3 segments (95 of 103, 92%; 95% CI: 85-97) (Central Illustration). Combining T_2 mapping with LV-SSR_{radial} increased specificity (48 of 50; 96%; 95% CI: 86-99) but reduced sensitivity (39 of 53; 74%; 95% CI: 60-85). Specificity increased (50 of 50 patients with healed myocarditis correctly identified; 100%; 95% CI: 93-100) when T_2 mapping was combined with elevation of either troponin or CRP.

DISCUSSION

Our study systematically evaluated the diagnostic performance of a multiparametric CMR protocol in the detection of ongoing inflammation and discrimination of chronic myocarditis from healed myocarditis. We found that T_2 mapping provided the best discrimination of chronic from healed myocarditis (AUC: 0.87; 95% CI: 0.79-0.93), displaying ongoing myocardial inflammation with a sensitivity of 98% (52 of 53) if T_2 was increased in ≥1 segment and an accuracy of 92% (95 of 103) if T_2 was abnormal in ≥3 segments. Specificity was improved by combining T_2 mapping with peak LV-SSR_{radial} (48 of 50; 96%) or with elevation of either troponin or CRP (50 of 50; 100%). Other myocardial tissue parameters—T_1 mapping, ECV, and LGE—demonstrated reduced diagnostic accuracy for discriminating chronic from healed myocarditis.

Apart from unspecific fatigue, which was more frequent in patients with chronic myocarditis (29 of 53; 55%) than in patients with healed myocarditis (14 of 50; 28%), cardiac symptoms remained a poor diagnostic guide in the setting of nonischemic cardiomyopathies, as previously described.[27] Patients with chronic myocarditis demonstrated significant higher troponin (77 ng/L [Q1-Q3: 21-518 ng/L] vs 10 ng/L [Q1-Q3: 0-29 ng/L]) and NT-proBNP levels (583 ng/L [Q1-Q3: 202-2,674 ng/L] vs 232 ng/L [Q1-Q3: 51-940 ng/L]), suggesting more advanced myocardial damage at this stage than in patients with healed myocarditis. Conversely, LVEF did not differ between both groups ($LVEF_{chronic}$: 45% [Q1-Q3: 30%-55%] vs $LVEF_{healed}$: 49% [Q1-Q3: 30%-57%]), and LGE was present in most patients of both groups (in 36 of 53 patients [68%] with chronic myocarditis vs 30 of 50 patients [60%] with healed myocarditis), emphasizing the value of LGE as a marker of irreversible myocardial injury. Patients with chronic myocarditis had a higher extent of LGE (4% ± 2% vs 3% ± 2%), which might be explained by the following: 1) ongoing inflammation; and 2) scar shrinking over time with reduced spatial extent. Septal LGE location was most common in chronic myocarditis (21 of 53 patients; 40%) and is known to be associated with serious adverse events,[28] underlining the need for closer monitoring in these patients. With a high prevalence in both groups, LGE might not serve for further differentiation in chronic vs healed myocarditis stages but remains an indispensable tool in the risk stratification of patients with suspected myocarditis because of its high predictive value.[20,28,29]

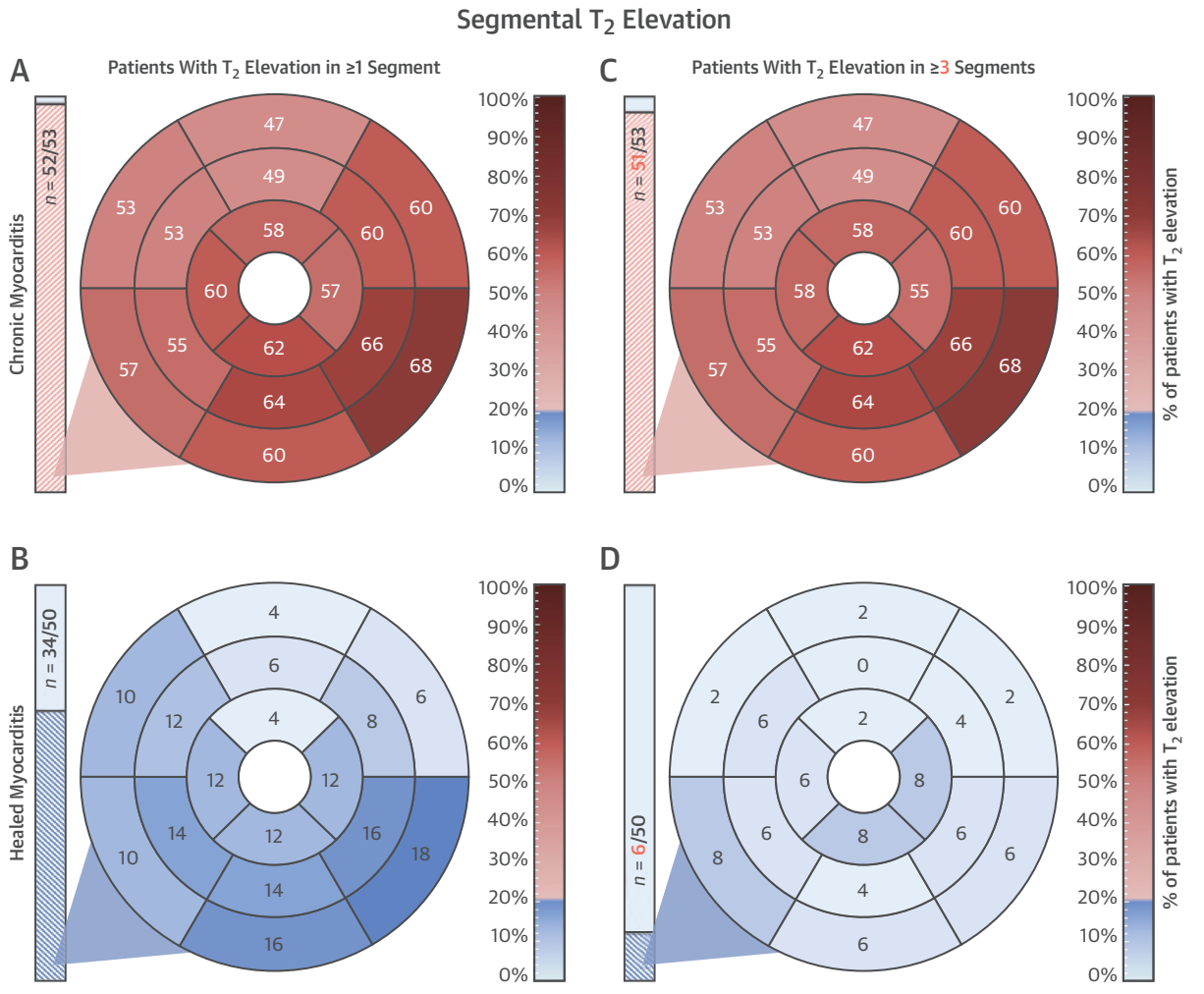
TABLE 3 Comprehensive CMR Tissue Characterization in Patients With Chronic Myocarditis and Healed Myocarditis

	Chronic Myocarditis (n = 53)	Healed Myocarditis (n = 50)	*P* Value
Late gadolinium enhancement			
Frequency	36/53 (68)	30/50 (60)	0.420
Number of positive segments	2 (0-3)	1 (0-3)	0.352
% LV mass	4 ± 2	3 ± 2	0.049
LGE location[a]			
LGE septal	21/53 (40)	13/50 (26)	0.150
LGE lateral	16/53 (30)	18/50 (36)	0.675
LGE anterior	5/53 (9)	2/50 (4)	0.438
LGE inferior	8/53 (15)	8/50 (16)	1.000
LGE distribution[a]			
Linear	27/53 (51)	19/50 (38)	0.235
Patchy	9/53 (17)	12/50 (24)	0.465
LGE pattern[a]			
Midwall	20/53 (38)	15/50 (30)	0.533
Subepicardial	18/53 (34)	18/50 (36)	0.839
Mapping			
T_1 global, ms	1,057 (1,046-1,062)	1,048 (1,042-1,056)	0.016
T_1 global elevated (>1,053 ms)[b]	33/53 (62)	19/50 (38)	0.018
T_1 elevated in ≥1 segment	47/53 (89)	42/50 (84)	0.572
Total number of elevated T_1 segments	8 (4-10)	6 (4-8)	0.037
ECV global, %	31 ± 3	30 ± 2	0.025
ECV global elevated >30%	36/53 (68)	32/50 (64)	0.684
ECV elevated in ≥1 segment	47/53 (89)	39/50 (78)	0.187
Total number of elevated ECV segments	9 (7-12)	7 (4-9)	0.001
T_2 global, ms	54 (53-55)	49 (48-51)	<0.001
T_2 global elevated >51 ms[b]	46/53 (87)	17/50 (34)	<0.001
T_2 elevated in ≥1 segment	52/53 (98)	34/50 (68)	<0.001
T_2 elevated in ≥2 segments	52/53 (98)	27/50 (54)	<0.001
T_2 elevated in ≥3 segments	51/53 (96)	6/50 (12)	<0.001
Total number of elevated T_2 segments	10 (8-11)	2 (0-2)	<0.001

Values are n/total (%), mean ± SD, or median (Q1-Q3). [a]Multiple possible. [b]>2 SD of control group.
CMR = cardiac magnetic resonance; ECV = extracellular volume fraction; LGE = late gadolinium enhancement; LV = left ventricular.

STRAIN IMAGING. As suggested by a recent study,[13] strain analysis seems to be a reproducible technique[14,30] with important prognostic implications in myocarditis patients[31] and is altered in various cardiomyopathies. Biventricular global radial and

FIGURE 3 **Segmental T_2 Elevation in Chronic Myocarditis vs Healed Myocarditis**

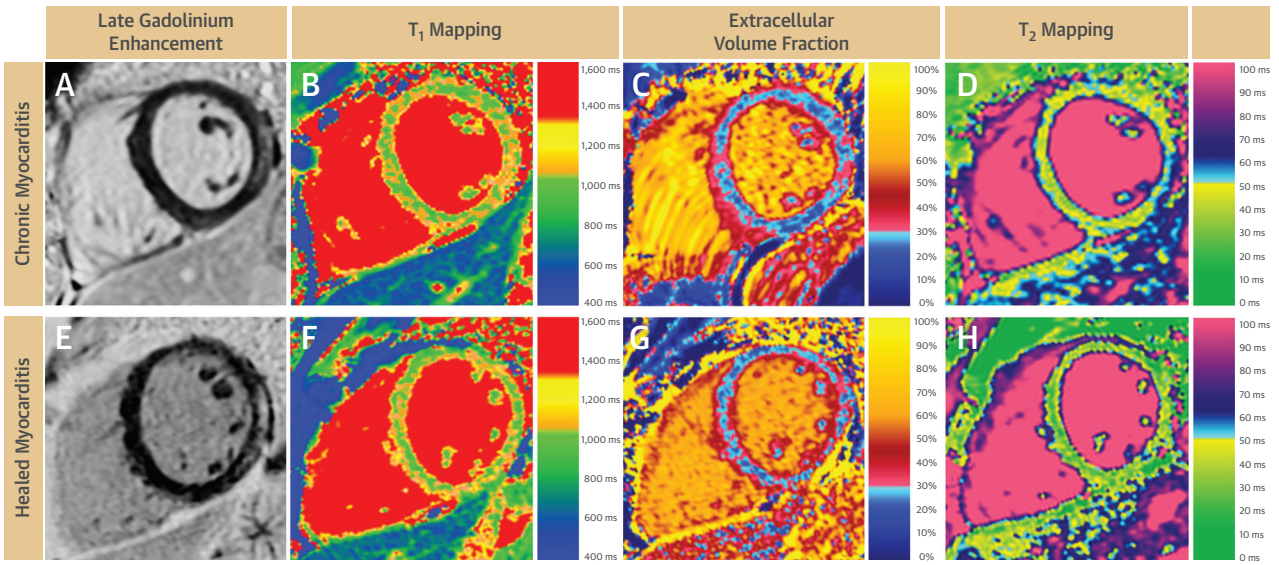


Data in bull's-eye graphs represent the frequency (percentage) of T_2 elevation in adapted 16-segment American Heart Association models in (A,B) patients with increased T_2 (>51 ms) in ≥1 segment and (C,D) patients with increased T_2 in ≥3 segments. Note: In healed myocarditis, segmental T_2 elevation was less frequent, and only n = 6 of 50 (12%) patients with healed myocarditis showed T_2 elevation in ≥3 segments.

longitudinal peak strain (GRS and global longitudinal strain) were lower in chronic than in healed myocarditis, suggesting an association with inflammatory changes of the myocardium,[32] and might therefore be useful in addition to T_2 mapping, potentially further increasing specificity. We found that biventricular peak SSR_{radial} values were even more accurate in detecting chronic myocarditis, which may be explained, at least in part, by myocardial fiber orientation. It could be hypothesized that reduced strain in chronic myocarditis may be attributed to inflammation of the midmyocardial and subepicardial layers, which contribute significantly to radial contractility. In contrast, impairment of longitudinally contracting fibers located in the subendocardial and subepicardial layers, leading to reduced longitudinal strain, is, rather, observed in acute myocarditis with focal damage to subepicardial fibers.[33]

T_1/T_2 MAPPING AND ECV. Because of the dynamic nature of different myocarditis stages, a quantitative approach for myocardial tissue characterization accompanied by functional parameters is highly desirable. T_1 and ECV values were frequently elevated in both groups, indicating a rather nonspecific degree of myocardial abnormality, which can be observed in

FIGURE 4 **CMR Tissue Characterization Findings**

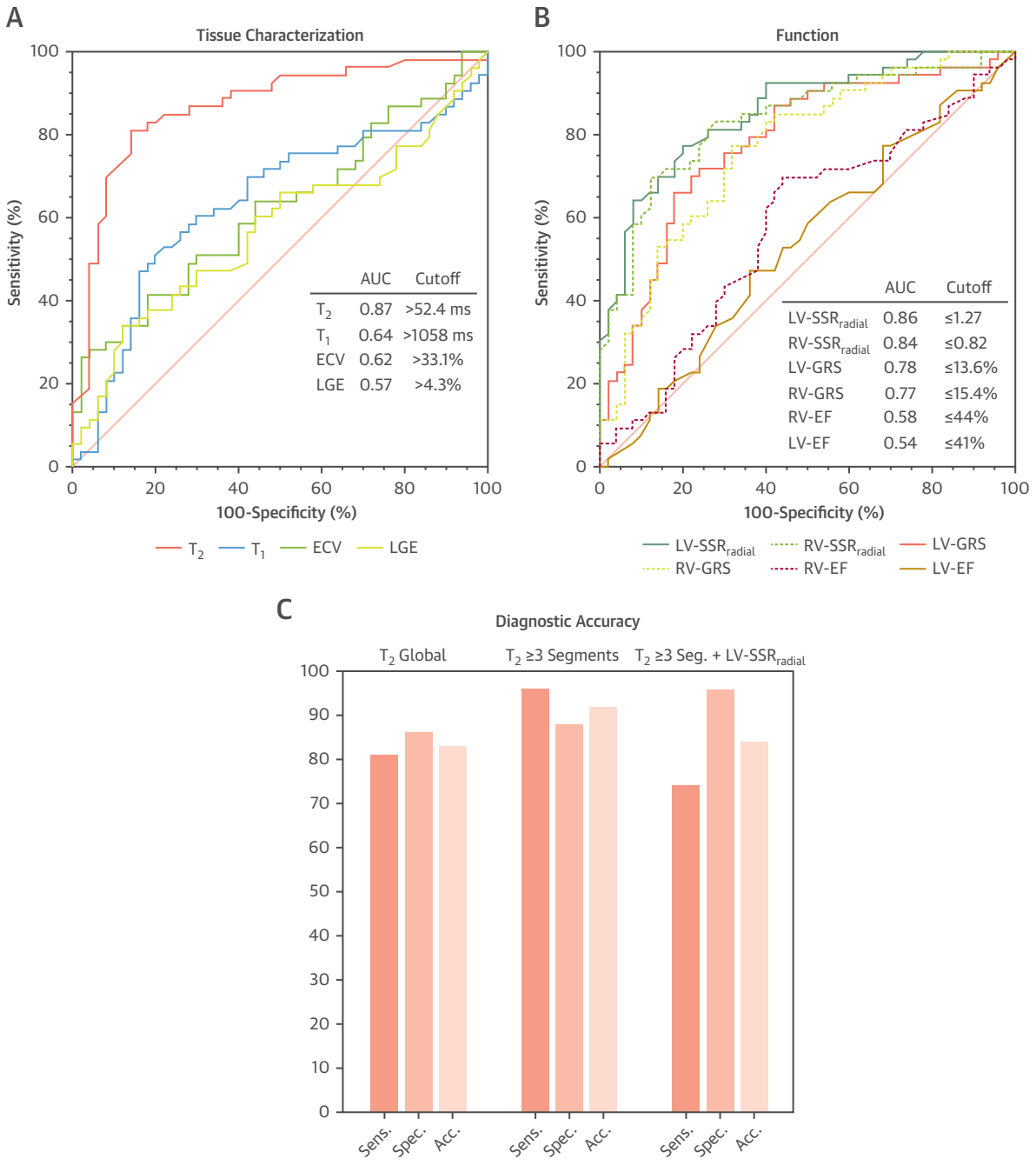


(Top row) Chronic myocarditis. CMR short-axis views in a 50-year-old man presenting with chest pain, reduced LVEF (47%), and increased troponin (177 ng/L [<57 ng/L]) and NT-proBNP (1,825 ng/L [<300 ng/L]). Coronary artery disease was ruled out by coronary angiography. CMR shows (A) nonischemic linear inferolateral LGE and elevated values for (B) T_1 (1,095 ms), (C) ECV (36%), and (D) T_2 (53 ms) with focal myocardial edema in the inferolateral wall (blue coloration) in the same segments where LGE is present. Endomyocardial biopsy revealed chronic lymphocytic myocarditis. (Bottom row) Healed myocarditis. CMR short-axis views in a 31-year-old man presenting with palpitations, normal LVEF (59%), troponin of <3 ng/L [<57 ng/L], and NT-proBNP of 90 ng/L [<300 ng/L]. CMR shows (E) nonischemic linear inferolateral LGE, (F) elevated T_1 (1,071 ms) and (G) elevated ECV (34%). (H) T_2 (46 ms) demonstrated normal values. Endomyocardial biopsy revealed healed myocarditis. CMR = cardiac magnetic resonance; ECV = extracellular volume fraction; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

all different stages of myocarditis, corroborating the results of another study comparing acute and healed myocarditis stages[11] and strengthening the role of T_1 and ECV for the diagnosis of myocarditis itself, irrespective of a distinct stage. However, specifically for the detection of chronic myocarditis and its distinction from healed myocarditis, of the 4 CMR tissue characterization parameters (LGE, T_1, ECV, T_2), only T_2 mapping demonstrated both a reasonable diagnostic performance (AUC: 0.87) to separate the 2 entities and the highest accuracy (95 of 103; [92%] if T_2 is abnormal in ≥3 segments) for detecting chronic myocarditis. In line with our results, other studies also suggest T_2 mapping as a potential technique to differentiate between active and healed stages of myocarditis.[7,11,12] In a previous study, T_2 has shown a higher sensitivity (71%) than T_1 (27%) in the detection of edema in chronic myocarditis,[25] allowing direct quantification of myocardial inflammation and edema as a sign of reversible myocardial injury, better mirroring the dynamic course of myocarditis from acute inflammation to chronic inflammation/fibrosis or healed stages. To date, there are no CMR studies comparing patients with chronic vs healed myocarditis using biopsy as a reference standard. Most CMR studies to date have focused on the separation of acute from chronic myocarditis or have monitored acute myocarditis by serial CMR follow-up without a histopathologic reference standard. Bohnen et al[12] investigated patients with acute myocarditis by CMR at baseline, 3 months, and 12 months. The investigators suggested that "healed" myocarditis depended on clinical and biomarker information and found that native T_1 and T_2 provided an excellent performance for assessing the stage of myocarditis by CMR. As a major drawback, they did not perform serial endomyocardial biopsy; therefore, they could not exclude the presence of persistent inflammation, which seems to be present at least in some cases with healed myocarditis, as demonstrated by our study.

Although pathology is the best available reference standard, distinguishing healed myocarditis from chronic myocarditis may be challenging. Moreover, endomyocardial biopsy is invasive and lacks

FIGURE 5 **Performance of CMR to Discriminate Chronic Myocarditis From Healed Myocarditis**



ROC curves demonstrate the AUCs for (A) CMR tissue characterization and (B) functional parameters in the discrimination of chronic myocarditis from healed myocarditis. T_2 performed best (AUC: 0.87 [95% CI: 0.79-0.93]; $P < 0.001$) with a cutoff of >52.4 ms, followed by the LV-SSR_{radial} (AUC: 0.86 [95% CI: 0.77-0.92]; $P < 0.001$). (C) T_2 showed the best accuracy in detecting chronic myocarditis if increased in ≥3 segments (92%). The combination of T_2 with LV-SSR_{radial} resulted in improved specificity (96%) with moderate loss of sensitivity (74%). Cutoff values were derived using Youden's index in ROC curve analysis. Acc. = accuracy; AUC = area under the curve; CMR = cardiac magnetic resonance; LV-SSR_{radial} = left ventricular radial peak systolic strain rate; ROC = receiver-operating characteristic; Sens. = sensitivity; Spec. = specificity.

TABLE 4 Diagnostic Accuracy of CMR for the Discrimination of Chronic Myocarditis From Healed Myocarditis

	Sensitivity	Specificity	PPV	NPV	Accuracy
T_2 based					
T_2 global	43/53 (81; 68-91)	43/50 (86; 73-94)	43/50 (86; 73-94)	43/53 (81; 68-91)	86/103 (83; 75-90)
T_2 ≥1 segment	52/53 (98; 90-99)	23/50 (46; 32-61)	52/79 (66; 54-76)	23/24 (96; 79-99)	75/103 (73; 63-81)
T_2 ≥2 segments	52/53 (98; 90-99)	27/50 (54; 39-68)	52/75 (69; 57-79)	27/28 (96; 82-99)	79/103 (77; 67-84)
T_2 ≥3 segments	51/53 (96; 87-99)	44/50 (88; 76-95)	51/57 (89; 78-96)	44/46 (96; 85-99)	95/103 (92; 85-97)
T_1 based					
T_1	25/53 (47; 33-61)	42/50 (84; 71-93)	25/33 (76; 58-89)	42/70 (60; 48-72)	67/103 (65; 55-74)
ECV	14/53 (26; 15-40)	49/50 (98; 89-99)	14/15 (93; 68-99)	49/88 (56; 45-66)	63/103 (61; 51-71)
LGE	18/53 (34; 22-48)	44/50 (88; 76-95)	18/24 (75; 53-90)	44/79 (56; 44-67)	62/103 (60; 50-70)
T_2 mapping plus ventricular strain					
T_2 ≥3 segments + LV-GRS	33/53 (62; 48-75)	48/50 (96; 86-99)	33/35 (94; 81-99)	48/68 (71; 58-81)	81/103 (79; 69-86)
T_2 ≥3 segments + RV-GRS	39/53 (74; 60-85)	45/50 (90; 78-97)	39/44 (89; 75-96)	45/59 (76; 63-86)	84/103 (82; 73-89)
T_2 ≥3 segments + LV-SSR_{radial}	39/53 (74; 60-85)	48/50 (96; 86-99)	39/41 (95; 83-99)	48/62 (77; 65-87)	87/103 (84; 76-91)
T_2 ≥3 segments + RV-SSR_{radial}	35/53 (66; 52-78)	48/50 (96; 86-99)	35/37 (95; 82-99)	48/66 (73; 65-80)	83/103 (81; 72-88)
T_2 mapping plus nonimaging parameters					
T_2 ≥3 segments + troponin or CRP	33/53 (62; 48-75)	50/50 (100; 93-100)	33/33 (100; 89-100)	50/70 (71; 64-78)	83/103 (81; 64-78)

Values are numerator/denominator (%; 95% CI). Cutoff values were derived using Youden's index in ROC curve analysis: 1,058 ms for T_1, 33.1% for ECV, 52.4 ms for T_2, and 4.3% of the left ventricular mass for LGE. Global or segmental values exceeding the cutoff were considered positive for chronic myocarditis. ROC-derived cutoff values for strain: ≤1.27 for LV-SSR_{radial}, ≤0.82 for RV-SSR_{radial}. The cutoff for troponin was >57 ng/L and the cutoff for CRP was >0.5 mg/dL. Elevated troponin or CRP was considered diagnostic for chronic myocarditis.

NPV = negative predictive value; PPV = positive predictive value; ROC = receiver-operating characteristic; RV = right ventricular; SSR_{radial} = radial peak systolic strain rate; other abbreviations as in Tables 1 to 3.

sensitivity. A clinical approach including not only imaging parameters but also biomarkers (eg, troponin and CRP) seems favorable instead of focusing on a single aspect.

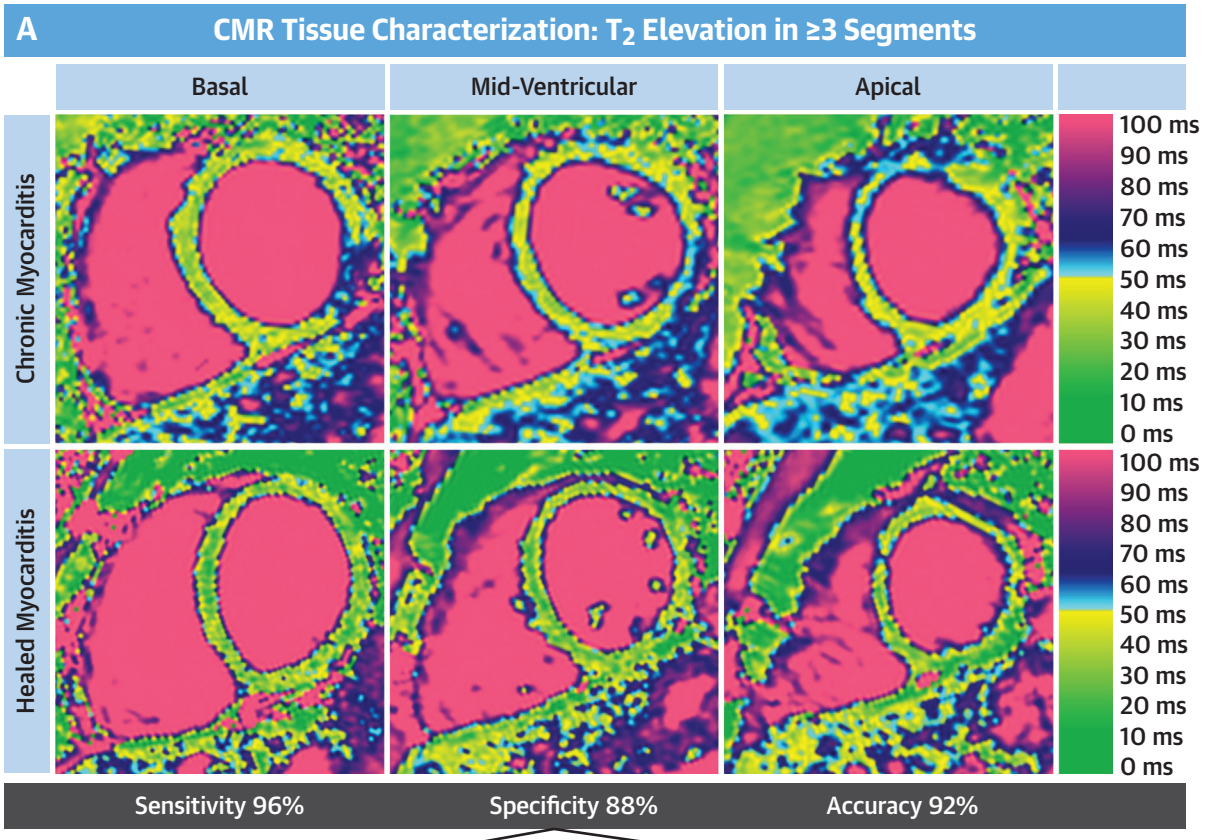
NEW FINDINGS. The current study further strengthens the role of T_2 mapping in the assessment of ongoing myocardial inflammation and as a potential arbitrator for different stages of myocarditis by defining T_2 elevation in ≥3 segments as a useful marker to separate chronic vs healed myocarditis. This finding is of paramount clinical importance because even healed myocarditis might have, at least in part, some regions of residual myocardial inflammation, as demonstrated by this study, hampering the diagnosis of chronic myocarditis even by the use of CMR with its excellent noninvasive tissue characterization. Thus, our study extends the findings of previous studies[16,25] that found T_2 mapping to be generally useful in the diagnosis of chronic myocarditis. Another new finding is that specificity can be improved by combining T_2 mapping with either CMR LV-SSR_{radial} or with the use of the serum biomarkers troponin or CRP.

STUDY LIMITATIONS. First, this was a single-center study with an overall limited sample size; mapping and strain values vary depending on field strength, sequence, and scanner type, so generalizability of these measures to other sites may be limited. Second, endomyocardial biopsy samples were exclusively taken from the RV septum, which may not necessarily reflect all myocardial alterations of the LV and RV, potentially underestimating the prevalence of myocardial inflammation in some cases. Third, only endomyocardial biopsy, but not T_2 mapping, can definitely differentiate between different types of myocarditis (lymphocytic, eosinophilic, giant cell, granulomatous), which is decisive for adequate therapy management.[24] We acknowledge that "healed myocarditis" is not yet recognized as a distinct entity in the absence of clear literature descriptions, pathology validation, or definitions. Additionally, the criteria we propose may overlap with various cardiomyopathies, including genetic, athletic, alcoholic, and aging hearts, making it challenging to exclusively categorize some cases as "healed myocarditis" without considering potential overlaps or misidentifications with other diseases. Despite these complexities, we believe we have made our best effort to distinguish "healed myocarditis" from other conditions with the information and methodologies currently available to us.

CONCLUSIONS

In conclusion, segmental T_2 mapping and biventricular strain analysis appear to be superior to T_1 mapping, ECV, and LGE in a multiparametric CMR protocol for the detection of ongoing cardiac inflammation and aid in the noninvasive discrimination of

CENTRAL ILLUSTRATION **Discrimination of Chronic Myocarditis From Healed Myocarditis**



Brendel JM, et al. JACC Cardiovasc Imaging. 2024;■(■):■-■.

(A) CMR revealed T_2 mapping with elevation in ≥3 myocardial segments as the best imaging parameter to discriminate chronic myocarditis from healed myocarditis. (B) Specificity improved by combining T_2 mapping with CMR strain analysis (especially LV systolic strain $rate_{radial}$) or with nonimaging parameters (elevation of either troponin or CRP). CMR = cardiac magnetic resonance; CRP = C-reactive protein; LV = left ventricular.

chronic lymphocytic myocarditis from healed myocarditis apart from biomarkers such as troponin or CRP. Undetected ongoing myocardial inflammation may lead to substantial underestimation of chronic myocarditis, which might progress to dilated cardiomyopathy instead of healed myocarditis, suggesting multiparametric CMR as an adequate noninvasive tool not only to diagnose myocarditis but also to monitor the course of the disease.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A multiparametric CMR protocol seems to be useful to differentiate chronic from healed myocarditis, with increased T_2 mapping values in ≥3 segments indicating substantial ongoing myocardial inflammation consistent with chronic myocarditis. Specificity can be improved when combined with either CMR LV-SSR_{radial} or with serum troponin or CRP.

TRANSLATIONAL OUTLOOK: Future studies are warranted to confirm the role of multiparametric CMR in the detection of different myocarditis stages in relation to the histopathologic standard and its potential implications on patient outcomes.

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KEY WORDS CMR, late gadolinium enhancement, myocarditis, strain, T_2 mapping

APPENDIX For an expanded Methods section as well as supplemental references and a table, please see the online version of this paper.