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Myocardial T1 and T2 Mapping by Magnetic Resonance in Patients With Immune Checkpoint Inhibitor–Associated Myocarditis

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ABSTRACT

BACKGROUND Myocarditis is a potentially fatal complication of immune checkpoint inhibitor (ICI) therapy. Data on the utility of cardiovascular magnetic resonance (CMR) T1 and T2 mapping in ICI myocarditis are limited.

OBJECTIVES This study sought to assess the value of CMR T1 and T2 mapping in patients with ICI myocarditis.

METHODS In this retrospective study from an international registry of patients with ICI myocarditis, clinical and CMR findings (including T1 and T2 maps) were collected. Abnormal T1 and T2 were defined as 2 SD above site (vendor/field strength specific) reference values and a z-score was calculated for each patient. Major adverse cardiovascular events (MACE) were a composite of cardiovascular death, cardiogenic shock, cardiac arrest, and complete heart block.

RESULTS Of 136 patients with ICI myocarditis with a CMR, 86 (63%) had T1 maps and 79 (58%) also had T2 maps. Among the 86 patients (66.3 ± 13.1 years of age), 36 (41.9%) had a left ventricular ejection fraction <55%. Across all patients, mean z-scores for T1 and T2 values were 2.9 ± 1.9 (p < 0.001) and 2.2 ± 2.1 (p < 0.001), respectively. On Siemens 1.5-T scanner (n = 67), native T1 (1,079.0 ± 55.5 ms vs. 1,000.3 ± 22.1 ms; p < 0.001) and T2 (56.2 ± 4.9 ms vs. 49.8 ± 2.2 ms; p < 0.001) values were elevated compared with reference values. Abnormal T1 and T2 values were seen in 78% and 43% of the patients, respectively. Applying the modified Lake Louise Criteria, 95% met the nonischemic myocardial injury criteria and 53% met the myocardial edema criteria. Native T1 values had excellent discriminatory value for subsequent MACE, with an area under the curve of 0.91 (95% confidence interval: 0.84 to 0.98). Native T1 values (for every 1-unit increase in z-score, hazard ratio: 1.44; 95% confidence interval: 1.12 to 1.84; p = 0.004) but not T2 values were independently associated with subsequent MACE.

CONCLUSIONS The use of T1 mapping and application of the modified Lake Louise Criteria provides important diagnostic value, and T1 mapping provides prognostic value in patients with ICI myocarditis.

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ABBREVIATIONS AND ACRONYMS

CI	= confidence interval
CMR	= cardiovascular magnetic resonance
ECG	= electrocardiogram
ECV	= extracellular volume fraction
EMB	= endomyocardial biopsy
LGE	= late gadolinium enhancement
LVEF	= left ventricular ejection fraction
ICI	= immune checkpoint inhibitor
MACE	= major adverse cardiovascular events

Immune checkpoint inhibitor (ICI)-associated myocarditis is an uncommon immune-related adverse event (1). However, ICI myocarditis is associated with major adverse cardiovascular events (MACE) in up to 40% (2), with a case fatality rate of up to 25% (3). The diagnosis of myocarditis is usually based on clinical symptoms or signs, troponin elevation, cardiac imaging features, or endomyocardial biopsy (EMB) (4); however, the latter is not commonly performed because of associated risks and the lack of widespread expertise. Among noninvasive methods, cardiovascular magnetic resonance (CMR) is the reference standard for both diagnosis and prognosis with non-ICI myocarditis (5-7). Recent work identified

that components of the original Lake Louise Criteria for the diagnosis of non-ICI myocarditis were not universally present among patients with pathologically confirmed ICI myocarditis. For example, among patients presenting with a preserved left ventricular ejection fraction (LVEF), late gadolinium enhancement (LGE) and abnormal T2-weighted imaging were observed in <50% of patients, and neither

predicted MACE (2). Tissue characterization has evolved to include quantitative parametric mapping techniques. These techniques, such as T1 and T2 mapping, have shown excellent diagnostic and prognostic value in patients with non-ICI myocarditis and are recommended in updated protocols (7-11). However, beyond case reports, there are limited data on the use of T1 and T2 mapping in patients with ICI myocarditis (12). In this study, the largest cohort of patients with ICI myocarditis, from multiple international centers, was leveraged to provide the first data on the application of T1 and T2 mapping to patients with ICI myocarditis.

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METHODS

PATIENT COHORT. This was a retrospective cohort study in which consecutive patients with ICI myocarditis, diagnosed by a board-certified cardiologist using standard criteria (see the following), at each site in an international multicenter registry (2,13-15), and with available CMR with T1 or T2 mapping data were included. Follow-up started with first ICI administration. For each patient, the following

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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](#).

was extracted from the medical records: demographics, cancer type, ICI treatment, prior cardiotoxic chemotherapy or radiation, cardiovascular risk factors, presentation, physical examination, initial troponin and B-type natriuretic peptide levels and peak values during hospitalization, electrocardiograms (ECGs), echocardiographic data, CMR, EMB, and autopsy results. When available, echocardiographic global longitudinal strain was measured as described (14). The study complied with the Declaration of Helsinki and was approved by each center's institutional review committee, the requirement for written informed consent was waived.

DIAGNOSIS OF ICI MYOCARDITIS. ICI myocarditis was diagnosed in 1 of 2 ways: 1) presence of standard histopathological features (16); or 2) meeting the European Society of Cardiology diagnostic criteria for clinically suspected myocarditis (6) (Supplemental Table 1). This standardized approach to the diagnosis of myocarditis has been used in multiple prior cohorts (17,18), including those with ICI myocarditis (2,13-15).

CMR PROTOCOL. The decision to undergo CMR at presentation with ICI myocarditis was at the discretion of the site practitioners. Applied CMR protocols complied with local institutional practices and were neither study specified nor aligned across sites; however, there were similarities in the key elements of the protocol. All CMR studies were either performed on a 1.5-T or 3-T Siemens (n = 82) (Siemens, Erlangen, Germany) or 1.5-T Philips (n = 4) (Philips, Best, the Netherlands) magnet including ECG gating, breath-holding, and local array coil signal reception (Supplemental Table 2). Across all sites, exam protocols included cine balanced steady-state free precession imaging for left ventricular functional and mass assessment (slice = 6 to 8 mm; gap = 0 to 2 mm) and T2-weighted imaging employing either T2 short tau inversion recovery or spectral attenuated inversion recovery techniques.

Pre-contrast T1 and T2 maps were performed in a single mid short-axis slice (Supplemental Table 2) (19). LGE images were performed 10 to 15 min after a gadolinium-based contrast agent (slice = 8 mm; gap = 0 to 2 mm); a subset of patients (n = 19) also had T1 maps at 15 min post-contrast administration for quantification of extracellular volume fraction (ECV) (20,21).

For both T1 and T2 maps, scanner- and site-specific motion correction was applied for map generation prior to further analysis. The CMR data, including T1 and T2 values, were interpreted at each site by experienced readers as part of clinical care. T1 and T2

TABLE 1 Demographics, Cancer, and Treatment Details for All Patients With ICI Myocarditis and Patients With Abnormal Versus Normal T1 Values

	With T1 Mapping (n = 86)*	Abnormal T1 Values (n = 67)†	Normal T1 Values (n = 19)	p Value‡
Age at start of ICI, yrs	66.3 ± 13.1	66.4 ± 12.9	65.7 ± 14.2	0.84
Female	28 (32.6)	17 (25.4)	11 (57.9)	0.012
CV risk factors				
Hypertension	47 (56.0)	36 (54.6)	11 (61.1)	0.79
Diabetes mellitus	15 (19.0)	9 (15.0)	6 (31.6)	0.108
No CV risk factors	23 (26.7)	20 (30.0)	3 (15.8)	0.073
Prior coronary artery disease	11 (14.3)	6 (10.2)	5 (27.8)	0.12
Prior stroke	3 (3.9)	2 (3.3)	1 (5.6)	0.55
Prior heart failure	1 (1.3)	1 (1.7)	0 (0.0)	1.00
Chronic kidney disease	4 (5.9)	4 (7.7)	0 (0.0)	0.24
Body mass index, kg/m ²	27.8 ± 6.3	27.2 ± 6.3	29.4 ± 6.3	0.20
Primary cancer type				
Head and neck	3 (3.5)	1 (1.5)	2 (10.5)	0.12
Breast	4 (4.7)	4 (6.0)	0 (0.0)	0.57
Hodgkin's lymphoma	1 (1.2)	1 (1.5)	0 (0.0)	1.00
Melanoma	37 (43.0)	30 (44.8)	7 (36.8)	0.61
Non-small cell lung cancer	11 (12.8)	8 (11.9)	3 (15.8)	0.70
Pancreatic	1 (1.2)	1 (1.5)	0 (0.0)	1.00
Renal cell carcinoma	6 (7.0)	6 (9.0)	0 (0.0)	0.33
Glioblastoma	1 (1.2)	1 (1.5)	0 (0.0)	1.00
Other	22 (25.6)	15 (22.4)	7 (36.8)	0.52
Prior chemotherapy or radiation				
Radiation	23 (26.7)	15 (22.4)	8 (42.1)	0.14
Anthracyclines	8 (9.3)	7 (10.5)	1 (5.3)	0.68
ICI regimen				
Monotherapy	58 (67.4)	45 (67.2)	13 (68.4)	1.00
Anti-PD1	51 (59.3)	38 (56.7)	13 (68.4)	0.43
Anti-CTLA4	6 (7.0)	6 (9.0)	0 (0.0)	0.33
Anti-PDL1	1 (1.2)	1 (1.5)	0 (0.0)	1.00
Dual therapy	28 (32.6)	22 (32.8)	6 (31.6)	0.49

Values are mean ± SD or n (%). *Percentages are represented as percentage of available data. †Abnormal T1 values were defined as values >2 SD above the site, CMR vendor/field strength specific mean reference value. ‡Comparison between patients with normal versus abnormal T1 values was performed using the Student's t-tests or Wilcoxon rank sum tests for continuous variables, as appropriate based on their normality and the chi-square test for categorical variables.
anti-CTLA4 = anti-cytotoxic T-lymphocyte-associated protein 4; anti-PD1 = anti-programmed cell death protein 1; anti-PDL1 = anti-programmed death-ligand 1; CMR = cardiovascular magnetic resonance; CV = cardiovascular; ICI = immune checkpoint inhibitor.

values were measured using a single region of interest placed in the septal wall of the mid short-axis slice; segments with LGE were excluded for T1 measurements. Site, CMR vendor, and field strength-specific normal T1 and T2 reference values were obtained from each site (Supplemental Table 2). Abnormal T1 and T2 values were defined as 2 SD above the mean of the reference values as per the Society for Cardiovascular Magnetic Resonance recommendations (20). To enable combined analysis of multicenter or multivendor data, T1 and T2 values were converted to a z-score (20) using the site-specific

TABLE 2 Clinical Presentation of All Patients With ICI Myocarditis and Patients With Abnormal Versus Normal T1 Values				
	With T1 Mapping (n = 86)*	Abnormal T1 Values (n = 67)†	Normal T1 Values (n = 19)	p Value‡
Time from starting ICI to admission for myocarditis, days	57 (27 to 110)	59 (27 to 116)	37 (22 to 82)	0.27
Myocarditis presentation				
Chest pain	23 (26.7)	17 (25.4)	6 (31.6)	0.57
Shortness of breath	52 (60.5)	44 (65.7)	8 (42.1)	0.11
Orthopnea	16 (19.1)	14 (21.2)	2 (11.1)	0.69
Paroxysmal nocturnal dyspnea	15 (17.7)	15 (22.7)	0 (0.0)	0.036
Fatigue	29 (36.7)	20 (32.8)	9 (50.0)	0.39
Syncope	6 (7.8)	5 (8.3)	1 (5.9)	0.26
Sudden cardiac death	1 (1.3)	1 (1.7)	0 (0.0)	0.23
Palpitation	19 (22.4)	15 (22.7)	4 (21.1)	1.00
Physical exam				
Jugular vein distention	24 (28.2)	21 (31.8)	3 (15.8)	0.14
Crackles	29 (34.5)	26 (40.0)	3 (15.8)	0.11
Lower extremity edema	27 (32.1)	25 (38.5)	2 (10.5)	0.020
SBP, mm Hg	125.9 ± 20.1	124.4 ± 20.4	130.9 ± 18.8	0.23
DBP, mm Hg	74.2 ± 10.1	74.4 ± 9.1	73.7 ± 13.1	0.82
Electrocardiogram at presentation				
Sinus rhythm	70 (82.4)	53 (80.3)	17 (89.5)	0.50
ST-segment or T-wave changes	43 (51.8)	32 (48.5)	11 (64.7)	0.28
Heart rate, beats/min	82.7 ± 21.3	83.4 ± 22.5	78.5 ± 13.5	0.55
Biomarkers				
Initial troponin T, ng/ml	1.3 (0.3 to 28.4)	1.3 (0.4 to 15.6)	21.0 (0.2 to 67.4)	0.63
Peak troponin T, ng/ml	2.0 (0.5 to 96.7)	2.0 (0.5 to 54.4)	16.2 (0.5 to 114.6)	0.73
Initial BNP, pg/ml	536.0 (183.6 to 1,200.0)	559.0 (194.0 to 1,500.0)	184.0 (152.0 to 672.0)	0.14
Peak BNP, pg/ml	1,130.0 (194.0 to 2,118.0)	1,130.0 (194.0 to 2,275.0)	1,027.5 (370.0 to 1,671.5)	0.75
Echocardiogram				
Pre-ICI LVEF, %	60.6 ± 4.9	59.9 ± 4.8	63.5 ± 4.0	0.021
Lowest LVEF at presentation, %	51.8 ± 14.9	50.0 ± 15.8	58.2 ± 8.8	0.034
Change of LVEF, %	11.0 ± 13.5	12.3 ± 14.3	5.3 ± 7.1	0.11
LVEF <50% at presentation	27 (31.4)	25 (37.3)	2 (10.5)	0.026
LVIDD, mm	46.9 ± 6.0	47.8 ± 5.7	44.2 ± 6.1	0.040
LA size, mm	37.5 (34 to 42)	37.5 (34 to 45)	38.0 (35.5 to 40)	0.91
Pericardial effusion	16 (27.6)	13 (29.6)	3 (21.4)	0.24
Global longitudinal strain by echo, %	-14.3 (-16.8 to -12.7)	-14.1 (-16.8 to -12.4)	-15.7 (-16.7 to -15.1)	0.27
CMR				
Time from admission to CMR	4 (2 to 8)	4 (2 to 8)	3 (2 to 5)	0.34
Time from start of ICI therapy to CMR	58 (28 to 118)	64 (34 to 119)	38 (20 to 103)	0.13
Corticosteroids use before CMR	54 (72.0)	42 (71.2)	12 (75.0)	1.00
1.5-T Siemens	60 (69.8)	45 (67.2)	15 (79.0)	0.14
1.5-T Philips	4 (4.7)	2 (3.0)	2 (10.5)	0.14
3-T Siemens	22 (25.5)	20 (29.8)	2 (10.5)	0.14
LVEDV, ml	142.5 (129 to 159)	142 (128 to 160)	143 (129 to 151)	0.76
LV mass index, g/m ²	70.6 (60.9 to 92.0)	69.0 (59.0 to 84.3)	78.0 (63.7 to 119.0)	0.11
LVEF by CMR, %	51.3 ± 13.8	49.6 ± 14.2	57.2 ± 10.6	0.034
LVEF <55%	36 (41.9)	30 (44.8)	6 (31.6)	0.30
LGE, %	48 (55.8)	35 (52.2)	13 (68.4)	0.30
Edema by T2-weighted STIR/SPAIR	22 (34.4)	18 (34.0)	4 (36.4)	1.00
Native T1 value (1.5-T Siemens), ms	1,070.1 ± 50.6	1,086.2 ± 46.3	1,021.9 ± 26.3	<0.001
Native T1 value (3-T Siemens), ms	1,212.5 ± 73.6	1,212.3 ± 76.7	1,214.5 ± 44.5	0.97
Average T2 value (1.5-T Siemens), ms	56.3 ± 4.9	57.0 ± 5.0	54.0 ± 3.7	0.041
Average T2 value (3-T Siemens), ms	48.9 ± 8.3	50.4 ± 7.9	39.0 ± 0.05	0.070
Extracellular volume, %	33.2 ± 2.1	33.2 ± 2.2	33.3 ± 0.6	0.91

Continued on the next page

TABLE 2 Continued

	With T1 Mapping (n = 86)*	Abnormal T1 Values (n = 67)†	Normal T1 Values (n = 19)	p Value‡
Corticosteroid treatment				
Time from admission to treatment				
≤24 h	43 (55.8)	30 (50.9)	13 (72.2)	0.019
24-72 h	17 (22.1)	12 (20.3)	5 (27.8)	
>72 h	17 (22.1)	17 (28.8)	0 (0)	
Initial corticosteroids dose				
Low (<60 mg/day)	12 (19.1)	9 (17.7)	3 (25.0)	0.28
Intermediate (60-500 mg/day)	28 (44.4)	21 (41.2)	7 (58.3)	
High (501-1,000 mg/day)	23 (36.5)	21 (41.2)	2 (16.7)	

Values are n (%), median (interquartile range), or mean ± SD. *Percentages are represented as percentage of available data. †Abnormal T1 values were defined as values >2 SD above the site, CMR vendor/field strength specific mean reference value. ‡Comparison between patients with abnormal and normal T1 values were performed using the Student's t tests or Wilcoxon Rank Sum tests for continuous variables, as appropriate based on their normality and the Chi-squared test for categorical variables. §Only 2 patients with identical values.

BNP = B-type natriuretic peptide; DBP = diastolic blood pressure; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diameter end-diastole; MACE = major adverse cardiovascular events; SBP = systolic blood pressure; STIR = short tau inversion recovery; SPAIR = spectral attenuated inversion recovery; other abbreviations as in Table 1.

reference values derived as follows: (patient value – mean of reference range) / (SD of the reference range). As applied here, a z-score provides an assessment of how many SD each patient's T1 or T2 value is above or below the mean for the normal range for each site, vendor, and CMR field strength.

ADVERSE CARDIOVASCULAR EVENTS. As in previous studies (22-24), MACE were defined as a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and complete heart block requiring pacemaker. When multiple events occurred in a single patient, time to MACE was considered the time to first event. If cardiac arrest, cardiogenic shock, or complete heart block led to a death, this was considered a cardiac death. The end of follow-up was on July 19, 2020.

STATISTICAL ANALYSIS. All data were first tested for normality using the Shapiro-Wilk test. Continuous variables were summarized as mean ± SD or median (interquartile range) and compared between groups using Student's t-tests or Wilcoxon rank sum tests. Categorical variables are presented as percentage and were compared between groups using the Fisher Exact test. A 1-sample t-test was used to compare the z-scores to 0. Kaplan-Meier curves were generated for MACE and compared with the log-rank test. Univariable and multivariable Cox proportional hazards models (model 1: adjusting for age, sex; model 2: adjusting for age, sex, number of cardiovascular risk factors, and left ventricular ejection fraction [LVEF] by CMR) were performed to examine the association between T1 and T2 values and MACE. We performed a sensitivity analysis by including LGE in the multivariable model 2 when assessing the association

between T1 and MACE. Proportional hazards assumption was tested using the Schoenfeld residuals method (25,26). The linearity assumption for continuous variables was tested by entering the square of the term into the model. Receiver-operating characteristic curves for MACE were generated for T1- and T2-related z-scores for all patients. A 2-sided p value <0.05 was considered significant. Analyses were performed with Stata 15 (StataCorp, College Station, Texas).

RESULTS

PATIENT CHARACTERISTICS. Among the 136 patients with a CMR in the ICI registry, 86 with T1 maps were included, of whom 79 also had T2 maps (i.e., 79 patients had both T1 and T2 maps). Of the 86 patients, 38 were diagnosed using pathology (EMB: n = 33; autopsy: n = 5) and 48 using the European Society of Cardiology diagnostic criteria (Supplemental Table 1) (6). Patient characteristics, cancer types, and cancer treatment are summarized in Table 1. The mean age was 66.3 ± 13.1 years, 28 (32.6%) were female, and 28 (32.6%) received combination ICI therapy. Obstructive coronary artery disease was excluded in 77 of 86 patients, either using coronary angiography (n = 54), coronary computed tomography angiography (n = 12), or stress tests with imaging (n = 11). The clinical, imaging, and biomarker characteristics of patients who did (n = 86) and did not (n = 50) have T1 mapping in our CMR cohort were largely similar (Supplemental Tables 3 and 4).

DIAGNOSTIC TESTS. Physical examination, ECG, and biomarker findings are summarized in Table 2. Among the 86 included patients, 71 (82.6%) were scanned

TABLE 3 T1 and T2 Mapping Values in Comparison With Reference Ranges and Also Dichotomized Based on Those With and Without MACE

	ICI Myocarditis Patients	Reference Ranges	p Value*	MACE	No MACE	p Value†
T1 z-score (n = 86)	2.9 ± 1.9	—	—	4.2 ± 1.0	2.3 ± 1.9	<0.001
T1 value—1.5-T Siemens (n = 67)	1,079.0 ± 55.5	1000.3 ± 22.1	<0.001	1,114.7 ± 40.9	1,061.6 ± 53.6	<0.001
T1 value—1.5-T Philips (n = 4)	1,014.0 ± 34.0	961.5 ± 23.0	0.007	1,013 ± 0	1,014.3 ± 41.6	N/A‡
T1 value—3.0T Siemens (n = 15)	1,239.3 ± 72.1	1,097.3 ± 144.6	<0.001	1,244.0 ± 64.0	1,237.5 ± 77.7	0.88
T2 z-score (n = 79)	2.2 ± 2.1	—	—	3.2 ± 2.4	1.8 ± 1.7	0.003
T2 value—1.5-T Siemens (n = 67)	56.2 ± 4.9	49.8 ± 2.2	<0.001	57.9 ± 6.5	55.4 ± 3.7	0.045
T2 value—1.5-T Philips (n = 4)	55.0 ± 4.1	51.9 ± 0.6	0.28	54.0 ± 0	55.3 ± 4.9	N/A‡
T2 value—3.0T Siemens (n = 8)	42.9 ± 4.6	39.3 ± 0.1	0.063	46.0 ± 0	42.4 ± 4.8	N/A‡

Values are mean ± SD. Data are presented a z-scores and for specific CMR magnets and field strength. *Student's t test comparing T1 or T2 values of patients with ICI-associated myocarditis with site- and magnet-specific normal mean values and SD. †Student's t test comparing T1 or T2 values of patients with and without major MACE. ‡Analysis could not be performed due to only 1 patient in the MACE group. N/A = not available; Abbreviations as in Table 2.

with a 1.5-T scanner (67 Siemens, 4 Philips) and 15 (17.4%) were scanned with a 3-T scanner (all Siemens). Overall, 36 (41.9%) patients had a CMR LVEF of <55%. The mean CMR LVEF was reduced (51.3 ± 13.8%), with abnormal LGE and T2 weighted imaging identified in 55.8% and 34.4% of these patients with available data, respectively. The average global longitudinal strain values, measured with echocardiography, were reduced (median -14.3% [interquartile range: -16.8% to -12.7%]) in the subgroup with these data.

ASSOCIATION BETWEEN ICI MYOCARDITIS AND T1 AND T2 VALUES. For the entire cohort, the mean ± SD z-scores for T1 and T2 values were 2.9 ± 1.9 (p < 0.001) and 2.2 ± 2.1 (p < 0.001) respectively. The native T1 and T2 values in our patients were higher

than the reference values regardless of the field strength and vendor (e.g., 1.5-T Siemens T1: 1,079.0 ± 55.5 ms vs. 1,000.3 ± 22.1 ms; p < 0.001; 1.5-T Siemens T2: 56.2 ± 4.9 ms vs. 49.8 ± 2.2 ms; p < 0.001) (Table 3). Among the cohort, 67 (78%) and 34 (43%) patients had abnormal T1 and T2 values, respectively. The mean T1 values in patients with LGE and T2 values in patients with abnormal T2 short tau inversion recovery or spectral attenuated inversion recovery are summarized in Supplemental Table 5.

When patients were dichotomized into those with normal and abnormal T1 values (Tables 1 and 2), patients with abnormal T1 values were more likely to be male, have paroxysmal nocturnal dyspnea and peripheral edema, have lower pre-ICI LVEF, and have lower LVEF at diagnosis and during admission. There were no differences between the groups in the time from admission to CMR or the proportion of patients treated with corticosteroids prior to CMR. Patients with normal T1 values were more likely to have received corticosteroids early, within 24 h, of hospital admission. In the 19 patients with ECV measurements, the mean value was 33.2 ± 2.1% compared with the site-specific normal reference value of 26.0 ± 1.6%.

ASSOCIATION BETWEEN HISTOPATHOLOGY AND T1 AND T2 MAPS. Among the 38 patients with histologically confirmed myocarditis, a lymphocytic infiltration was observed in 36 (95%) patients, among whom 29 (80.6%) patients had abnormal T1 values. T2 maps were available in 30 of the 36 patients, among whom, T2 values were abnormal in 15 (50.0%) patients. Twenty-three patients had pathological fibrosis, of whom 19 (82.6%) had abnormal T1 values. Among the 6 patients with ECV within this latter group, 83.3% had abnormal ECV values.

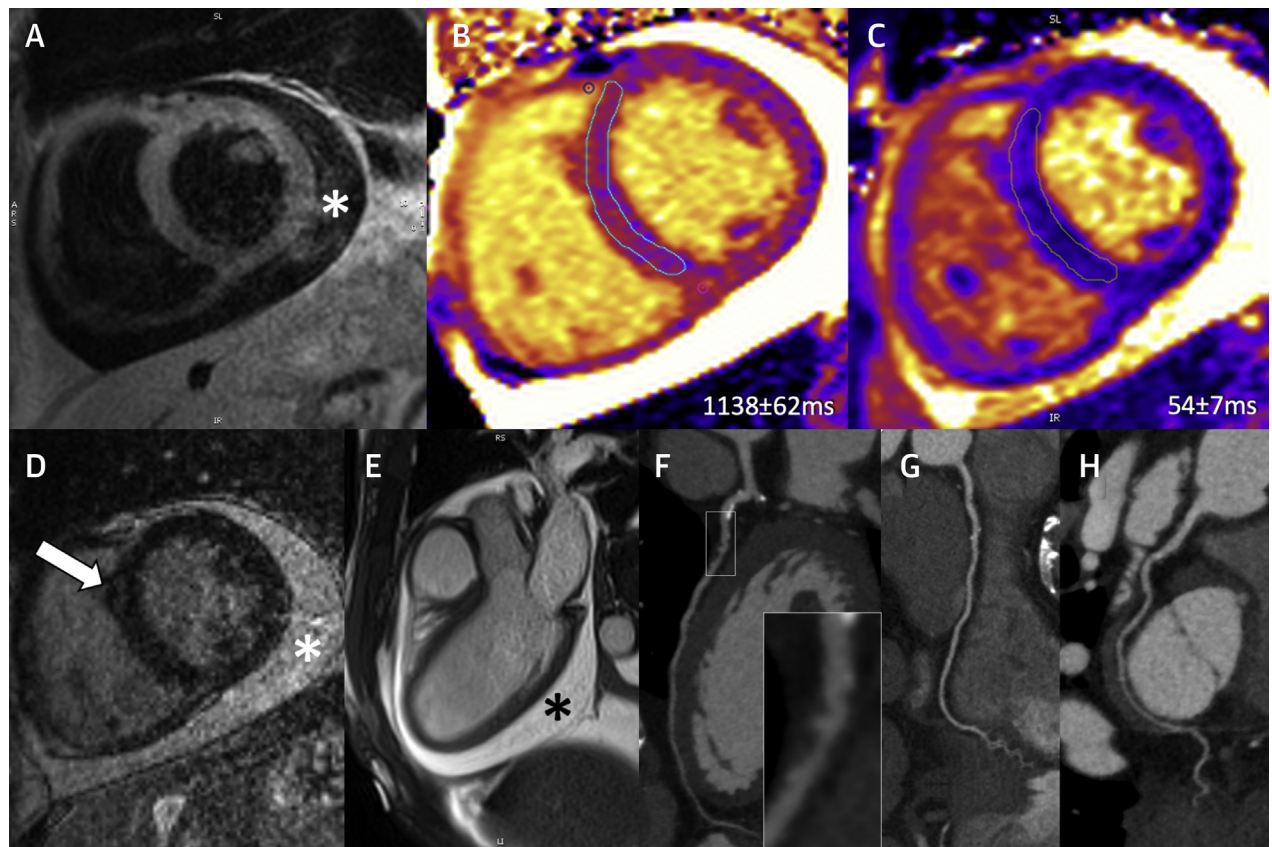
LAKE LOUISE CRITERIA AND ICI MYOCARDITIS. We applied the modified Lake Louise Criteria to the

TABLE 4 Proportion of Patients Meeting the Various Components of the Modified Lake Louise Criteria in All Included Patients and Those With Biopsy-Proven ICI Myocarditis

	All Cases (n = 79)*	Biopsy-Proven Cases (n = 31)*
Main criteria		
Nonischemic myocardial injury (abnormal T1, ECV,† or LGE)	75 (95)	28 (100)
Myocardial edema (T2 mapping or T2W images)	42 (53)	19 (63)
Supportive criteria		
Pericarditis	14 (18)	8 (26)
Systolic LV dysfunction (<55%)	33 (42)	16 (52)
Combinations		
Patients with both main criteria	38 (48)	16 (52)
Patients with either main criteria	79 (100)	31 (100)
Patients without T1 or T2 elevation or supportive criteria	0 (0)	0 (0)

Values are n (%). Abnormal T1 and T2 values were defined as mean + 2 SD above site, CMR vendor, and field strength-specific reference ranges. *These numbers refer to patients who had both T1 and T2 maps. †ECV was only available in 19 patients in the entire cohort of 79 patients, and 10 patients among those with biopsy-proven disease. ECV = extracellular volume fraction; LV = left ventricular; T2W = T2-weighted; other abbreviations as in Table 2.

FIGURE 1 Multicontrast and Parametric Cardiovascular Magnetic Resonance Imaging in a Patient With Confirmed Immune Checkpoint Inhibitor Myocarditis (1.5-T)



(A) Representative short-axis T2-weighted spectral attenuated inversion recovery without focal signal abnormality. (B) The mid-ventricular short-axis modified Look-Locker imaging (MOLLI) T1 map demonstrates diffusely elevated T1 values (local normal reference: 1006 ± 24 ms), while (C) the same slice T2 map demonstrates normal global T2 values (local normal reference: 52 ± 3 ms). (D) Post-contrast late gadolinium enhancement imaging demonstrates faint mid-myocardial enhancement (arrow) in the mid-ventricular anteroseptum. (E) The 3-chamber cine balanced steady-state free precession image demonstrates a pericardial effusion. (F to H) Coronary computed tomography angiography performed for exclusion of possible coronary artery disease demonstrated calcified and noncalcified changes (predominately in left anterior descending artery; panel F) without significant coronary artery stenosis. The asterisk indicates pericardial effusion.

patients with both T1 and T2 maps ($n = 79$) (7). Data are presented for all patients and the subgroup with pathology (Table 4). When considering abnormal T1 or T2 values along with T2 weighted imaging and LGE, 95% of patients met the nonischemic myocardial injury criteria, 53% met the myocardial edema criteria, and 48% met both these main criteria. At least 1 of the main modified Lake Louise Criteria for myocarditis was present in 100% of the patients. A clinical example is shown in Figure 1.

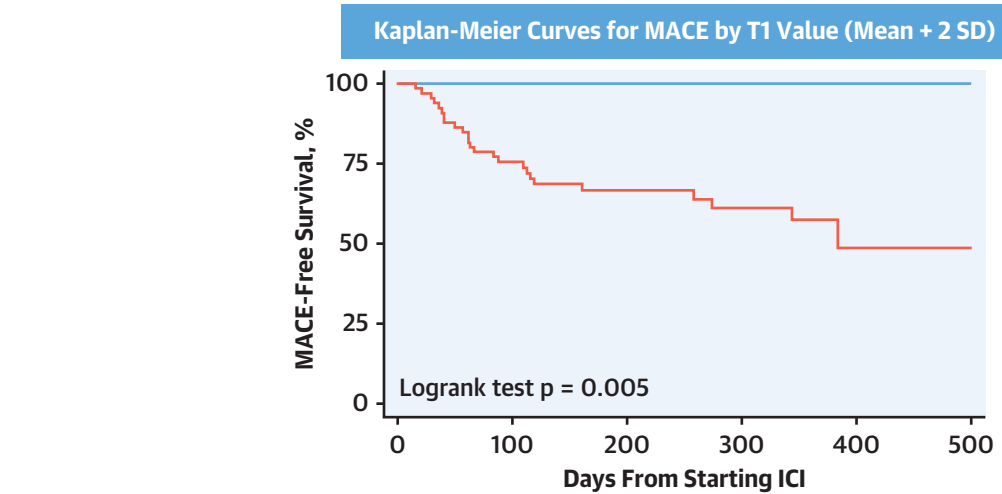
MAJOR ADVERSE CARDIOVASCULAR EVENTS. During a median follow-up time of 158 days, 27 (31.4%) patients developed MACE (Table 5). Patients who developed MACE had higher T1 and T2 z-scores (Table 3). Similarly, in the subgroup imaged with a

TABLE 5 MACE in All Patients and in Those Dichotomized Based on Normal Versus Abnormal T1 Values

	All Patients (N = 86)	Abnormal T1 Values (n = 67)*	Normal T1 Values (n = 19)	p Value
Follow-up time for MACE, days†	158 (78-333)	161 (78-333)	154 (68-407)	0.92
MACE‡	27 (31.4)	27 (40.3)	0 (0)	<0.001
Complete heart block	8 (9.5)	8 (12.1)	0 (0)	0.19
Cardiogenic shock	10 (12.1)	10 (15.4)	0 (0)	0.11
Cardiac arrest	12 (14.5)	12 (18.5)	0 (0)	0.072
Cardiovascular death	12 (14.0)	12 (17.9)	0 (0)	0.061

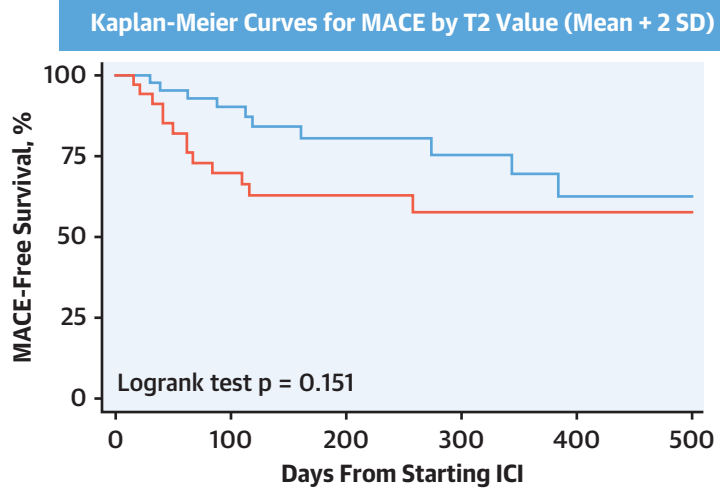
Values are median (interquartile range) or n (%). *Abnormal T1 values were defined as values >2 SD above the site, CMR vendor/field strength-specific mean reference value. †Time of the MACE was defined by the date of the earliest event when multiple MACE happened. ‡Patients may have multiple MACE. MACE = major adverse cardiovascular events.

FIGURE 2 Kaplan-Meier Curves of MACE-Free Survival in Patients With Normal and Abnormal T1 Values and T2 Values



Number at risk

— T1 Value Below Mean + 2 SD	19	11	8	5	5	4
— T1 Value Above Mean + 2 SD	67	47	29	21	10	5



Number at risk

— T2 Value Below Mean + 2 SD	45	32	20	15	9	6
— T2 Value Above Mean + 2 SD	34	21	13	7	3	2

Abnormal values were defined as above mean + 2 SD of the site, with cardiovascular magnetic resonance vendor/field strength-specific reference ranges. ICI = immune checkpoint inhibitor; MACE = major adverse cardiovascular events.

1.5-T Siemens magnet, those who developed MACE had higher T1 and T2 values (Table 3). The incidence of MACE in patients with normal versus abnormal T1 and T2 values were 0.0% versus 40.3% ($p < 0.001$) (Table 5) and 19.5% versus 42.1% ($p = 0.029$), respectively. The MACE-free survival was significantly lower in patients with abnormal compared

with normal T1 values (Figure 2A), but no significant difference was seen with T2 values (Figure 2B). Using z-scores, a receiver-operating characteristic curve for T1 and T2 values demonstrated an area under the curve of 0.91 (95% confidence interval [CI]: 0.84 to 0.98) and 0.70 (95% CI: 0.56 to 0.83) for MACE, respectively (Figure 3).

TABLE 6 Univariable and Multivariable Analysis of Association Between CMR T1 and T2 Maps and MACE

	Univariable Model		Multivariable Model 1*		Multivariable Model 2†	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Native T1 value, per 1-unit increase in z score	1.31 (1.14-1.50)	<0.001	1.54 (1.26-1.87)	<0.001	1.44 (1.12-1.84)	0.004‡
Native T1 value (1.5-T Siemens), per 10-ms increase	1.10 (1.03,1.17)	0.004	1.14 (1.05-1.23)	0.001	1.11 (1.02-1.21)	0.017§
Abnormal T1 values	—	—	—	—	—	—
T2 value, per 1-unit increase in z score	1.36 (1.12-1.65)	0.002	1.32 (1.07-1.61)	0.008	1.22 (0.98-1.52)	0.077
T2 value (1.5-T Siemens only), per 1-ms increase	1.10 (1.00-1.20)	0.042	1.07 (0.98-1.18)	0.143	1.05 (0.96-1.15)	0.312
Abnormal T2 values	2.86 (1.17-6.99)	0.022	2.48 (1.00-6.13)	0.049	2.19 (0.81-5.91)	0.122

*Cox proportional hazards model adjusting for age and sex. †Cox proportional hazards model adjusting for age, sex, number of cardiovascular risk factors, and LVEF by CMR during the index hospitalization. ‡In sensitivity analysis, when presence of LGE was added to multivariable model 2, the HR per 1-unit increase in z-score remained significantly associated with MACE (HR: 1.45; 95% CI: 1.14, 1.84; p = 0.003). §Similarly when LGE was added to multivariable model 2, native T1 values on the 1.5-T magnet remained significantly associated with MACE (HR per 10-ms increase: 1.12; 95% CI: 1.02 to 1.22; p = 0.013). ||Because all MACE occurred in patients abnormal with T1 value s (i.e., >mean + 2 SD) an HR could not be calculated.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

Using the T1 z-score as a continuous parameter, regression analysis indicated that the z-score was associated with greater hazards of MACE (Table 6) even after adjusting for age, sex, number of cardiovascular risk factors, and LVEF (hazard ratio: 1.44; 95% CI: 1.12 to 1.84; p = 0.004). This association was similar when T1 values were examined only on a 1.5-T Siemens magnet. When T1 values were dichotomized into normal versus abnormal values, all MACE occurred in patients with abnormal T1 values (Table 6). Finally, in our sensitivity analysis, T1 remained significantly associated with MACE after additional adjustment for presence of LGE (Table 6). Higher T2 z-score was also associated with MACE and remained associated after adjusting for age and sex, but became nonsignificant after additional adjustment for cardiovascular risk factors and LVEF (Table 6).

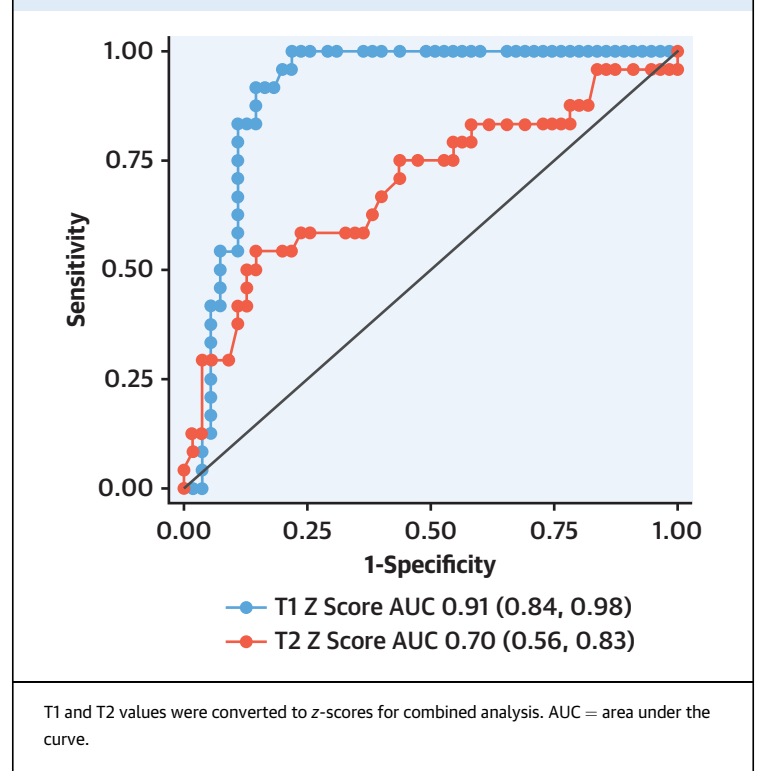
DISCUSSION

In this report, we provide the first comprehensive data on the use of CMR parametric mapping techniques in patients with ICI myocarditis. We report the following novel findings: 1) myocardial T1 and T2 values were significantly elevated in 78% and 43% of patients with ICI myocarditis, respectively; 2) patients with abnormal T1 values were more symptomatic and had lower cardiac function; 3) the association between histopathological changes and T1 measurements was stronger than the association with T2 measurements; 4) all patients in our study met at least 1 of the 2 main modified Lake Louise Criteria; and 5) higher T1 values had independent prognostic value for the subsequent development of MACE.

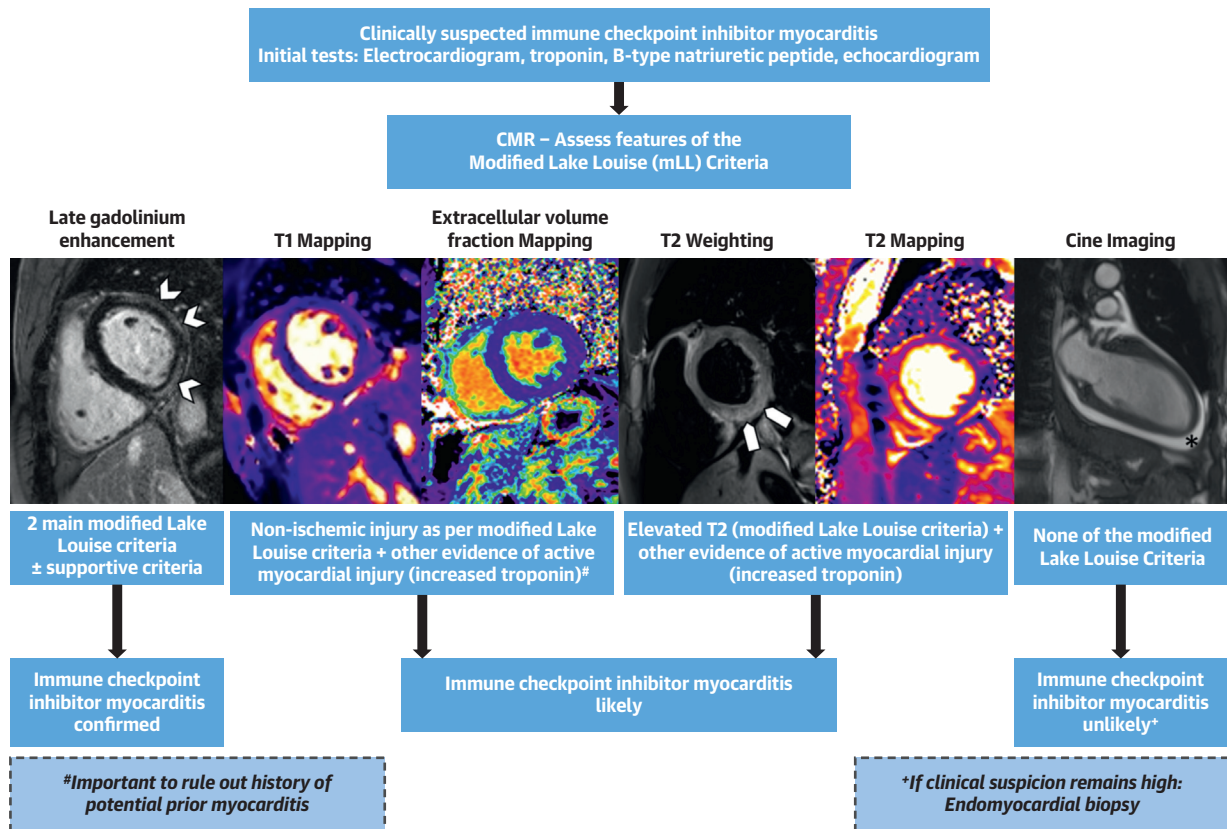
The clinical application of CMR for the diagnostic work-up of patients with suspected myocarditis is based on the Lake Louise Criteria (27). The updated criteria incorporate parametric mapping techniques

and require the presence of myocardial edema (based on T2 maps or T2-weighted imaging) and nonischemic myocardial injury (based on T1 maps, ECV quantification, or LGE) as the 2 main criteria (7). The addition of parametric mapping improves the diagnostic yield for non-ICI acute myocarditis from an area under the curve of 84% for the original criteria to as high as 96% with the use of a combination of T1 mapping and LGE images (7). Among the individual techniques, T1 mapping provides the greatest diagnostic yield for

FIGURE 3 Receiver-Operating-Characteristic Curves for Major Adverse Cardiovascular Events for Cardiovascular Magnetic Resonance T1 and T2 Mapping



CENTRAL ILLUSTRATION A Proposed Approach to Cardiovascular Magnetic Resonance Assessment of Immune Checkpoint Inhibitor Myocarditis With Incorporation of Parametric Mapping Techniques



Thavendiranathan, P. et al. J Am Coll Cardiol. 2021;77(12):1503-16.

Arrowheads delineate band-like subepicardial late gadolinium enhancement, block arrows highlight elevated signal intensity on T2 weighted image, and the asterisk demonstrates the presence of pericardial effusion on a cine balanced steady-state free precession image.

non-ICI acute myocarditis, with a diagnostic odds ratio of 44.1 (7,28). The literature on CMR tissue characterization techniques in patients with ICI myocarditis is limited. We recently demonstrated that, among patients with ICI myocarditis presenting with a preserved LVEF, LGE and abnormalities on T2 weighted imaging were only present in 48% and 28% of the patients, respectively (2). The application of T1 or T2 mapping in these patients has been limited to a case report (12) and our prior report in a small group of patients (2).

Using our ICI registry, we identified abnormal native T1 and T2 values in 78% and 43% of the patients, respectively. When we applied the modified Lake Louise Criteria (combining T1 and T2 mapping with T2-weighted imaging and LGE), 48% of the patients met both main criteria for myocarditis, 95%

met the nonischemic myocardial injury criteria and 100% met either of the 2 main criteria of myocarditis. Owing to the lack of patients without ICI myocarditis for comparison, we are unable to provide data on the diagnostic performance of the modified Lake Louise Criteria or thresholds of T1 and T2 values for the diagnosis of ICI myocarditis.

Therefore, although further investigation is needed, our data suggest that in the appropriate clinical setting, the presence of nonischemic myocardial injury criteria maybe the most prevalent finding in patients with ICI myocarditis.

The greater prevalence of T1, compared with T2 elevation, in patients with ICI myocarditis is consistent with reports of better diagnostic accuracy of native T1 values in patients with non-ICI myocarditis (28-30). In acute myocarditis, both T1 and T2

elevations reflect inflammation and edema (20). However, T1 mapping can also identify fibrosis, which can be present early during myocarditis (31). In our subgroup with histopathology, 95% had lymphocytic infiltration, and the majority had elevated T1 values, with only 50% having elevated T2 values. Furthermore, 61% of the patients had myocardial fibrosis, among whom the majority had elevated in T1 values. Therefore, although our patients likely had inflammation or edema at the onset of myocarditis, this may have improved at the time of CMR in some patients, given that 72% of our patients received corticosteroids before the CMR study, and may explain the lower prevalence of T2 abnormalities. However, our findings reflect the real-world use of CMR in these patients. Alternatively, the difference in prevalence of T2 versus T1 abnormalities may reflect lower sensitivity of the T2 mapping sequences to detect myocardial inflammation (28) or the fact that patchy areas of myocardial edema may have been missed due to the use of septal measurements from a single slice. However, for practical purposes, single-slice T2 maps are common clinical practice. It is also likely that the higher prevalence of T1 abnormalities in our cohort reflects the greater degree of myocardial injury from myocarditis and the presence of early myocardial fibrosis. Alternatively, given the time from initiation of ICI therapy to CMR of ~58 days, there could have been ongoing indolent myocardial inflammation that contributed to the total burden of fibrosis. Therefore, until further studies of CMR parametric mapping techniques are available, our study suggests that it is more likely to identify elevated T1 than elevated T2 values in patients with acute ICI myocarditis. Based on our data, we have proposed a potential approach to using CMR to assess patients with suspected ICI myocarditis (Central Illustration). However, this will require further validation.

Approximately 30% to 40% of patients with ICI myocarditis develop MACE, with a mortality that ranges from 15% to 25% (1-3,13). Therefore, robust prognostic markers are necessary to guide corticosteroid dosing, the need for intensification of immunosuppression beyond corticosteroids, the duration of immunosuppression, the frequency of cardiac monitoring, and the potential reinitiation of ICI therapy (32). Previously identified prognostic measures in these patients include elevated troponin levels (13) and lower echocardiography global longitudinal strain (14). In prior work, neither LGE nor T2-weighted imaging was prognostic for MACE. In this study, T1 values had good discriminatory and prognostic value for subsequent MACE, with 100% of the

MACE occurring in patients with abnormal T1 values. This association remained significant even after adjusting for relevant covariates and the presence of LGE. Although T2 values were also associated with MACE, this lost significance after adjusting for cardiovascular risk factors and LVEF. Other than a small sample size, one potential rationale for the lack of independent relationship with T2 values may relate to the challenges of reliably measuring the extent of inflammation or edema in this patient population as described previously. Alternatively, T2 changes may demonstrate reversible edema that may not be as prognostically important as changes in T1, and the latter, based on the subgroup with pathology, seems to relate to myocardial injury and fibrosis. This may be the rationale for the presence of an independent relationship between T1 values and MACE. It is also possible that the presence of elevated T1 reflects a pre-existing underlying cardiomyopathy, differences in cardiovascular risk factors, or cancer treatment that may have driven prognosis. However, we did not identify such differences in these factors between patients with and without elevated T1 values.

There are limited prior data on the prognostic value of T1 and T2 mapping in patients with non-ICI myocarditis (33). In a single-center study of 46 patients, elevated T2 values >4 SD above the mean and a T2 time >80 ms had an odds ratio of 6.3 (95% CI: 1.2 to 24.9) and 4.9 (95% CI: 1.1 to 18.9), respectively, for MACE and hospitalization for heart failure. However, owing to the use of different sequence and scanner techniques, average T2 values in the patients with myocarditis in that study were 68.1 ms, which is markedly higher than the average value in our patients with ICI myocarditis (~56 ms) (11). This may reflect differences in the mechanisms and degree of myocardial injury or alternatively the use of steroids prior to CMR in our patients. Furthermore, T2 values were based on average of 3 slices as compared with a single slice in our study. In a separate larger study of 670 patients with acute or subacute non-ICI myocarditis, 179 patients had ECV measurements. Every 10% increase in ECV was associated with a hazard ratio of 2.09 (95% CI: 1.07 to 4.08) and 3.93 (95% CI: 1.11 to 13.86) for MACE and death respectively (34,35). Unfortunately, we did not have an adequate number of patients with ECV values to assess its prognostic value.

STUDY STRENGTHS AND LIMITATIONS. Strengths of this study include a relatively large sample size of patients with ICI myocarditis, with ~45% of the patients having histopathology and CMR data providing

a unique opportunity to determine associations. However, this was a retrospective multicenter study and institutional standards were employed, with a non-prespecified CMR protocol, different magnet strengths, and local site reads. To address this limitation and enable a combined analysis, including data from all centers, respective data were translated into *z*-scores. Although *z*-scores are recommended by the Society of Cardiovascular Magnetic Resonance for clinical routine (20), they can be challenging to comprehend. Therefore, we also divided and analyzed our cohort based on site, CMR vendor, and field strength normal and abnormal T1 and T2 values defined as mean + 2 SD (20). We used T1 and T2 measurements obtained at the individual sites as opposed to a core-lab read. Although this may contribute to interobserver variability, we believe that this pragmatic approach adds to the strength and clinical relevance of our findings. Additionally, we only had a single short-axis slice to measure T1 and T2 values. Furthermore, the majority of our patients received corticosteroids prior to their CMR study. Therefore, it is possible that with a CMR performed prior to corticosteroids or immunosuppression, more complete imaging of the myocardium (i.e., multiple slices), and consideration of regional changes in T1 or T2 values, the diagnostic yield of these approaches may be higher. However, prior studies in non-ICI myocarditis suggest that a single slice provides similar diagnostic accuracy to multiple slices (36). Furthermore, there are no data to suggest that ICI myocarditis is regional. Although this is the largest report of T1 and T2 mapping in ICI myocarditis, the statistical power is still likely limited, and thus the lack of stronger association between T2 mapping and MACE needs to be tested in future studies. One set of our multivariable models included 5 variables. This may result in overfitted models; however, we chose to adequately adjust for confounders, given that these are association models (37). Finally, we also did not have patients with negative biopsies to allow the calculation of sensitivity and specificity for T1 and T2 mapping for the diagnosis of ICI myocarditis.

CONCLUSIONS

In patients with ICI myocarditis, elevated native T1 values were more common than elevated T2 values. Patients with higher native T1 values had signs of greater myocardial injury. Using the modified Lake Louise Criteria, the nonischemic myocardial injury

criteria were seen almost uniformly in our patients, with only 53% meeting the edema criteria. Although the latter was higher than the prevalence of abnormalities on qualitative T2-weighted imaging in our prior work (2), it still appears that it is best to rely on the presence of nonischemic myocardial injury for the diagnosis of ICI myocarditis. In follow-up, higher T1 values, but not T2 values, were independently associated with MACE. Overall, the CMR-measured myocardial native T1 value was the most robust parameter to identify myocarditis and its prognosis in patients receiving ICI therapy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: The vast majority of patients with myocarditis associated with ICI chemotherapy undergoing CMR with T1 and T2 mapping satisfy the modified Lake Louise Criteria for nonischemic myocardial injury. Higher myocardial T1 values are associated with more severe myocardial injury and a higher risk of MACE.

TRANSLATIONAL OUTLOOK:

Further studies are needed to fully characterize and improve the diagnostic performance of CMR mapping for diagnosis of ICI-associated myocarditis.

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KEY WORDS cardiovascular magnetic resonance, immune checkpoint inhibitor, Lake Louise Criteria, major adverse cardiovascular event, myocarditis, T1 mapping, T2 mapping

APPENDIX For an expanded References section and supplemental tables, please see the online version of this paper.