**Cardiovascular Magnetic Resonance in Immune Checkpoint Inhibitor-associated Myocarditis**

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**Total word count**: 4,664 words

**Abstract**

**Aims** Myocarditis is a potentially fatal complication of immune checkpoint inhibitors (ICI). Sparse data exist on the use of cardiovascular magnetic resonance (CMR) in ICI-associated myocarditis. In this study, CMR characteristics, the association between CMR features and cardiovascular events among patients with ICI-associated myocarditis are presented.

**Methods and results** From an international registry of patients with ICI-associated myocarditis, clinical, CMR, and histopathological findings were collected. Major adverse cardiovascular events (MACE) were a composite of cardiovascular death, cardiogenic shock, cardiac arrest, and complete heart block. In 103 patients diagnosed with ICI-associated myocarditis who had CMR, mean left ventricular ejection fraction (LVEF) was 50%, 61% of patients had an LVEF≥50%. LGE was present in 48% of overall, 55% of the reduced EF and 43% of the preserved EF cohort. Elevated T2-weighted STIR was present in 28% of overall, 30% of the reduced EF and 26% of the preserved EF cohort. The presence of LGE increased from 21.6% when CMR was performed within 4 days of admission to 72.0% when CMR was performed on day 4 of admission or later. Fifty-six patients had cardiac pathology. LGE was present in 35% of patients with pathological fibrosis and elevated T2-weighted STIR signal was present in 26% with lymphocytic infiltration. Forty-one patients (40%) had MACE over a follow-up time of 5 months. The presence of LGE, LGE pattern and elevated T2-weighted STIR were not associated with MACE.

**Conclusions** These data suggest caution in reliance on LGE or qualitative T2-STIR-only approach for the exclusion of ICI-associated myocarditis.

**Keywords:** cardiovascular magnetic resonance; immune checkpoint inhibitor; myocarditis.

**One-sentence Summary:**

Patients with ICI-associated myocarditis have many unique features on CMR and LGE and elevated T2-weighted STIR were not associated with cardiovascular outcomes.

**Abbreviations:**

anti-CTLA4 = anti-cytotoxic T-lymphocyte-associated protein 4

anti-PD1 = anti-programmed cell death protein 1

anti-PDL1 = anti-programmed death-ligand 1

BNP = b-type natriuretic peptide

CHB = complete heart block

CMR = cardiovascular magnetic resonance

ECG = electrocardiogram

EMB = endomyocardial biopsy

LGE = late gadolinium enhancement

ICI = immune checkpoint inhibitor

LVEF = left ventricular ejection fraction

MACE = major adverse cardiac events

STIR = short tau inversion recovery

**INTRODUCTION**

Harnessing the power of the immune system has revolutionized cancer treatment.1, 2 Immune checkpoint inhibitors (ICI) are antibodies that block tumor-driven inhibition of T-cell activation and function and facilitate an immune-mediated attack on cancer cells. These therapies are currently approved for a multitude of cancer indications and the use of ICI is rapidly expanding from late stage disease to the first line metastatic and adjuvant settings.3 For context, there are currently 2004 immuno-modulatory agents against 303 targets, from 864 companies in 3042 active clinical trials.4 Myocarditis is an uncommon toxicity associated with ICI with wide incidence varying from 0.1-1%;5, 6 however, reporting of ICI-associated myocarditis has increased, likely due to heightened awareness.7, 8 Myocarditis related to an ICI is generally known to have a fulminant course, with a case fatality rate of 30-50%.9-12 Cardiovascular magnetic resonance imaging (CMR), with the use of tissue characterization techniques such as late gadolinium enhancement (LGE) and the presence of myocardial edema, is the gold-standard non-invasive imaging test for the diagnosis and risk prediction in myocarditis of other etiologies.13-18 Endomyocardial biopsy (EMB) is the diagnostic gold standard for myocarditis; however, it is underutilized due to its invasive nature and associated potential complications (rate 0.3-6%).14, 19 Beyond case reports and small case series, there are sparse data characterizing the use of CMR and correlating with EMB findings in the assessment of ICI-associated myocarditis.20-22 In this study, the largest cohort of ICI-associated myocarditis was leveraged to provide the first data on CMR characteristics, to describe the correlation between CMR findings and histopathology, and to test the association between CMR features with cardiovascular events among patients with ICI-associated myocarditis.

**METHODS**

**Patient cohort**

ICI-associated myocarditis is uncommon and, to provide insight an international multicenter registry of ICI-associated myocarditis from 23 sites across the United States, Canada and Europe (Supplemental Table 1) was established.10 We included consecutive patients who were diagnosed with ICI-associated myocarditis by board-certified cardiologists from the participating sites. The first case in the registry was diagnosed in November 2013, and cases were included in this report until April 2019. The beginning of follow-up was the time of first use of ICI. Patients’ clinical characteristics, CMR features, myocardial biopsy or autopsy data and outcomes were collected by investigators at each study site. 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-associated myocarditis**

ICI-associated myocarditis was diagnosed in one of two ways: 1) standard features present on histopathology;23 or 2) diagnostic criteria for clinically suspected myocarditis based on the European Society of Cardiology (ESC) guideline.14 This standardized diagnostic strategy has been applied to multiple cohorts.24, 25

**Covariates**

Demographics, cardiovascular risk factors, electrocardiograms (ECG), and echocardiograms were extracted from electronic medical records of each study site at the time of the index presentation with myocarditis. Additional covariates included clinical presentation, physical examination, initial and peak cardiac biomarkers, CMR, EMB, and autopsy results. Initial troponin and b-type natriuretic peptide (BNP) were defined as the first measured serum troponin and BNP at time of admission during the index hospitalization. Peak troponin and BNP were the maximum measured troponin and BNP at the index hospitalization. Cancer-specific covariates included the cancer type, ICI treatment, prior cardiotoxic chemotherapy, and prior radiation.

**CMR protocol**

Patients underwent a CMR at the discretion of the local physician at the time of presentation with suspected ICI-associated myocarditis. The CMR protocol was not protocol-specified and thus reflects local practice. In summary, all images were acquired with ECG gating, breath-holding, and the patient in a supine position. Subjects were imaged on either a 1.5-T or 3.0-T CMR system. Each CMR protocol included balanced cine steady-state free precession imaging for cardiac function and mass. The typical slice thickness was 8 mm with no gap. The protocol also included black-blood T2-weighted short tau inversion recovery (STIR) imaging sequences in three short-axis slices and a single long-axis view for qualitative assessment of myocardial edema.26 Qualitative T2-weight STIR signal was evaluated by visual assessment. Where available, the early gadolinium enhancement ratio was acquired in a free breathing spin echo sequence in four identical short-axis slices (basal, mid-basal, mid-apical and apical) both before and within the first 3 minutes after intravenous injection of contrast. Early gadolinium enhancement was defined as enhancement of myocardium divided by enhancement of skeletal muscle in a ratio of greater than or equal to 4.15, 18 The presence of LGE was determined 10-15 minutes after contrast administration using both magnitude and phase-sensitive inversion recovery images. Slices were 8 mm thick with 2 mm gaps. In a subset of patients, T1 measurements and T1 mapping were available (n=15). T1 measurements were performed using a Look-Locker sequence in a single mid-ventricle slice on a 3.0-T CMR system, pre- and post-contrast, as previously described.27 T1 mapping sequences were only performed pre-contrast on a 3-T system using a 5(3)3 MOLLI in a single mid-ventricle slice. The CMR studies was interpreted at each site by experienced readers as part of clinical care. The LGE pattern was categorized as sub-endocardial/transmural; sub-epicardial; mid-myocardial and diffuse.28 If more than one pattern was present, the predominant pattern was reported.

**Histopathology**

Histopathological analysis of cardiac samples obtained by either EMB or postmortem autopsy was reported. The performance of histopathological sampling was not protocol-specified and thus varied per local practice and was performed at the time of presentation with myocarditis (biopsy) or with death from a cardiovascular complication with ICI-associated myocarditis. Typically, at least five biopsies were preferentially taken from the apical septum of the right ventricle (RV); no LV biopsies were performed. The findings were reported by pathologists at each study site according to the 2001 consensus statement on from the Association for European Cardiovascular Pathology.23

**Outcomes**

The primary outcome of interest, major adverse cardiac events (MACE), was a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and complete heart block (CHB) requiring pacemaker. In case where cardiac arrest, cardiogenic shock, or CHB led to a death, that case was counted as a cardiac death. When a patient had multiple MACEs, the time of MACE was defined as the date of the earliest event. Standard definitions were used for cardiovascular death,29 cardiac arrest,30 cardiogenic shock31 and CHB. The end of follow-up was on April 9th 2019.

**Statistical Analysis**

Continuous variables were described as mean ± standard deviation or median (interquartile range) and were compared with the use of Student’s t-tests or Wilcoxon Rank Sum tests, as appropriate based on their normality. Normality of continuous variables was tested using Shapiro-Wilk test. Categorical variables were presented as percentage and were compared using the Chi-squared test. The overall agreement and the Cohen’s kappa coefficient between the site read and a blinder reviewer for LGE and T2-weighted STIR assessment were assessed. Covariates were compared between patients with and without LGE. Univariable and multivariable (adjusting for age, sex, number of cardiovascular risk factors, and lowest left ventricular ejection fraction (LVEF)) Cox proportional hazards models were performed to examine the association of CMR and histopathology features with MACE. Harrell’s C-statistics was obtained to assess the performance of the survival models.32 Sensitivity analysis was performed by adding study sites in the multivariable adjusted Cox proportional hazards models. Kaplan-Meier curves for MACE by LGE, myocardial edema and pathological fibrosis were presented and compared with the Logrank test. A 2-sided P value <0.05 was considered significant. Analyses were performed with Stata15 (StataCorp, College Station, Texas).

**RESULTS**

**Patient Characteristics**

All 103 ICI-associated myocarditis patients in the registry through April 9th, 2019 who had a CMR were included. Of these 103 patients, 56 patients were diagnosed with endomyocardial biopsy or autopsy and 47 were diagnosed using the ESC diagnostic criteria for clinically suspected myocarditis (Supplemental Table 2).14 The mean age was 65.6 ±15.3 years and 29.1% were female (Table 1). More than half of the patients presented with shortness of breath. Other common symptoms included chest pain,33 orthopnea, paroxysmal nocturnal dyspnea and fatigue (Table 2). At the time of presentation, obstructive coronary artery disease was excluded in 65 patients using coronary angiography, 16 patients by coronary computed tomography angiography and 16 patients by stress test with imaging (nuclear stress test or stress echocardiography). The 6 patients without an ischemia evaluation all had pathology-proven myocarditis (Supplemental Table 2).

**Cancer and Treatment Characteristics**

The most common indications for ICI were melanoma and non-small cell lung cancer (Table 1). All cases with ICI-associated myocarditis had ICI permanently discontinued. Most patients (71.8%) received ICI monotherapy and, among them, 90.5% had anti-programmed cell death protein 1 (anti-PD1) therapy (including nivolumab and pembrolizumab), 8.1% had anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4) therapy (including ipilimumab and tremelimumab) and 1.4% had anti-programmed death-ligand 1 (anti-PDL-1) therapy (including avelumab and atezolizumab). Dual ICI therapy was used in 28.2% of patients (Table 1).

**CMR Characteristics**

A 1.5-T scanner was used in 81 patients and a 3.0-T scanner in 22 patients. The mean LVEF, LVEDV, LV mass index were 49.1%, 147.0 ml and 72.4 g/m2, respectively (Table 2). A trivial or small pericardial effusion was noted in 19 patients (23.5%) (Table 2). In total, 40 patients (38.8%) had an LVEF of <50% and 63 patients (61.2%) had EF of ≥50% (Figure 1A). LGE was present in 49 patients (47.6%) of the entire cohort, 42.9% of cases with a preserved LVEF and 55.0% of cases with a reduced EF (Figure 1A). The predominant LGE pattern included sub-endocardial/transmural (3), sub-epicardial (13), mid-myocardial (24) and diffuse (9) (Figure 2). In the 14 patients with history of CAD before starting ICI, including 5 patients with prior myocardial infarction, 4 patients with prior coronary stenting, 6 patients with prior coronary artery bypass grafting (not mutually exclusive), 8 had LGE; with a sub-epicardial pattern in 2 patients, mid-myocardial in 4 patients and diffuse pattern in 2 patients. We did not find difference in history of CAD in patients with (17.4%) or without LGE (12.2%, relative ratio (RR)=1.4, 95% CI 0.5, 3.8, P=0.568). LGE was predominantly distributed at the anteroseptal, inferoseptal, inferior and inferolateral segments (Supplemental Figure 1A). Two of the three patients with sub-endocardial/transmural pattern had pathology-proven myocarditis. The third patient had LGE in multiple distributions (apical, apical anterior, and apical lateral segments), no obstructive coronary artery disease and a clinical presentation consistent with myocarditis. Qualitative myocardial edema by T2-weighted STIR was present in 28 patients (27.5%), in 30% of the reduced EF and 26% of the preserved EF cohort. Elevated T2-weighted STIR signal was predominantly distributed at the anteroseptal, inferoseptal, and inferior segments (Supplemental Figure 1B). Eighteen patients had both LGE and elevated T2-weighted STIR signal, 31 patients had LGE and no elevated T2-weighted STIR signal, 10 patients had elevated T2-weighted STIR signal and no LGE, and 43 patients had neither elevated T2-weighted STIR signal or LGE (Figure 1A). Patients with LGE more often had elevated T2-weighted STIR signal (36.7%) than patients without LGE (18.9%, RR=2.0, 95% CI (1.0, 3.9), P=0.037). In 44 randomly selected patients, the overall agreement between the site read and a blinder reviewer was 0.97 for LGE assessment and 0.95 for T2-weighted STIR assessment. The Cohen’s kappa coefficient was 0.94 for LGE assessment and 0.85 for T2-weighted STIR assessment.

The early gadolinium enhancement ratio was available in a subset of patients and was normal (n=15, mean 2.8±0.6). Fifteen patients underwent T1 measurements or T1 mapping. The mean native T1 value in these 15 patients was 1167.2 ± 32.9ms, higher than the normal T1 value at the institution (1100-1150ms on 3T; 1000-1100ms on 1.5T). The native T1 was similar between patients with and without LGE (1174.3 ± 34.1 vs 1162.4 ± 33.2ms, P=0.513, Table 2). The extracellular volume (ECV) was measured in 8 patients with mean value at 34.3 ± 2.1%, higher than normal ECV values of 25.3 ± 3.5% in healthy individuals.34 We did not find difference in ECV between patients with (34.5% ± 1.9%) and without LGE (34.0% ± 2.6%, difference 0.1% (-0.5%, 0.8%), P=0.766) (Table 2).

The demographics, clinical presentation, cancer characteristics and outcomes were similar between patients with and without LGE (Table 1 and Table 2), except that patients with LGE were more likely to have non-small cell lung cancer (22.5 vs 7.4%, P=0.048) and had higher levels of troponin T on admission (1.0 vs 0.4 ng/mL, P=0.021). The characteristics of patients who did (n=103) and did not (n=39) have a CMR were mostly similar (Supplemental Table 3 and 4). However, the percentage of patients with prior heart failure, renal cell carcinoma, the presence of shortness of breath were higher in patients who did not undergo a CMR. Diastolic blood pressure and follow-up time were greater in patients who underwent a CMR. The characteristics of patients diagnosed by the ESC criteria (n=68) and by histopathological criteria (n=74) were also compared (Supplemental Table 5 and 6).

**Histopathology Features**

Among the 103 patients with a CMR, 56 patients had histopathology data available, either through EMB (46) or autopsy (10), all of which were consistent with myocarditis (Figure 1B). In these pathology-proven patients, analysis reported a lymphocytic infiltration in 55 patients (98.2%), among whom 21 patients (38.2%) had LGE and 14 patients (25.5%) had elevated T2-weighted STIR signal. Thirty-one patients had pathological fibrosis, among whom 11 patients (35.5%) had LGE. A representative case of pathology-proven ICI-myocarditis with normal LGE and normal T2-weighted STIR images is presented in Supplemental Figure 2. Additionally, two representative cases from patients with an autopsy showing diffuse myocarditis in every segment but with normal LGE and normal T2-weighted STIR images are presented in Supplemental Figure 3.

**Time from Admission to CMR**

To better understand the CMR findings, the association between time from onset of myocarditis to CMR and CMR findings was tested. The time of admission with suspected myocarditis was used as a surrogate of time of symptom onset. Specifically, the time (in days) from admission to CMR in those with and without LGE was compared. The time from admission to CMR was longer in patients with LGE (median time 6 days), compared to patients without LGE (median time 2 days, P<0.001) (Table 3). The Locally Weighted Scatterplot Smoothing method was performed to graphically demonstrate the relationship between the time from admission to CMR and the presence of LGE (Figure 3).35 The presence of LGE varied with the time from admission to CMR. When a CMR was performed on day 4 of admission or later, LGE was present in 72.0% of patients. Whereas, when a CMR was performed within 4 days of admission, LGE was only present in 21.6% of patients (P<0.001, Table 3). Performing a CMR on day 4 of admission or later was significantly associated with the presence of LGE (odds ratio=9.35, 95% CI 3.77, 23.21, P<0.001). The time from admission to CMR was not different in patients with (median 4 days) or without (median 3 days) elevated T2-weighted STIR signal (P=0.877). Those patients with positive pathological fibrosis, but negative LGE, had a longer time from admission to biopsy (median time 11 days), but a shorter time between admission to CMR (median time 2 days).

**Major Adverse Cardiovascular Events**

During a median follow-up time of 148.5 days, 41 patients (39.8%) developed MACE. The presence of LGE, LGE pattern, elevated T2-weighted STIR signal on CMR, and pathological fibrosis at the time of diagnosing ICI-associated myocarditis were not associated with MACE as their hazard ratios were not statistically significant (Table 4) and Kaplan–Meier curves by subgroups overlapped with each other with Logrank test P>0.05 (Figure 4). In a multivariable model, a reduced EF was significantly associated with higher risk of MACE (hazard ratio 2.07, 95% CI 1.10-3.93, P=0.025) (Table 4). The results of univariable Cox proportional hazard model were similar (Table 4). Sensitivity analysis by adding study site as a covariate did not change the results meaningfully.

**DISCUSSION**

There are increased reports of myocarditis related to ICI and this condition may be fulminant with a mortality rate of 20-50%.6, 10 Our understanding of ICI-associated myocarditis needs to improve as these revolutionary therapies are being increasingly applied to a broader range of cancers and to cancers in earlier stage. CMR is the gold-standard imaging test for the diagnosis of myocarditis and this real-world study is the first to describe the use of CMR in the largest international multicenter cohort of ICI-associated myocarditis. The study reports the following important and novel findings: 1. More than half the cases presented with a preserved EF; 2. LGE was present in less than half of patients with ICI-associated myocarditis, and less among those with a preserved EF; 3. Qualitative myocardial edema by T2-weighted STIR was present in less than one third of patients; 4. Varying pattern of LGE was noted including sub-endocardial/transmural, sub-epicardial, mid-myocardial and diffuse; 5. The time from admission to CMR affected the likelihood of LGE such as the presence of LGE increased from 21.6% when CMR was performed within 4 days of admission to 72.0% when a CMR was performed on day 4 of admission or later; 6. The presence of LGE or an increase in qualitative T2-weighted STIR signal was not associated with subsequent major adverse events; 7. The correlation between LGE and pathological fibrosis and between myocardial edema by T2-weighted STIR and lymphocytic infiltration was, at best, modest. Strengths of the current study include the comparatively large sample size of patients with ICI-associated myocarditis and the large subset having both histopathology and CMR data which enabled the unique opportunity to dissect the relationship between LGE and pathological fibrosis in ICI-associated myocarditis.

The strengths of CMR for the diagnosis of myocarditis reside in its excellent spatial resolution and, more importantly, its ability to provide tissue characterization.13, 14, 17, 36, 37 Thus, appropriately, CMR is a primary cardiac imaging modality recommended for the evaluation of patients with suspected myocarditis.16, 17 Beyond research letters and case reports, there are limited data on the use of CMR for the diagnosis of ICI-associated myocarditis and no data comparing CMR to histopathological findings.20 In the current analysis, LGE was present in less than 50% of cases with ICI-associated myocarditis, and 42% of cases had neither LGE nor an elevated T2-weighted STIR signal. In a research letter with 15 patients with ICI-associated myocarditis who underwent a CMR, Escudier and colleagues noted LGE among 23% of patients and qualitative edema among 33% of patients.20 The rate of LGE and qualitative edema by T2-weighted STIR is far lower than that reported for acute myocarditis not related to ICI.16, 17, 38 For example, in a study with 374 patients with acute myocarditis not related to ICI, LGE was noted in 93% of patients and signs of myocardial edema by T2-weighted STIR were noted in 94% of patients.17 Similarly, Mahrholdt et al. reported that 95% of patients (83/87) diagnosed with active myocarditis had LGE.38 An important strength of this paper is the presence of pathology-proven myocarditis cohort which noted similar results to the larger cohort. Specifically, 56 of our patients had both a CMR and histopathological analysis of the heart and parallel findings were noted where LGE was present in 39% and elevated T2-weighted STIR signal was present in 25% of patients with pathology-proven myocarditis.

To understand the absence of LGE in patient with myocarditis, factors associated with the presence of LGE were tested. Clinical and imaging parameters were similar in patients with or without LGE. Initial troponin T levels were higher in patients with LGE, suggesting more myocardial damage may prompt the presence of LGE on a CMR. The association between the timing of the CMR study and the presence of LGE was tested. Time of onset of symptoms was not used because while many patients had new cardiovascular symptoms, some had vague symptoms. Patients usually had a troponin and/or EKG performed due to these vague symptoms and these abnormal tests triggered the admission. When a CMR was performed on day 4 of admission or later, the presence of LGE increased from 21.6% to 72.0%. Myocardial fibrosis/scar, reflected by LGE, is considered a subacute or chronic sequel of myocardial inflammation in myocarditis, thus it may take some time for myocardial fibrosis to develop and accumulate before becoming detectable on CMR or biopsy. This finding of a relationship between onset of myocarditis and the presence of fibrosis has also been noted in animal studies of myocarditis. Specifically, in a murine model of viral myocarditis, myocardial fibrin deposition first appeared on day 3 after infection, and myocardial fibrosis was not detectable until day 14 after infection.39 In experimental autoimmune myocarditis rat model, LGE was detected in 3 out of 15 rats at 2 weeks after immunization and LGE was detected in 5 of 8 rats at 5 weeks after immunization.40 However, due to the retrospective nature of the registry, the timing of CMR was determined by treating physicians and was likely affected by the severity of presentation and availability of the test and none of the patients underwent serial CMR. Thus, these results generated a hypothesis that the time might affect the presence of LGE in patients with ICI-associated myocarditis and future prospective studies are warranted to test this hypothesis. The finding of a limited association between CMR and histopathology was also consistent among pathology-proven cases. In the current cohort (and illustrated in the case), CMR was typically performed early (median time 2 days) and the histopathology was typically performed later (median time 11 days) in patients with negative LGE and positive histopathological fibrosis. The current results suggest performing CMR later in the clinical course (≥ 4 days) could potentially improve its diagnostic performance. However, delays in the diagnosis and treatment are not recommended as these delays are likely to have clinical importance. Specifically, in a prior report of 35 cases, earlier treatment of suspected cases was associated with a trend toward a lower rate of MACE.10

These findings indicate that, in clinically suspected ICI-associated myocarditis, the absence of LGE or the absence of increased T2-weighted STIR signal on a CMR does not exclude the potential diagnosis and, until our understanding improves and until future research offers insights into the role of T1, T2 mapping and calculation of the ECV, an EMB should still be pursued when clinical suspicion remains after a normal CMR. In addition, it is known that T2-weighted STIR method offers limited sensitivity.41 LGE and T2-weighted STIR imaging are dependent on local variations in fibrosis or inflammation to become qualitatively apparent. Therefore, CMR techniques sensitive to myocardial inflammation and edema, such as T1, T2 mapping and calculation of the ECV can be instrumental to identify early changes in myocardium before LGE appears. The native T1 value and ECV of patients with ICI-associated myocarditis appeared to be higher than normal values based on a small subset of our patients. Future studies on T1 mapping and T2 mapping with standard protocol and a large sample size are warranted.

Histopathology has been reported in a small number of cases with ICI-associated myocarditis.6, 20 In the study by Escudier et al., lymphocytic infiltration was found in 8 of 9 patients. In the current study, a lymphocytic infiltration was shown in 98% of patients, while fibrosis was found in 55% of 56 patients who underwent histopathology analysis. Subclinical ICI-associated myocarditis cases have also been reported.22, 42 For example, in a case of metastatic melanoma treated with ipilimumab and nivolumab, cardiac involvement was clinically unapparent, but patchy fibrosis and diffuse mononuclear infiltrates of myocardium was found in postmortem autopsy.42 Given the potential of subclinical presentations, the lack of LGE in more than 50% of patients, the presence of characteristic histopathological findings with a normal troponin, it is reasonable to hypothesize that ICI-associated myocardial injury remains underrecognized and underdiagnosed.43

Outcomes with ICI-associated myocarditis are significantly worse than myocarditis in broad populations. In this cohort, 40% of patients developed MACE and 16.5% of patients had a cardiovascular death during a median follow-up time of about 5 months. By contrast, among 670 patients admitted to hospital with myocarditis regardless of etiology, MACE occurred in 15% of patients and death occurred in 4% of patients during a median follow-up time of 4.7 years.16 This several-fold increase in MACE in a very short period highlights the fulminant nature of ICI-associated myocarditis. However, the predictors of such a marked increase in adverse outcomes with ICI-associated myocarditis are not well characterized. In contrast to studies among patients with non-ICI myocarditis, the presence of LGE was not found to have prognostic significance.16, 17 There are several possible reasons for this discrepancy. First, LGE was only present in less than 50% of patients and, had the CMR been performed later, there would likely have been more patients with LGE and had an improved statistical power to assess the association between LGE and outcomes. Second, the follow-up time was much shorter (5 months) compared to other studies on prognostic performance of LGE (4-5 years).16, 17, 36 Thus, future studies with larger sample size, a longer follow-up time, should outcomes be improved, and better characterization of LGE are warranted.

**Limitations**

However, results of the present study should be interpreted in context. This was a retrospective study and institutional standards were employed. CMR protocol was not pre-specified and CMR was read at local sites. Thus, this study is hypothesis-generating and may have unmeasured confounding caused by different practice pattern and variation between readers. Additional CMR sequences such as T1 mapping, T2 mapping and measurement of the ECV, which have additive value in non-ICI myocarditis,15, 18 and in patients at risk of cardiovascular toxicities from cancer therapy,44 were not routinely performed. However, these results reflect CMR practice in real-life clinical settings and reflect the difficulties in describing an evolving disease. These findings will reflect the next stage of this iterative process, where these data have provided the basis for discussions on disease-specific standardization of imaging and non-imaging protocols. In addition, T2-weight STIR imaging was performed in three short-axis slices and a single long-axis view, instead of whole short-axis stack. EMB was taken from the apical septum of the RV; no LV biopsies were performed. However, due to the diffuse inflammatory nature of ICI-associated myocarditis as seen in the autopsy samples, it is possible that the possibility of missing the diagnosis by RV biopsy is less. While limited, 2 CMR/autopsy overlaps were provided and there was pathological myocarditis noted at sites where both the LGE and the black-blood imaging were normal (Supplemental Figure 3). It is unclear how our registry presents the broader population with ICI myocarditis. Some of the early cases may be missed due to atypical presentation, reliance on LGE-based approaches and limited awareness. However, as insight has improved over time, we believe that those included in more recent years are generalizable to the broad population with ICI-associated myocarditis. The data collection protocol was standardized but the definitions for such features as clinical symptoms and physical exam findings (e.g. JVD) were not standardized. Therefore, it is important to acknowledge that there is likely variability between investigators and sites which limited these findings. Lastly, the statistical power is likely limited due to the modest sample size, thus the lack of association between CMR and EMB features and MACE needs to be tested in future studies with a larger sample size.

**CONCLUSIONS**

In this study, the CMR and histopathology features of ICI-associated myocarditis are presented. LGE is present in more than 80% of patients with non-ICI myocarditis; in contrast, LGE is present in less than 50% of patients with ICI-associated myocarditis. Increased time between clinical presentation and CMR is associated with greater detection of LGE; however, delays in diagnosis are not recommended as delayed treatment in ICI-associated myocarditis may be associated with an increase in MACE.10 These data suggest caution if using an LGE or qualitative T2-weighted STIR imaging-only approach to diagnose or exclude ICI-associated myocarditis, especially among the majority of patients who have a normal EF, and suggest that when there is a clinical suspicion of myocarditis, a biopsy be strongly considered in those with a negative CMR using the sequences applied in this study especially while future studies determine if alternative CMR techniques such as T1 and T2 mapping offer improved diagnostic and prognostic value.

**Acknowledgements: None.**

**Sources of Funding:**

This work was supported by the Sarnoff Cardiovascular Research Foundation to Dr. S. S. Mahmood. Dr. R.J. Sullivan was supported, in part, through the National Institutes of Health (NIH)/ National Cancer Institute (NCI) (RO1CA229851, UH2CA207355, RO1CA193970). Dr. C.L. Chen, and Dr. D. Gupta were supported, in part, through the National Institutes of Health (NIH)/ National Cancer Institute (NCI) P30CA008748. Dr. P. Thavendiranathan was supported, in part, through the Canadian Institutes of Health Research New Investigator Award (FRN 147814). Dr. C.G. Tocchetti was supported by a Ricerca di Ateneo/Federico II University grant. Dr. T.G. Neilan was supported, in part, through the Kohlberg Foundation, NIH/NHLBI (1RO1HL130539-01A1, 1RO1HL137562-01A1, and K24HL113128–06), and NIH/Harvard Center for AIDS Research (P30 AI060354).

**Disclosures:** Dr. Mahmood has received consultancy fees from OMR Globus, Alpha Detail, and Opinion Research Team. Dr. Nohria has received research support from Amgen; and has been a consultant for Takeda Oncology. Dr. Heinzerling has received consultancy, advisory board, and speaker fees from MSD, BMS, Roche, Novartis, Amgen, and Curevac. Dr. Sullivan has been a consultant to Merck and Novartis. Dr. Moslehi has served as a consultant/advisor for Novartis, Pfizer, Bristol-Myers Squibb, Takeda/Millennium, Ariad, Acceleron, Vertex, Incyte, Rgenix, Verastem, Pharmacyclics, StemCentRx, Heat Biologics, Daiichi-Sankyo, and Regeneron. Dr. Groarke has received research support from Amgen. Dr. Neilan has received advisory fees from Parexel, BMS, H3 Biomedicine, Aprea Therapeutics and Intrinsic Imaging. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**Figure Legends:**

Figure 1. Patient Cohort of ICI-associated Myocarditis.

CMR = cardiovascular magnetic resonance; ICI = immune checkpoint inhibitor; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; STIR = short tau inversion recovery.

Figure 2. Representative LGE Pattern.

Representative late gadolinium enhancement (LGE) images from patients with ICI-associated myocarditis, showing a patient with no LGE (A); a patient with sub-endocardial/transmural LGE (B); a patient with sub-epicardial LGE (C); a patient with mid-myocardial LGE (D); a patient with diffuse LGE (E); a patient with mixed LGE (sub-epicardial, mid-myocardial and transmural) (F). Regions of LGE are highlighted using white arrows.

Figure 3. Locally Weighted Scatterplot Smoothing method demonstrating the relationship between the time from admission to CMR and the presence of LGE.

CMR=cardiovascular magnetic resonance; LGE=late gadolinium enhancement.

Figure 4. Kaplan-Meier curves for major adverse cardiovascular events by late gadolinium enhancement (A), T2-weighted STIR imaging for edema (B) and pathological fibrosis (C).

LGE = late gadolinium enhancement.

Take home figure. Proposal Algorithm for Diagnosing Immune Checkpoint Inhibitor-associated Myocarditis.