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Cardiovascular Magnetic Resonance Imaging Features and Prognostic Value in Immune Checkpoint Inhibitor-Induced Myocarditis

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ABSTRACT

Objectives: We sought to analyze the cardiovascular magnetic resonance imaging (CMR) features of immune checkpoint inhibitor (ICI)-induced myocarditis (ICI-M) and to explore their prognostic value.

Background: ICI-M is an emerging and severe complication of cancer treatment, for which diagnosis and risk stratification are challenging.

Methods: In this case-control multicenter study, the clinical, biological, and CMR findings (including late gadolinium enhancement [LGE], T1/T2 mapping, and extracellular volume fraction [ECV] values) of adults with ICI-M (n=33) were compared with those of two other groups, including cancer patients without myocarditis scheduled to receive ICIs (w/o-M, n=21) and patients with non-ICI-induced myocarditis (NI-M, n=85). As secondary objective, we explored the potential value of LGE and T1/T2/ECV for predicting major adverse cardiovascular events (MACE) in ICI-M patients.

Results: Compared with w/o-M, the global native T1, ECV, and T2 z-scores were significantly higher in ICI-M ($p<0.001$ for T1, $p=0.03$ for ECV, and $p=0.004$ for T2). LGE was more frequently observed in ICI-M than in w/o-M (82% *vs.* 9%, $p<0.001$). No significant difference was found between ICI-M and NI-M in terms of the global native T1, ECV, and T2 z-scores. LGE was less frequent in ICI-M (82% *vs.* 100%, $p<0.001$) but was more likely to involve the midwall layer ($p<0.001$) and septal segments ($p<0.001$) than in NI-M.

For ICI-M patients, septal LGE was the only CMR predictor of MACE even after adjustment for magnitude of increase in peak troponin I or T (adjusted hazard ratio, 2.66; 95% CI, 1.06-6.66; $p=0.03$).

Conclusions: Immune checkpoint inhibitor-induced myocarditis demonstrates differences in LGE prevalence, pattern, and localization in comparison with NI-M. Septal LGE may be a predictor of poor prognosis in ICI-M patients.

KEY WORDS

myocarditis; cardiovascular magnetic resonance; cardio-oncology; immune checkpoint inhibitor; Lake Louise Criteria

CONDENSED ABSTRACT

This multicenter study sought to analyze the cardiovascular magnetic resonance imaging (CMR) findings of immune checkpoint inhibitor (ICI)-associated myocarditis (ICI-M). The CMR results of 33 patients with ICI-M were compared to those of 85 patients with non-ICI-induced-myocarditis (NI-M) and to 21 cancer patients without myocarditis scheduled to receive ICIs. Significant differences between the groups were observed, allowing the identification of ICI-M features. In particular, late gadolinium enhancement was less frequent in ICI-M than in NI-M but more often involved the midwall myocardial layer and septal segments. This septal involvement was associated with a worse cardiovascular prognosis in ICI-M patients.

ABBREVIATIONS AND ACRONYMS

CMR = cardiovascular magnetic resonance

ECV = extracellular volume fraction

ICI = immune checkpoint inhibitor

ICI-M = immune checkpoint inhibitor-induced myocarditis

LGE = late gadolinium enhancement

MACE = major adverse cardiovascular events

NI-M = non-immune checkpoint inhibitor-induced myocarditis

TTE = transthoracic echocardiography

w/o-M = without myocarditis

INTRODUCTION

Immune checkpoint inhibitor (ICI)-induced myocarditis (ICI-M) is one of the most serious cancer treatment-related toxicities (1–4). By reactivating the immune response against the tumor, ICIs can lead to numerous immune-related adverse events, including ICI-M. Although uncommon (5), the case-fatality rate of this cardiovascular event is dramatically high, approximately 30% to 50% (5,6), and early administration of corticosteroids is required to improve the prognosis (7). Therefore, we need better knowledge of the features of this emerging cardiovascular disease to improve our ability to provide an accurate diagnosis and modify the management of patients.

Endomyocardial biopsy (EMB) is the gold standard for the diagnosis of myocarditis but is not systematically employed because of its potential complications and low sensitivity (8). Cardiovascular magnetic resonance imaging (CMR) is now considered the best noninvasive imaging modality for the diagnosis of non-ICI-induced myocarditis (NI-M) based on the Lake Louise (LL) criteria, which identify myocardial abnormalities, including global or regional nonischemic injury and edema (9). Initially established in 2009, the LL criteria were updated in 2018 to incorporate the latest CMR techniques, including myocardial T1 and T2 mapping and extracellular volume fraction (ECV) quantification (10). In addition, CMR has prognostic value based on late gadolinium enhancement (LGE) presence, locations, and patterns (11–13). Very few data exist on CMR findings and predictive value in ICI-M. Recently, two retrospective studies investigated the results of CMR in patients with ICI-M (14–15). They found notably that (i) LGE was present in less than half of the patients, with a predominant distribution in anteroseptal, inferoseptal, and inferolateral segments (14); (ii) and the native T1 value measured in the mid septal wall could be a predictor of major adverse cardiovascular events (MACE) (15). However, these studies were unable to strictly conclude that the CMR abnormalities observed were only due to myocarditis because of the lack of a cancer patients

control group. Indeed, cancer patients treated with ICIs usually have concurrent cardiovascular risk factors, coronary artery disease, and previous chemo- or radiotherapy that may induce myocardial injury (16). Moreover, the T1 and T2 values were measured only in the septal region (15), whereas an increase in these parameters in other segments or in the whole left ventricle could have been a major LL criterion. Finally, a substantial number of MACE were collected while they occurred between first ICI administration and the CMR day.

Therefore, the primary objective of our study was to describe the CMR features of ICI-M by comparing them to those observed in cancer patients without myocarditis prior their first ICI therapy (w/o-M), and to identify whether these findings differed from those of NI-M. The secondary objective was to analyze of the potential CMR findings that could predict MACE in ICI-M patients.

METHODS

Study population

This case-control comparative study took place in two tertiary university French hospitals with cardiology departments specializing in cardio-oncology. The study was approved by the local ethics committee (RGPD/APHM 2020-132), and informed consent was obtained from all patients.

ICI-M and NI-M groups

We reviewed the electronic medical records of adults with a diagnosis of acute myocarditis (ICD-10 diagnosis code: I40) from May 2017 to January 2020. Eligible patients were adults with the diagnosis based on the European Society of Cardiology (ESC) guideline-scoring system, which incorporates clinical, biomarker, and imaging variables (17). Briefly, acute myocarditis was clinically suspected if ≥1 clinical presentation criterion and ≥1 diagnostic criterion from different categories (ECG, troponin, cardiac imaging) were met in the absence

of (i) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%) or (ii) known preexisting cardiovascular disease or extracardiac causes that could explain the syndrome. If the patient was asymptomatic, ≥2 diagnostic criteria had to be met. Acute myocarditis was also diagnosed through standard histological features present on EMB (18). In the two centers, the policy was to perform EMB only in cases of diagnostic discrepancy for hemodynamically unstable patients (two patients in this study). For the patients treated with ICIs and fulfilling the ESC criteria, the diagnosis of ICI-M was retained only if they had a definite or probable cancer therapeutic-related myocarditis according to the Bonaca criteria (19). Regardless of the myocarditis group, the CMR diagnosis was based on the main 2018-LL criteria, including imaging of myocardial edema (global or regional increase in myocardial native T2 relaxation time or T2 signal intensity) and nonischemic myocardial injury (global or regional increase in myocardial native T1 relaxation time or ECV or regional LGE signal increase) (10). All patients, including those who were treated with ICIs, had undergone systematic viral serology and autoantibody testing as well as coronary imaging (angiography or computed tomography). Patients with systemic disease (lupus, amyloidosis, or sarcoidosis) and a history of cardiomyopathy were excluded. Patients who had not undergone CMR or had unsuitable images (image artifacts, incorrectly orientated plane acquired) were also excluded.

w/o-M group

Cancer patients without myocarditis and scheduled to receive ICIs constituted the w/o-M group. It was derived from a prospective cohort study approved by the local ethics committee (NCT03313544). After giving written consent, cancer patients underwent clinical evaluation, ECG examination, biological tests (troponin, natriuretic peptides, C-reactive protein), and CMR within two weeks before the first infusion of ICI therapy.

Data collection

Demographics, cardiovascular risk factors, symptoms, ECG, transthoracic echocardiography, and laboratory testing (including leukocytes, C-reactive protein, peak brain natriuretic peptide (BNP) or N-terminal prohormone of BNP (NT-pro-BNP), thyroid stimulating hormone (TSH), peak high-sensitivity (hs)-troponin T or I, and histologic results were extracted from electronic medical records; cancer-specific covariates including the cancer type and ICI treatment and time of introduction were also extracted.

CMR acquisition, protocol, and analysis

All CMRs were performed on a 1.5-T Siemens (Magnetom® Amira, Avanto, or Aera; Siemens Healthcare, Erlangen, Germany), 3-T Siemens (Magnetom® Skyra; Siemens Healthcare, Erlangen, Germany), or 1.5-T Philips (Ingenia; Philips Healthcare, Best, the Netherlands) scanner. The CMR protocol was similar between centers. Cine sequences were performed as multi-slices in vertical and horizontal long-axis and multi-slices stacks in short-axis view covering the whole left ventricle (7mm thick with 10% gap). LGE sequences were performed 10 minutes after intravenous administration of 0.2 mL/kg gadoteric acid (Dotarem®, Guerbet, Roissy CDG, France) as multi-slice stacks in short-axis, horizontal and/or vertical long-axis views (6.5 mm thick with 20% gap for fast low angle shot [FLASH] sequence and 7.5 mm thick with no gap for phase-sensitive inversion recovery [PSIR] sequence). T2 mapping was performed before contrast media injection with three slices on the short-axis view (base, mid, apex; 8 mm thick each) and one slice in the vertical and/or horizontal long-axis view based on T2-prepared balanced SSFP sequence. Native T1 mapping was performed before contrast media injection with one slice in the vertical and/or horizontal long-axis view and three slices in the short-axis view (base, mid, apex; 8 mm thick each), based on a modified Look-Locker inversion (MOLLI) recovery sequence using a 5(3)3

scheme. Postcontrast T1 mapping was performed 15 minutes after contrast application with a 5(1)1(1) short MOLLI sequence or a 4(1)3(1)2 MOLLI with three single slices in the short axis view (same slice position as native T1 mapping, 8mm thick each). ECV quantification was performed using pre- and postcontrast T1 values and patient hematocrit collection (20). T1, T2, and ECV quantification were performed for all the LV segments (except segment 17), and the respective global values were calculated as the mean of the different segmental values.

All images were analyzed blinded in a core lab fashion by two senior radiologists (U.S. and F.C.) experienced in cardiac imaging through Universal Viewer software (GE Healthcare, Milwaukee, Wisconsin). Postprocessing for functional parameters, mapping, and ECV was performed with Intellispace Portal 9 software (Philips, Best, The Netherlands). CMR data included left ventricular ejection fraction (LVEF), end-diastolic volume, end-systolic volume, and myocardial mass, indexed to the body surface; evaluation of the segmental kinetics; and presence of pericardial effusion. Data on LGE included its localization (septal, inferior, lateral, anterior), its distribution (patchy, linear, diffuse), and its pattern (subepicardial, subendocardial, midwall, transmural). T1 and T2 mapping were available in line. T1 and T2 mapping data were collected for each segment according to the 17 myocardial segment-scheme (segment 17 was not analyzed) to get a complete analysis of regional behavior and to provide a segmental analysis. Analysis was performed by postprocessing on the abovementioned software by placing a region of interest in each segment that was placed according to the Society of Cardiovascular Magnetic Resonance (SCMR) (20).
Calibration of the T1, ECV, and T2, values was performed for each CMR scanner machine to consider scanner-dependent variations in reference values **(Supplemental Table 1)**. To enable combined analysis of multicenter/multivendor data, T1, T2, and ECV values were converted to a z-score using the CMR-specific reference value as follows: (patient value –

mean of reference range) / (standard deviation [SD] of reference range). Abnormal T1, ECV, and T2 values were defined as 2 SDs above the mean of the reference values according to the SCMR recommendations (20).

Outcome

All patients with ICI-M suspicion were treated with the same protocol, including systematic admission to the coronary care unit with immediate administration of high-dose corticosteroids before CMR (intravenous methylprednisolone 1 g/day for three days, then oral prednisolone 2 mg/kg/day for 2 weeks and 1 mg/kg/day for 14 days, which was tapered over 4-6 weeks) as previously described (1,21). In cases of hemodynamic or electrical instability despite corticosteroid administration, the intensified immunosuppressive therapy strategy employed was at the discretion of the physicians.

The primary outcome of interest was MACE that occurred within one year after CMR. It was a composite of death from cardiovascular causes, cardiac arrest, documented sustained (>30 sec) ventricular tachycardia, complete atrioventricular heart block, or cardiogenic shock. When more than one event occurred in a patient, the first event was used. The outcome data were collected through electronic medical records and by systematic phone calls to the patients and their physicians in January 2021. The cause of death was the cause reported by the medical team taking care of the patient or on the death certificate. They were adjudicated by independent investigators.

Statistical Analysis

Continuous variables were expressed as the mean ± SD or as median and interquartile range (IQR) depending on the normality of the distribution. Categorical variables were presented as the number of patients and percentages. Continuous variables were compared using Student's

t-test or the Mann-Whitney test, and categorical variables were compared using the chi-square test or Fisher's exact test as appropriate.

For the analysis of potential CMR predictors of MACE, time-to-event data were evaluated from the date of CMR with the use of Kaplan–Meier estimates and Cox proportional-hazards models. The LGE presence/localization/distribution/pattern and the values of global/mid septal wall native T1, ECV, and T2 were first tested in a single-variable analysis and then after adjustment for magnitude of increase in peak troponin I or T (an-fold increase in the in peak troponin I or T above the 99^{th} percentile). Hazard ratios, 95% confidence intervals, and two-sided p values were calculated with the use of the Cox models. Proportional hazards assumption was tested using the Schoenfeld residuals method. The linearity assumption for continuous variables was tested by entering the square of the term into the model. Kaplan-Meier curves were compared with the logrank test.

IBM SPSS statistics version 27 (IBM, Armonk, New York) and R software (Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses. Left ventricle bull's eyes were obtained using Matlab (MathWorks Inc., Natick, MA). All tests were two sided, and $p<0.05$ was considered significant.

RESULTS

Of the 164 patients admitted for acute myocarditis, 118 patients were finally included (ICI-M, n=33 and NI-M, n=85) (**Figure 1**). In ICI-M, the diagnosis was definite in 15 patients (45%) and probable in 18 patients (55%) according to the Bonaca criteria **(Supplemental Table 2)**. The median times from ICI introduction and last infusion to ICI-M were 41 days and 17 days, respectively. The median time between steroids introduction to CMR performance was 3 days. Four patients (12%) had in addition an intensified immunosuppressive therapy strategy,

with regard to their clinical condition and not based on their CMR findings. The w/o-M group included 21 cancer patients.

ICI-M compared to w/o-M

Patient characteristics

Comparisons between the characteristics of the ICI-M and w/o-M patients are summarized in **Table 1**. The ICI-M patients did not differ from those of w/o-M in the baseline characteristics, except for a higher prevalence of diabetes mellitus in patients who had ICI-M. The patients of the two groups were also similar in terms of cancer type and cancer treatment, including ICIs. Compared with w/o-M, ICI-M patients presented with higher cardiac biomarker serum levels, ECG abnormalities including T-wave inversion, and sustained supraventricular arrhythmias on admission. There was no significant difference in TTE characteristics.

CMR findings

Compared with w/o-M, ICI-M had a lower LVEF (p=0.02), but only 21% of them had an LVEF<50%. Pericardial effusion (p<0.001) and wall motion abnormalities (p=0.005) were more frequently observed in ICI-M. The global native T1, ECV, and T2 z-scores were significantly higher in ICI-M (p<0.001 for T1, p=0.03 for ECV, and p=0.004 for T2), with more frequent abnormal values (36% *vs.* 0%, p=0.002 for T1, 69% *vs.* 19% for ECV, p=0.01, and 24% *vs*. 0%, p=0.02 for T2). Of note, no cancer patients of the w/o-M had abnormal global and septal native T1 or T2 values **(Table 2)**. In the segmental analysis, ICI-M presented higher native T1 and T2 z-score values in respectively 14 and 11 segments **(Figure 2 and Supplemental Table 3)**. LGE was observed in 9% w/o-M but was more frequent in ICI-M (82%, p<0.001). The preferential features of LGE in ICI-M were lateral and septal

segment localization, patchy distribution, and subepicardial or midwall patterns **(Table 2, Figure 2, and Supplemental Table 3)**.

Fulfillment of the main 2018-LL main criteria significantly differed between the two groups (p<0.001) (**Table 2**). Only 61% of ICI-M patients fulfilled the two main 2018-LL criteria, while none of these criteria were met in two ICI-M patients. One of these patients presented with a definite ICI-M based on the Bonaca criteria with new wall motion abnormalities associated with clinical syndrome, elevated cardiac biomarkers, and ECG abnormalities suggestive of myopericarditis. The other patient presented with a probable ICI-M with nonspecific CMR findings suggestive of myocarditis with clinical syndrome, elevated biomarkers, and ECG abnormalities suggestive of myopericarditis.

ICI-M compared to NI-M

Patient characteristics

Comparisons between the characteristics of the ICI-M and NI-M patients are summarized in **Table 1**. ICI-M patients were older (p<0.001), had more cardiovascular risk factors (p=0.001), and were less symptomatic (45% *vs.* 100%, p<0.001). Compared with NI-M patients, ICI-M patients were more likely to have a longer QTc segment (p=0.003), T-wave inversion (p<0.001), atrioventricular conduction abnormalities (p=0.02), sustained supraventricular arrhythmia (p<0.001), but lower peak troponin levels (p<0.001 for troponin T and p=0.002 for troponin I). Endomyocardial biopsy was only required for two patients with ICI-M, which showed myocarditis findings with cardiomyocyte necrotic foci, macrophages and CD4+/CD8+ T-cell infiltration.

CMR findings

The morphological and functional left ventricular parameters were similar between the groups. In terms of global native T1, ECV, and T2 z-scores, no significant difference was

found between the two groups (**Table 2**). The segmental analysis of these parameters showed only minor differences **(Figure 2 and Supplemental Table 3)**. LGE was less frequently observed in ICI-M (82% *vs.* 100%, p<0.001). As a result, distribution of the main 2018-LL criteria significantly differed between the two groups (p=0.03) **(Table 2)**. LGE localization and patterns were significantly different between the two groups. ICI-M more frequently presented with LGE in the septal segments (p<0.001) and in the midwall layer (p<0.001). Conversely, the LGE of NI-M was more likely to be in the inferior and lateral segments (p<0.001 for both) as well as in the subepicardial layer (p<0.001) **(Table 2, Figure 2, and Supplemental Table 3)**.

Outcome

The median time of follow-up for ICI-M, w/o-M, and NI-M patients was 182 days, 172 days, and 365 days, respectively. The rates of MACE at one year were 67%, 18%, and 5% in the three groups, respectively (p<0.001). Details on MACE are shown in **Supplemental Tables 4 and 5.** In ICI-M patients MACE occurred after a median time of 33 (8-108) days. Magnitude of increase troponin I or T was associated with the occurrence of MACE (HR,1.01; 95% CI, 1.01-1.02; p=0.03). The only significant CMR predictor of MACE was septal LGE **(Table 4, Figure 5)**, even after adjustment for magnitude of increase in peak troponin I or T (adjusted HR, 2.66; 95% CI, 1.06-6.66; p=0.03). The median time to MACE in ICI-M patients with and without septal LGE was respectively of 44 (8-138) days and 11 (0-63) day (p=0.23). Septal LGE was present in 2 of 6 patients who experienced confirmed atrioventricular block or sustained ventricular arrhythmia, and in 7 of 8 patients in whom sudden death or cardiac arrest was reported as the cause of death but without documented block or arrythmia.

DISCUSSION

Our study investigated the CMR features of ICI-M and reported the following main results: 1) compared with similar cancer patients without myocarditis, ICI-M patients had significant elevation in global native T1, ECV, and T2 values and had LGE more frequently; 2) compared with NI-M, the proportion of patients demonstrating LGE was lower, but LGE was more frequently localized in the septum and midwall layer; 3) the presence of septal LGE was a CMR predictor of MACE independently of troponin elevation in ICI-M patients.

CMR in ICI-M

CMR is the gold-standard noninvasive test for the diagnosis of NI-M (10). However, only a few data exist on CMR in patients with suspected ICI-M (2,5,14,15). The present work is the first to our knowledge that included control group of cancer patients with CMR prior to ICI introduction (w/o-M group) to ensure that their findings were related to ICI-M and not to other myocardial damage seen in the cancer patient population. Indeed, cancer and cardiovascular disease share many risk factors, and the prevalence of hypertension, smoking, diabetes, and obesity is higher in cancer patients than in noncancer patients (22). These risk factors and previous cancer therapy are also associated with a higher prevalence of ischemic or nonischemic myocardial fibrosis, which can lead to LGE and an increase in global native T1 (23) that may wrongly lead to fulfillment of 2018-LL criteria whereas the latter have not been validated in a cancer population. In this regard, we found that 9% of cancer patients without myocarditis had LGE while none presented with a significant native T1 and T2 elevation. This is important to consider in clinical practice when CMR shows only LGE in patients with suspected ICI-M and this is the range of bias that should be considered when observing LGE in cancer patients with suspected ICI-M.

Comparing the CMR scans of control cancer patients with those with ICI-M, we were able to show that ICI-M led to an increase in the global native T1, ECV, and T2 values as well as

LGE frequency. However, we found lower T1 and T2 z-scores than those reported in the study by Thavendiranathan et al. (15) probably due to the higher doses of corticosteroids we used in an early setting. Indeed, all our patients received 1g of methylprednisolone during the first 3 days after admission, whereas the doses were much lower in 46% of the patients in the Thavendiranathan et al.'s work (15). Since we performed CMR within a median of 3 days after corticosteroid initiation, their anti-inflammatory effect may have reduced T1 and T2 values. Interestingly, 82% of our ICI-M patients presented LGE which was relatively consistent with the 72% of LGE reported by Zhang et al. when CMR was performed at least for 4 days after admission (14). The higher prevalence of LGE in ICI-M in our study may also be due to our more restrictive inclusion criteria for ICI-M (both ESC and at least probable myocarditis Bonaca criteria) and thinner LGE slices with multiple orientations compared to other studies (14,15). Another finding is that ICI-M patients were more likely to develop pericardial effusion in case of myocarditis compared to w/o-M patients, however without significant difference compared to NI-M patients. This is consistent with the pericardial effusion being a supportive criteria of 2018-LL criteria (10). Nevertheless, pericardial effusion in ICI patients could also be due to cancer progression and not related to myocarditis. Focus on this point in further studies may be of interest to base a strategy of monitoring in case of pericardial effusion.

CMR predictors of MACE in ICI-M

With a 67% one-year rate of MACE, our study confirms the catastrophic cardiovascular outcome of patients with ICI-M (6). Troponin T (admission, peak, and discharge values) has been known to be predictive of MACE in patients with ICI-M (5,14). Troponin levels reported in our study were lower than in those of previous works (5,14), although heterogeneous. This is probably related to the systematic troponin screening strategy we

adopted long time ago in all patients before each ICI infusion (21). This may lead to an earlier detection of ICI-M in our reference centers.

Our work found for the first time that the presence of septal LGE might be also a strong predictor of MACE independently of troponin. A similar predictive value of septal LGE was showed in a large population of NI-M (13). Interestingly, we found that LGE septal localization were significantly more frequent in ICI-M than in NI-M, who has a better prognosis. A recent work found that the mid septal wall native T1 value was a predictor of MACE (15). Our study did not confirm this result probably because of differences in the corticosteroids' doses used and in the method of MACE analysis. Indeed, to investigate the predictive value of T1/T2/ECV/LGE parameters, we have considered the MACE that occurred after CMR was performed. Thavendiranathan et al. chose to consider all MACE that occurred after the start of the ICI therapy (15). Thus, a substantial number of MACE in this study were considered even though they happened before CMR was performed. Possible inclusion of MACE that occurred after the first ICI infusion but before ICI-M episode could explain why Thavendiranathan et al. found longer time to MACE than ours. Nevertheless, these data suggest worse cardiovascular outcome when the septal wall is involved. The underlying mechanism of this poor outcome may be related to damages of the cardiac conduction system, which could lead to atrioventricular block and ventricular arrhythmias (13). However, our retrospective data do not allow to confirm this hypothesis because only 2 of 6 patients who experienced confirmed atrioventricular block or sustained ventricular arrhythmia had septal LGE.

Study limitations

First, our study has a retrospective design and no randomization of any specific therapy. Thus, there are potential biases introduced by the CMR findings to patient outcomes due to medical

or procedural therapies. However, both centers used the same standardized treatment protocol, which may have limited this bias. Second, few patients underwent EMB to confirm the diagnosis of myocarditis. However, in addition to its invasive nature, this technique has limited spatial coverage in a potentially localized condition. To overcome the lack of EMB, we used a recent uniform definition of myocarditis dedicated for application in clinical trials of cancer immunotherapies (19). In this regard, we only included definite and probable diagnoses. Third, native T1 and ECV were not performed in all patients. Finally, it remains difficult to guarantee the cardiovascular cause of death in patients with severe cancer progression. We tried to limit this bias by independent adjudication.

Conclusions

Cardiovascular magnetic resonance imaging showed differences between ICI-M and NI-M in terms of LGE prevalence, pattern, and localization. In ICI-M, the proportion of patients demonstrating LGE was lower, but LGE was more frequently localized in midwall layer and the interventricular septum. The presence of septal LGE might identify high-risk patients.

CLINICAL PERSPECTIVES

Clinical competencies: ICI-M has special features on CMR. Compared with NI-M, septal and midwall LGE localizations are more frequent. The presence of a septal LGE might be an independent predictor of MACE that could help in risk stratification.

Translational outlook: Future research is warranted to test whether repeated CMR in ICI-M suspicion improves diagnostic yield and whether management based on the presence of septal LGE is able to affect clinical outcome.

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FIGURES

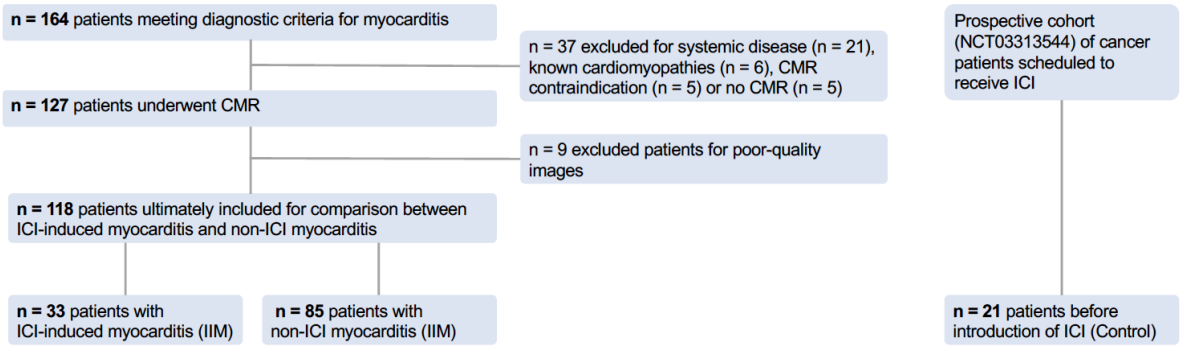


Figure 1. Study Flow Chart

CMR=cardiovascular magnetic resonance imaging; ESC=European Society of Cardiology

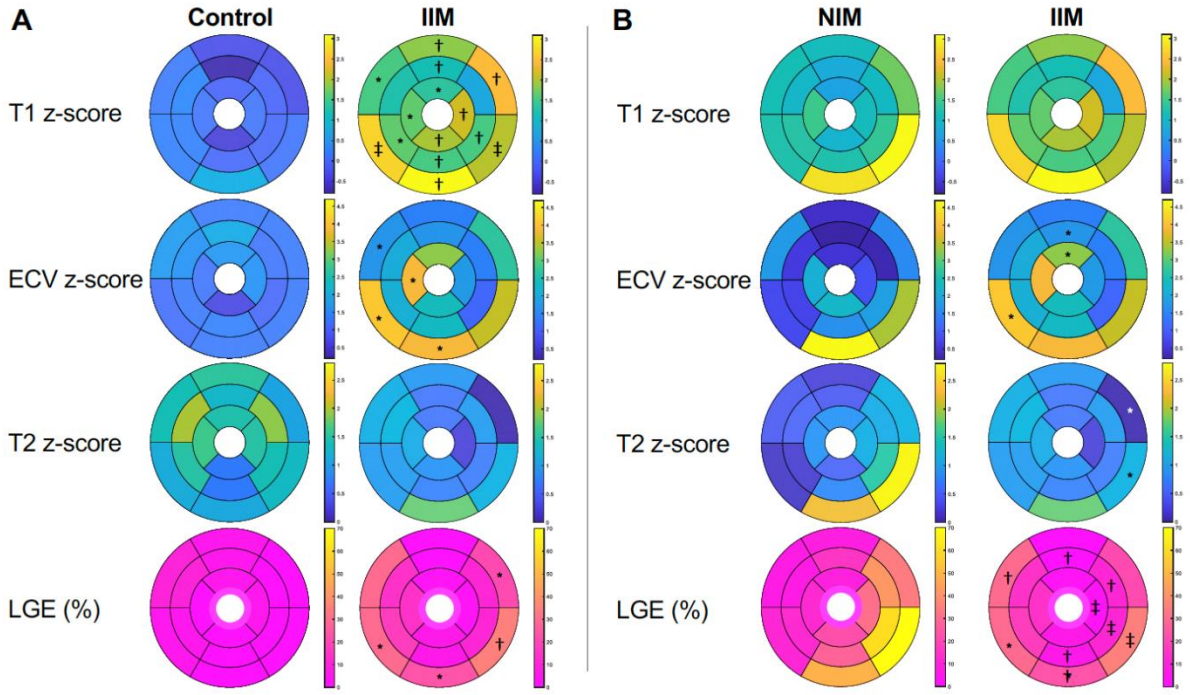


Figure 2. Segmental Comparison of Native T1, ECV, T2 z-Scores and Late Gadolinium Enhancement (LGE) between Immune Checkpoint Inhibitor-Induced Myocarditis (ICI-M) and Cancer Patients without Myocarditis Scheduled to Received ICI (w/o-M) (Panel A) and between ICI-M and Non-ICI-Induced Myocarditis (NI-M) (Panel B).

The blue-derived colored scale represents the mean values of parametric parameters with native T1, T2, and ECV z-scores for each segment and the pink-derived colored scale represents the percentage of patients with LGE for each segment.

*p<0.05; †p<0.01; ‡p<0.001.

§Analyzed in 20 w/o-M, 25 ICI-M, and 32 NI-M

||Analyzed in 16 w/o-M, 16 ICI-M, and 11 NI-M

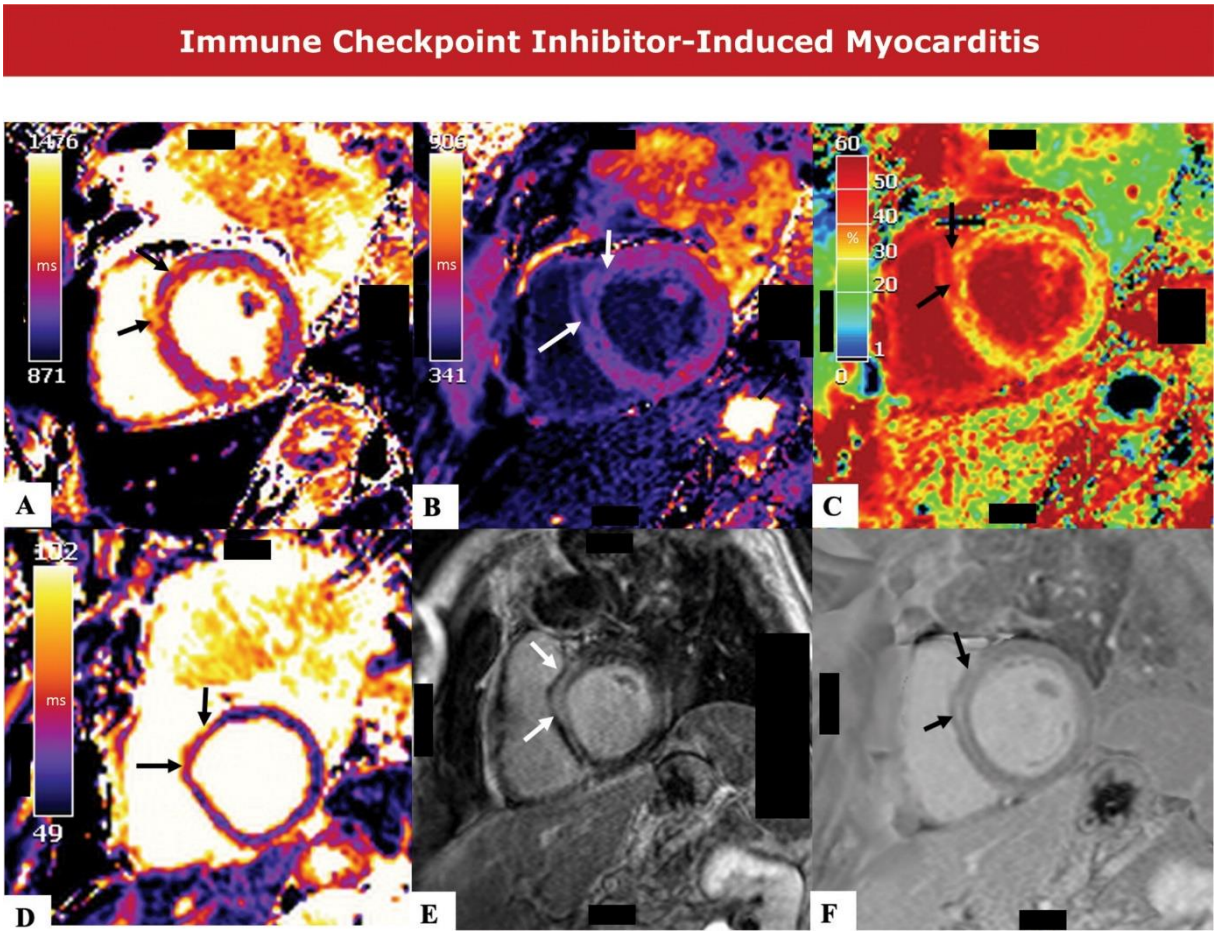


Figure 3. Distinctive Findings on CMR between Immune Checkpoint Inhibitor-Induced Myocarditis (ICI-M) and Nonimmune Checkpoint Inhibitor-Induced Myocarditis (NI-M).

ICI-M: An asymptomatic 62-year-old female with melanoma treated with nivolumab and elevated hs-troponin T (35ng/L) during regular monitoring. CMR showed abnormalities (arrows) in the midwall of the septum with increased native T1 values (1223ms) (A),

decreased postcontrast T1 values (449ms) (B), increased ECV values (37%) (C), increased T2 values (60ms) (D) and corresponding LGE on FLASH (E) and PSIR (F) sequences.

NI-M: A 39-year-old male with acute chest pain and elevated hs-troponin T (570ng/L). CMR showed abnormalities (arrows) in the subepicardial layer of the inferolateral wall with increased native T1 values (1335ms) (A), decreased postcontrast T1 values (384ms) (B), increased ECV values (38%) (C), increased T2 values (69ms) (D), and corresponding LGE on FLASH (E) and PSIR (F) sequences.

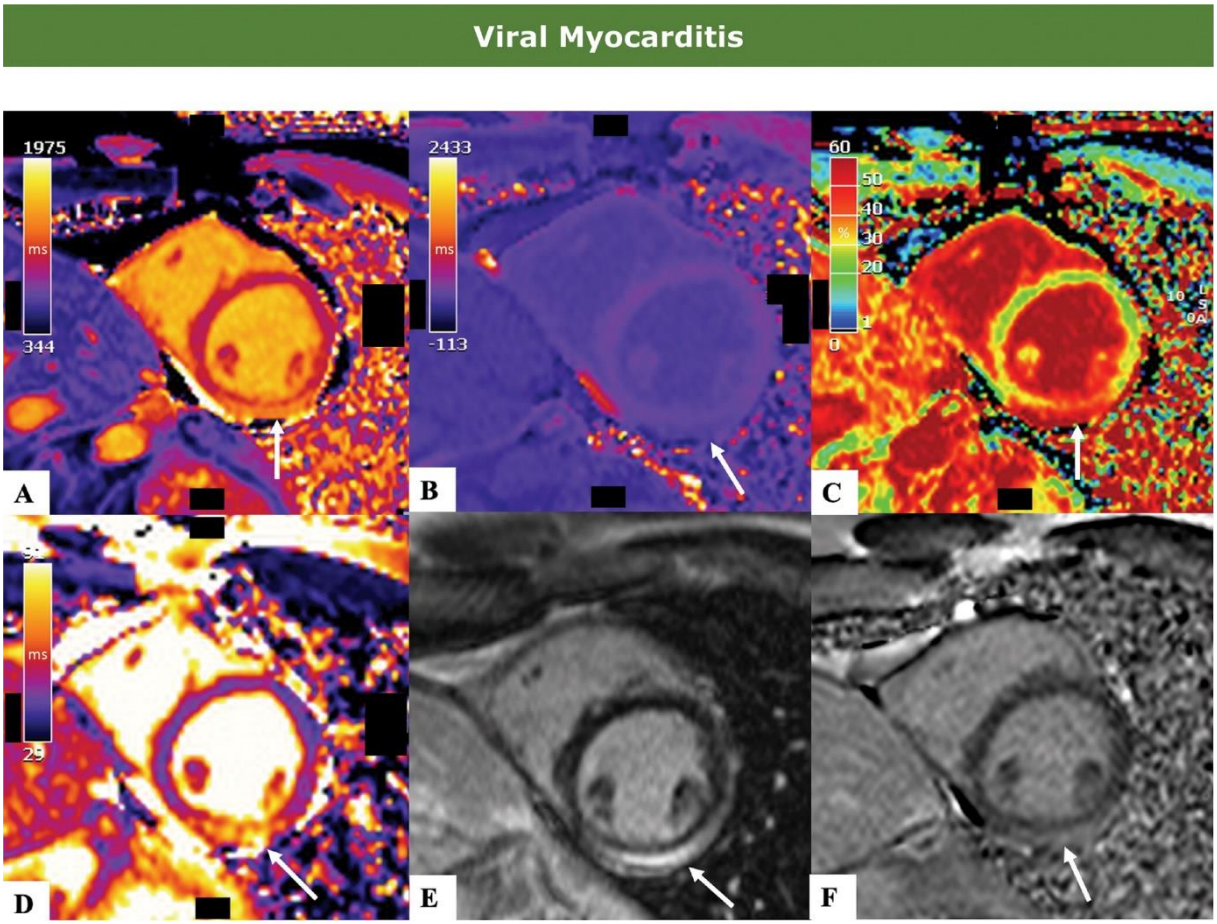


Figure 4: **Findings at cardiac MRI in acute viral myocarditis in a 39-year-old man with acute chest pain and elevated high-sensitivity troponin T (570 ng/L)**. Cardiac MRI scans of the mid left ventricle short-axis plane show abnormalities (arrows) in the subepicardial layer of the inferolateral wall, with (A) high native T1 values (1335 msec) on 5(3)3 modified Look-Locker inversion sequence image, (B) low T1 values 15 minutes after administration of

0.2 mL/kg gadoterate meglumine (Dotarem; Guerbet) (384 msec) on 5(1)1 (1) short modified Look-Locker inversion sequence image, (C) high extracellular volume fraction values (38%) on corresponding mapping, (D) high T2 values (69 msec) on T2-prepared balanced steady-state free precession sequence image, and corresponding late gadolinium enhancement 10 minutes after administration of 0.2 mL/kg gadoterate meglumine on (E) fast low-angle shot and (F) phase-sensitive inversion-recovery sequence images.

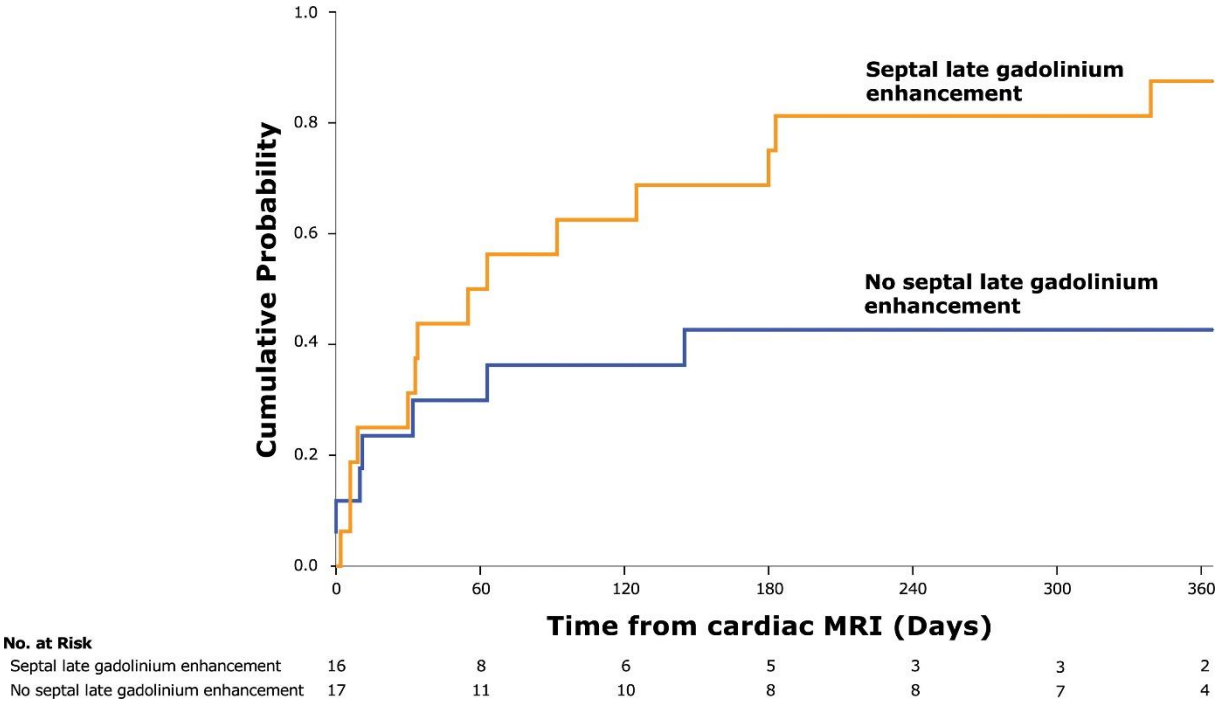
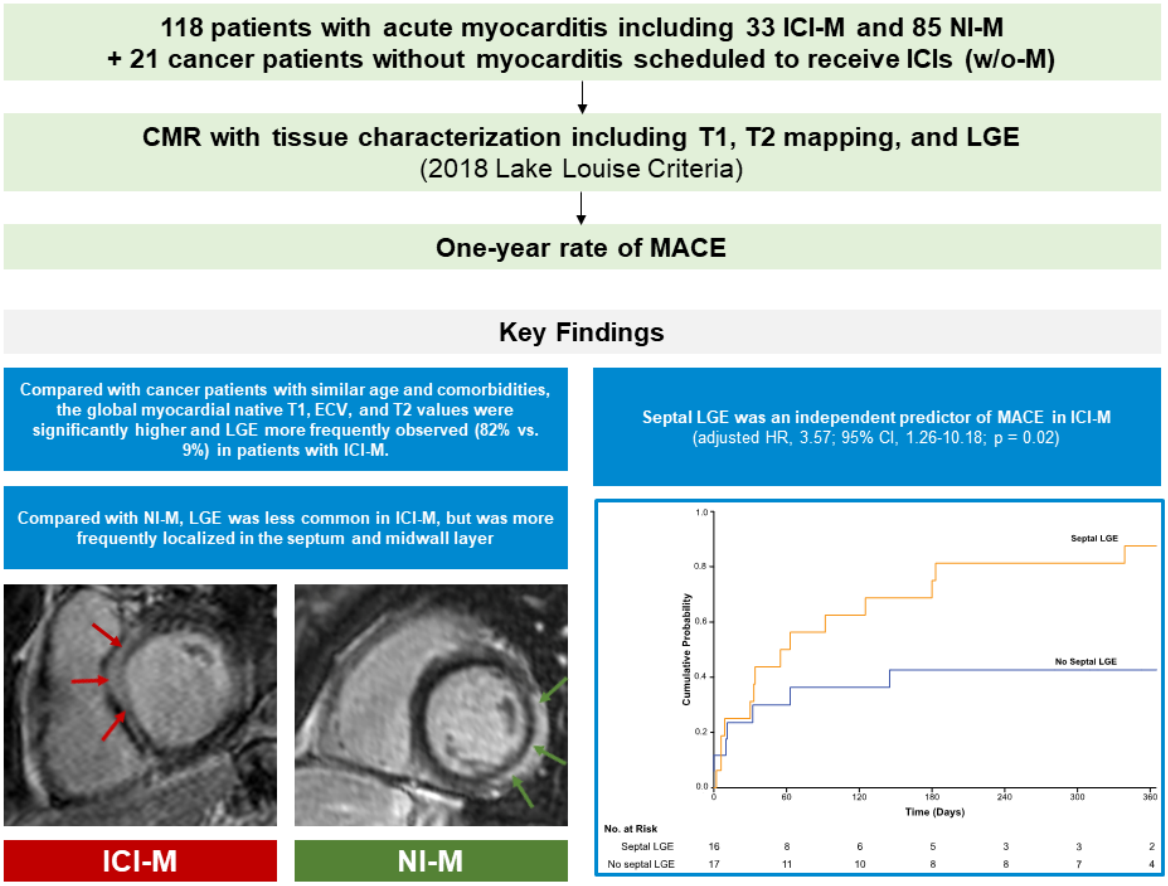


Figure 5. Cumulative Probability of MACE in Patients with Immune Checkpoint Inhibitor-Induced Myocarditis According to the Presence of Septal Late Gadolinium Enhancement (LGE, in orange)

Septal LGE was associated with a higher risk of MACE (HR, 2.53; 95% CI; 1.02-6.32; p=0.03) even after adjustment for age, sex, risk factors, LVEF<50%, and magnitude of increase in peak troponin I or T (adjusted HR, 3.57; 95% CI, 1.26-10.18; p=0.02).



Central Illustration. ICI-M demonstrates specific features on CMR, and septal LGE may be a predictor of poor prognosis. Red arrows delineate midwall septal LGE in a patient with ICI-M. Green arrows delineate subepicardial lateral LGE in a patient with NI-M.

TABLES

Table 1. Patient Characteristics

	ICI-M (n = 33)	w/o-M (n = 21)	NI-M (n = 85)	p Value ICI-M *vs.* w/o-M	p Value ICI-M *vs.* NI-M
Demographics					
Age (years)	68 ±14	65 ±14	32 ±13	0.37	<0.001
Female	10 (30)	7 (33)	18 (21)	1.0	0.30
BMI (kg/m^2)	24 ±4	24 ±3	24 ±4	0.64	0.43
Number of cardiovascular risk factors	1.1 ±1.1	1.0 ±0.8	0.5 ±0.6	0.52	0.001
Dyslipidemia	4 (12)	7 (33)	3 (3)	0.08	0.09
Smoking	12 (36)	5 (24)	34 (40)	0.38	0.83
Hypertension	19 (57)	9 (43)	4 (5)	0.29	<0.001
Diabetes mellitus	7 (21)	0 (0)	1 (1)	0.03	<0.001
Coronary heart disease	0 (0)	1 (5)	0 (0)	0.39	1.0
Clinical data					
Heart rate (bpm)	80 ±16	77 ±15	78 ±23	0.49	0.25
SBP (mmHg)	130 ±24	136 ±16	123 ±19	0.18	0.09
DBP (mmHg)	71 ±13	75 ±11	73 ±13	0.27	0.65
Symptoms	15 (45)	4 (19)	85 (100)	0.08	<0.001
Chest pain	4 (12)	0 (0)	76 (89)	0.15	<0.001
Dyspnea	11 (33)	4 (19)	5 (6)	0.36	<0.001
Fatigue	1 (3)	0 (0)	9 (10)	1.0	0.28
Palpitations	2 (6)	1 (0)	4 (5)	1.0	1.0
Syncope	0 (0)	0 (0)	4 (5)	1.0	1.0
Fever	2 (6)	0 (0)	24 (28)	0.52	0.01
Laboratory test					
CRP (mg/L)	16 (4-35)	7 (5-11)	36 (13-69)	0.16	0.04
Peak hs-troponin T (ng/L) *	58 (20-517)	8 (6-13)	587 (215-1144)	<0.001	<0.001
Peak hs-troponin I (ng/L) †	550 (120-1001)	6 (6-12)	14000 (8000-24000)	0.001	0.002
Peak NT-pro-BNP (ng/L) ‡	710 (230-1836)	126 (86-232)	316 (131-865)	0.005	0.07

Peak BNP (ng/L) [§]	143 (86-283)	20 (13-24)	47 (37-114)	0.04	0.10
ECG					
Sinus rhythm	30 (91)	21 (100)	84 (99)	0.27	0.06
PR duration (ms)	155 ±34	148 ±26	155 ±26	0.49	0.97
QRS duration (ms)	78 ±37	74 ±23	89 ±35	0.71	<0.001
QTc duration (ms)	427 ±37	406 ±44	394 ±32	0.08	0.003
T-wave inversion	13 (39)	0 (0)	9 (10)	<0.001	<0.001
ST-segment modification	6 (18)	1 (5)	31 (36)	0.23	0.08
Atrioventricular conduction abnormalities	3 (9)	0 (0)	0 (0)	0.27	0.02
Sustained supraventricular arrhythmia	8 (24)	0 (0)	2 (2)	0.02	<0.001
Sustained ventricular arrhythmia	0 (0)	0 (0)	2 (2)	1.0	1.0
Transthoracic echocardiogram					
LVEF (%)	60 ±11	64 ±7	59 ±9	0.33	0.10
LV GLS (%)	18 ±4	19 ±3	19 ±4	0.34	0.54
Interventricular septum (mm)	10.0 ±2.7	9.8 ±2.0	9.5 ±1.9	0.74	0.60
Pericardial effusion	4 (12)	0 (0)	7 (8)	0.15	0.50
Cancer type					
Melanoma	14 (42)	10 (48)	-	0.47	-
Lung	13 (39)	8 (38)	-	1.0	-
Ears, nose and throat	1 (3)	0 (0)	-	1.0	-
Urothelial	4 (12)	3 (14)	-	1.0	-
Digestive	1 (3)	0 (0)	-	1.0	-
Metastatic stage	30 (91)	20 (95)	-	1.0	-
Cancer therapy					
Previous thoracic radiotherapy	0 (0)	0 (0)	-	1.0	-
Previous chemotherapy[‖]	13 (39)	5 (24)	-	0.37	-
Nivolumab	10 (30)	7 (33)	-	1.0	-
Pembrolizumab	8 (24)	7 (33)	-	0.54	-
Atezolizumab	5 (15)	0 (0)	-	0.14	-
Durvalumab	1 (3)	0 (0)	-	1.0	-
Nivolumab + Ipilimumab	4 (12)	7 (33)	-	0.09	-
Nivolumab + Relatlimab	3 (9)	0 (0)	-	0.27	-

Nivolumab + Ipilimumab + Relatlimab	2 (6)	0 (0)	-	0.52	-

Values are mean ± SD or median (interquartile range) or n (%).
BMI= body mass index; CRP= C reactive protein; DBP= diastolic blood pressure; ECG= electrocardiogram; ICI-M= immune checkpoint inhibitor-induced myocarditis; LVEF= left ventricular ejection fraction; LV GLS= left ventricle global longitudinal strain; NI-M= non-ICI myocarditis; NT-pro-BNP= NT- prohormone of BNP; SBP= systolic blood pressure; TSH= thyroid stimulating hormone; w/o-M= without myocarditis.
[*]Measured in 11 w/o-M, 25 ICI-M patients, and 56 NI-M patients. The laboratory cut-off was of 14 ng/L.
[†] Measured in 10 w/o-M, 8 ICI-M patients, and 29 NI-M patients. The laboratory cut-off was of 4 ng/L.
[‡] Measured in 11 w/o-M, 25 ICI-M patients, and 56 NI-M patients.
[§] Measured in 10 w/o-M, 8 ICI-M patients, and 29 NI-M patients.
[‖] Including pemetrexed, 5-FU, platinum-based antineoplastic drugs, cyclophosphamide, and BRAF and MEK inhibitors.

Table 2. CMR Characteristics

	ICI-M (n = 33)	w/o-M (n = 21)	NI-M (n = 85)	p Value ICI-M *vs.* w/o-M	p Value ICI-M *vs.* NI-M
LVEF (%)	58 ±14	67 ±7	57 ±10	0.02	0.09
LVEF ≥50%	26 (79)	21 (100)	69 (81)	0.03	0.80
EDV indexed (mL/m^2)	76 ±25	59 ±14	81 ±20	0.004	0.31
ESV indexed (mL/m^2)	33 ±22	22 ±10	36 ±15	0.04	0.03
LV mass indexed (g/m^2)	53 ±18	60 ±14	60 ±16	0.15	0.08
Pericardial effusion	13 (39)	0 (0)	28 (33)	<0.001	0.52
Wall motion abnormality	13 (39)	1 (5)	24 (28)	0.005	0.27
T1 mapping*					
Global native T1 z-score	1.79 ±1.93	0.03 ±0.85	1.21 ±2.69	<0.001	0.54
Increased global native T1†	9 (36)	0 (0)	11 (34)	0.002	0.90
Mid septal wall native T1 z-score	1.44 ±2.06	0.20 ±1.17	1.14 ±2.09	0.01	0.69
Increased mid septal wall native T1†	7 (28)	0 (0)	9 (28)	0.01	1.0
ECV‡					
Global ECV z-score	2.59 ±1.97	1.34 ±0.57	1.46 ±2.35	0.03	0.24
Increased global ECV†	11 (69)	3 (19)	5 (45)	0.01	0.26
Mid septal wall ECV z-score	2.12 ±2.44	1.35 ±0.73	0.68 ±1.99	0.25	0.11
Increased mid septal wall ECV†	8 (50)	3 (19)	2 (18)	0.14	0.12
T2 mapping					
Global T2 z-score	0.88 ±1.96	-0.76 ±1.41	0.93 ±1.90	0.002	0.88
Increased global T2†	8 (24)	0 (0)	19 (22)	0.02	0.82
Mid septal wall T2 z-score	1.04 ±2.31	-0.43 ±1.61	0.30 ±2.28	0.03	0.06
Increased mid septal wall T2 l†	10 (30)	0 (0)	15 (18)	0.004	0.14
LGE					
LGE presence	27 (82)	2 (9)	85 (100)	<0.001	<0.001

LGE localization					
Septal	16 (48)	2 (9)	25 (29)	<0.001	<0.001
Inferior	10 (30)	0 (0)	58 (68)	0.004	<0.001
Lateral	19 (58)	1 (5)	81 (95)	<0.001	<0.001
Anterior	1 (3)	1 (5)	18 (21)	1.0	0.11
LGE distribution					
Patchy	19 (58)	1 (5)	65 (76)	<0.001	0.16
Linear	7 (21)	1 (5)	10 (12)	0.13	0.24
Diffuse	1 (3)	0 (0)	10 (12)	1.0	0.19
LGE pattern					
Subepicardial	16 (48)	0 (0)	83 (98)	<0.001	<0.001
Midwall	11 (33)	1 (5)	2 (2)	0.02	<0.001
Subendocardial	0 (0)	1 (5)	0 (0)	0.39	1.0
Transmural	0 (0)	0 (0)	0 (0)	1.0	1.0
2018-Lake-Louise criteria				<0.001	0.03
0	2 (6)	20 (95)	0 (0)		
1	11 (33)	1 (5)	20 (24)		
2	20 (61)	0 (0)	65 (76)		

Values are mean ± SD or n (%)

ECV=extracellular volume; EDV=end-diastolic volume; ESV=end-systolic volume; ICI-M=immune checkpoint inhibitor (ICI)-induced myocarditis; LGE=late gadolinium enhancement; LV=left ventricle; LVEF=left ventricular ejection fraction; NI-M=non-ICI myocarditis; w/o-M=without myocarditis.

* T1 mapping were analyzed in 20 w/o-M, 25 ICI-M patients, and 32 NI-M patients

† Abnormal T1, ECV, and T2 values were defined as >2 SD above the mean of reference value for each site, vendor, and CMR field strength.

‡ ECV were analyzed in 16 w/o-M, 16 ICI-M, and 11 NI-M

Table 4. Univariable Association for MACE in Patients with Immune Checkpoint Inhibitor-Induced Myocarditis

Potential Predictors	HR (95% CI)	p Value
LGE presence	1.43 (0.42-4.85)	0.57
LGE septal	2.53 (1.02-6.32)	0.03
LGE inferior	0.80 (0.31-2.05)	0.64
LGE lateral	0.95 (0.40-2.24)	0.90
LGE anterior*	-	-
LGE patchy	3.01 (0.38-23.83)	0.30
LGE linear	1.75 (0.73-4.17)	0.21
LGE diffuse	0.51 (0.22-1.21)	0.15
LGE subepicardial	1.07 (0.45-2.55)	0.88
LGE midwall	1.09 (0.46-2.58)	0.84
Abnormal global native T1 z-score†	0.82 (0.28-2.42)	0.72
Abnormal mid septal native T1 z-score†	0.97 (0.31-3.06)	0.96
Abnormal global ECV z-score†	0.80 (0.80-2.50)	0.10
Abnormal mid septal ECV z-score†	1.29 (0.39-4.26)	0.67
Abnormal global T2 z-score†	1.28 (0.46-3.57)	0.64
Abnormal mid septal T2 z-score†	1.61 50.61-4.26)	0.34

* Not applicable because of only one patient in this subgroup.
†Abnormal T1, ECV, and T2 values were defined as >2 SD above the mean of reference value for each site, vendor, and CMR field strength.
HR=hazard ratio; CI=confidence interval; ICI-M=immune checkpoint inhibitor (ICI)-induced myocarditis; LGE=late gadolinium enhancement; LVEF=left ventricular ejection fraction; MACE=major adverse cardiovascular events