Role of cardiac MRI in the diagnosis of immune checkpoint inhibitor-associated myocarditis

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List of abbreviations

- AI = Artificial intelligence
- anti-CTLA-4 = Cytotoxic T-Lymphocyte Antigen 4
- anti-PD-1 = Programmed cell death-1
- AUC = Area under curve
- BNP = Circulating brain natriuretic peptide
- CK-MB = Creatine kinase MB
- CMR = Cardiac magnetic resonance
- COVID-19 = Coronavirus disease - 19
- CPK = Creatine phosphokinase
- CS = Circumferential strain
- EACVI = European Association of Cardiovascular Imaging
- ECG = Electrocardiogram
- ECV = Extracellular volume
- EMB = Endomyocardial biopsy
- ESC = European society of cardiology
- FDG = ^{18}F-fluoro-deoxy-glucose
- GLS = Global longitudinal strain
- HFA = Heart Failure Association
- ICI = Immune checkpoint inhibitors
- irAE = Immune related adverse event
- LA εe = Left atrial passive strain
- LA SRe = Left atrial peak early negative strain rate
- LGE = Late gadolinium enhancement
- LLC = Lake Louise Criteria
- LS = Longitudinal strain

- LV = Left ventricle
- LVEF = Left ventricular ejection fraction
- MACE = Major adverse cardiovascular events
- MINOCA = Myocardial infarction with non-obstructive coronary arteries
- NT-proBNP = N-terminal pro-brain natriuretic peptide
- PET = Positron emission tomography
- RS = Radial strain
- SLE = Systemic Lupus Erythematosus
- T2-STIR = T2-weighted short tau inversion recovery

Abstract

Immune Checkpoint Inhibitor (ICI)-induced cardiotoxicity is a rare immune-related adverse event (irAE) characterized by a high mortality rate. From a pathological point of view, this condition can result from a series of causes, including binding of ICIs to target molecules on non-lymphocytic cells, cross-reaction of T lymphocytes against tumor antigens with off-target tissues, generation of autoantibodies, and production of pro-inflammatory cytokines. The diagnosis of ICI-induced cardiotoxicity can be challenging, and cardiac magnetic resonance (CMR) represents the diagnostic tool of choice in clinically stable patients with suspected myocarditis. CMR is gaining a central role in diagnosis and monitoring of cardiovascular damage in cancer patients, and it is entering international cardiology and oncology guidelines.

In this narrative review, we summarized the clinical aspects of ICI-associated myocarditis, highlighting its radiological aspects and proposing a novel algorithm for the use of CMR.

1. Introduction

The wide employment of immune checkpoint inhibitors (ICIs) in cancer immunotherapy, ranging from early to advanced disease, has been associated with an increased detection of immune-related adverse events (irAEs)[1–7].With an incidence between 0.04 and 1.14% and a mortality rate of up to 50%, ICI-induced cardiotoxicity is a rare irAE that is characterized by a high death rate[8]. Among the immune-related cardiovascular sequelae of ICIs (including myocarditis, pericarditis, arrhythmias, acute myocardial infarction, heart failure, and vasculitis), which are severe in the majority of cases (>80%), myocarditis is associated with the highest incidence of death[9], further harboring the highest mortality amongst whole irAEs[10].

Remarkably, optimal management and early detection of this rare irAE is important for a prompt stop of the treatment with ICIs, start of high-dose corticosteroids, and early referral to a cardiologist[5]. A recent meta-analysis revealed that ICIs did not increase the risk of myocarditis *versus* non-ICI treatments, though its incidence was numerically higher in patients receiving cancer immunotherapy[11]. This could be due to potential biases in the report of such rare irAEs, making it a priority to investigate their occurrence in a real world patient scenario[12].

Among non-invasive imaging modalities, Cardiac Magnetic Resonance (CMR) represents the diagnostic tool of choice in clinically stable patients with suspected myocarditis[13–15]. CMR is able to provide functional, morphological, and tissue characterization data aiding in the diagnosis of myocarditis, as well as providing crucial prognostic information[13–16].

The principal aim of this narrative review is to summarize the clinical aspects of ICI-associated myocarditis and to propose a novel algorithm for the use of CMR in ICI-associated myocarditis.

2. General overview of myocarditis

Myocarditis is an inflammation of the myocardium, often associated with that of pericardium (myopericarditis)[17]. It is idiopathic in 50% of cases, and in the remnant 50% of cases, it can be caused by infections, treatments, toxins, and immunological causes[17,18].

Myocarditis can present with a wide spectrum of clinical manifestations, from sub-clinical and mild forms to more severe ones, with symptoms and signs similar to those of an acute coronary syndrome (chest pain in the case of associated myopericarditis and/or dyspnea) or heart failure (dyspnea and fatigue) with possible additional non-specific symptoms[17,19,20]. Remarkably, severe myocarditis can appear as decompensated heart failure, cardiogenic shock, and sudden cardiac death[17,19,20,22]. Differential diagnosis includes: acute coronary syndromes, pneumonitis, other causes of cardiomyopathy (e.g., sarcoidosis or arrhythmogenic cardiomyopathy)[21–23], heart failure, and endocrinopathies[24].

Electrocardiography can show ST changes and T-wave inversions, atrial arrhythmias, transient atrio-ventricular block, QT prolongation, ventricular ectopy, and ventricular tachycardia[17,19]. Blood C-reactive protein, troponin, creatine kinase MB (CK-MB), erythrocyte sedimentation rate, and natriuretic peptides (circulating brain natriuretic peptide (BNP) and amino terminal pro-BNP levels) might be elevated[25]. Viral serology, swabs tests (including those for SARS-CoV-2) conducted to exclude a viral etiology and additional investigations in order to consider possible infections from bacteria, spirochaetes and protozoa, or to exclude the etiology from treatments (cyclophosphamide, trastuzumab, ICIs,[26] penicillin, chloramphenicol, sulfonamides, methyldopa, spironolactone, phenytoin, carbamazepine, anti-Coronavirus disease-19 (COVID-19) vaccines[27–29], etc.), or toxins or immunological causes (e.g., Systemic Lupus Erythematosus (SLE), sarcoidosis, Kawasaki, scleroderma, heart transplant rejection), should be further performed for investigating the underlying causes of myocarditis. Transthoracic echocardiography represents the first-line imaging test for the evaluation of patients with suspected ICI-associated myocarditis thanks to its versatility and availability. Abnormalities observed during echocardiography can include new left ventricular (LV) dysfunction, diastolic dysfunction, and regional wall abnormalities[30].

CMR is performed when the patient is clinically stable and represents a fundamental tool, also thanks to technological innovation, with the introduction of parametric mapping techniques [17,13]. Endomyocardial biopsy should be performed as standard in patients with unstable condition or stable conditions with worsening of LV dysfunction[13]. Positron emission tomography (PET) scan is not usually employed in the diagnosis of myocarditis. Current literature is limited to case observations showing a ^{18}F-fluoro-deoxy-glucose (FDG) uptake in the site of the myocardium with active inflammation[31]. Further longitudinal studies are needed to confirm the applications of FDG PET in the diagnosis and management of myocarditis.

Treatment should be supportive (for arrhythmias and heart failure) and should be addressed to the underlying cause. Avoidance of physical activity should be indicated to prevent arrhythmias. From a prognostic point of view, 50% of the patients recover within 4 weeks[32]. Unfortunately, up to 25% of patients can develop dilated cardiomyopathy and severe heart failure. Dilated cardiomyopathy can occur years after apparent recovery[17]. Supportive management can include inotropic therapy and even mechanical circulatory support, including extracorporeal membrane oxygenation[33].

3. Role of CMR in the diagnosis of myocarditis

Due to its unique ability to non-invasively assess tissue characteristics, CMR has become the reference standard technique for assessment of myocardial inflammation in patients with suspected myocarditis. CMR allows for an evaluation of different features of myocarditis, namely hyperemia, edema, and late gadolinium enhancement (LGE), as well as ancillary findings, including contractile dysfunction and pericardial effusion[34,35].

The recent expert consensus document regarding the management of acute myocarditis and chronic inflammatory cardiomyopathy recommended CMR in hemodynamically stable patients with clinically suspected acute myocarditis or in patients with chest pain, high troponin, and normal coronaries to rule out other ischemic or nonischemic origins[33].[29] Indeed, CMR findings are crucial in making a differential diagnosis with Takotsubo cardiomyopathy, which includes different myocardial wall edema and diffuse myocardial inflammation without LGE, myocardial infarction with a different pattern of LGE (subendocardial or transmural distribution), regional wall motion abnormalities with a coronary distribution, and myocardial infarction with non-obstructive coronary arteries (MINOCA), which is characterized by myocardial edema in a coronary distribution pattern. In addition, the expert consensus published by *Ammirati et al.* suggested CMR in fulminant myocarditis in hemodynamically stable patients to assess the presence, extent, and location of scar/fibrosis[33]. The role of CMR in the clinical setting of fulminant myocarditis has also been addressed by the Scientific Statement from the American Heart Association as a reasonable tool for the diagnosis of acute myocarditis in clinically stable patients, and in the early diagnosis of fulminant myocarditis, represents a class II recommendation with a level C of evidence[36].

CMR can achieve a sensitivity of 67% and a specificity of 91% with a diagnostic accuracy of 78% when 2 out of 3 CMR characteristics are present[34]. This is based on the 2009 Lake Louise Criteria (LLC) that comprise: (1) detection of edema on T2-weighted short tau inversion recovery (T2-STIR) CMR images, (2) detection of hyperemia and early capillary leakage on the basis of T1-weighted early gadolinium enhancement, and (3) detection of necrosis and fibrosis by LGE[34]. Concerning the fact that LGE and regional T2-STIR abnormalities may not optimally represent myocardial inflammation and fibrotic myocardial alterations, parametric mapping has emerged with additional diagnostic markers (e.g., T1, T2 mapping, and extracellular volume fraction). T1 mapping is susceptible to intracellular and extracellular changes in free water content, and its relaxation time rises during acute inflammation, vasodilation, and hyperemia. T1 mapping is able to detect chronic myocardial tissue injury[13]. Conversely, T2 mapping can detect acute myocardial edema and has several advantages in comparison with traditional T2-STIR sequences, including a higher signal-to-noise ratio and shorter breath-holds with a reduction of breathing motion artifacts[13,15,37]. Lastly, extracellular volume (ECV) reveals an expanded extracellular space and compared with LGE, may assess diffuse fibrosis and inflammation[13].

The diagnostic performance of CMR for detecting myocarditis has been shown to improve with the updated 2018 LLC[13], which includes one positive T2-based criterion and one T1-based criterion. In particular, T2-based criterion is considered to be positive if an increase of T2 native relaxation time or high T2 regional intensities on T2-weighted images exist. On the other hand, T1-based criterion is positive in the case of increased native T1 relaxation times, increased ECV, or positive LGE[13]. In a meta-analysis of 22 studies, novel CMR parameters for the diagnosis of acute myocarditis achieved high diagnostic accuracies with an area under the curve (AUC) of 0.95 for T1 mapping, of 0.88 for T2 mapping, and of 0.81 for ECV[38]. *Lagan et al.* reported a pooled weighted sensitivity, specificity, and diagnostic accuracy of 70, 91, and 79%, respectively, for T2 mapping and of 82, 91, and 86%, respectively, for T1 mapping[39]. The LLC update of 2018 proposed a “2 out of 2” combination[35], achieving a sensitivity of 87.5% and a specificity of 96.2% when both a T1 and T2-based criterion are fullfied[40]. Nevertheless, in a patient with a significant clinical probability, the presence of only one positive CMR parameters (either T1- or T2-based) makes the diagnosis still probable but with less sensitivity[13,35].

Recently, myocardial strain analysis using CMR has been shown to be a reproducible, feasible, and useful tool in the diagnosis of several cardiovascular diseases, including myocarditis[37,41–45]. In a clinical cohort of 125 patients with suspected myocarditis, bi-ventricular strain analysis using CMR yields good to excellent inter-observer and intra-observer reproducibility for all systolic strain parameters and early diastolic strain rates[46]. Myocardial strain analysis provides quantitative measurements of global and regional myocardial function that allows a more precise detection of wall motion abnormalities acting as an additional marker to enhance risk stratification, as well as to identify subclinical myocardial dysfunction[35,37,45].

Luetkens et al. evaluated LV strain parameters and their association with myocardial edema in 48 patients with suspected acute myocarditis demonstrating reduced longitudinal strain (LS), circumferential strain (CS), and radial strain (RS) compared with healthy control[47]. The diagnostic performance of a combined score of LS with T1 and T2 mapping was significantly higher when compared to LLC (AUC=0.98 *versus* AUC 0.89, $p=0.003$) with sensitivities, specificities, accuracies, positive predictive values, and negative predictive values of 92%, 97%, 93%, 98%, and 89%, respectively. In addition, the authors reported that LS was the only strain parameter, which showed a significant correlation between all myocardial inflammation CMR parameters, suggesting that strain parameters may be regarded as alternative parameters to quantify myocardial edema in acute myocarditis[47]. Also, atrial strain parameters combined with ventricular strain parameters were shown to improve diagnostic performance in patients with suspected myocarditis[45]. *Doerner et al.* reported an impairment of left atrial passive strain (LA εe: 26.3 ± 14.5 vs. $33.5 \pm 10.1\%$, $p = 0.007$) and left atrial peak early negative strain rate (LA SRe: -1.94 ± 0.59 1/s vs. -1.46 ± 0.62 1/s, $p < 0.001$) in comparison with healthy subjects[45]. In addition, LA SRe represented the best performing single parameter with an AUC of 0.72[45].

The aforementioned expert consensus document for the management of acute myocarditis and chronic inflammatory cardiomyopathy recommended CMR as a useful tool in the follow up of acute myocarditis and is generally performed from 6 to 12 months after the onset of the symptoms to evaluate the persistence of edema and LGE[33]. The persistence of scar/fibrosis and disappearance of edema represent unfavorable predictors of prognosis in comparison with complete resolution or persistence of both scars/fibrosis and edema[48]. LGE is a well-known prognostic predictor in patients with myocarditis[16,49]. *Gräni et al.* demonstrated that LGE was independently related to major adverse cardiovascular events (all-cause deaths, heart failure, ventricular tachycardia, transplantation, and recurrent myocarditis) in 670 patients over a median follow-up of 4.7 years[16]. In a multicenter Italian report of 374 patients with myocarditis, the presence and the location of LGE in the antero-septal mid-wall was independently associated with an adverse prognosis[49]. Also, ECV has shown to be a prognostic factor in a study of 79 patients with biopsy-proven myocarditis, demonstrating a significant univariable association with major adverse cardiovascular events (HR 3.3, 95% CI 1.43–7.97, p=0.005)[50].

Recently, myocardial strain analysis—particularly left ventricular global LS (GLS)—has been shown to be a useful predictor of major adverse cardiovascular events (MACE)[43]. *Fischer et al.* demonstrated that GLS assessed with feature tracking CMR was independently associated with MACE (hospitalization for heart failure, sustained ventricular tachycardia, or death) in 455 patients with clinically suspected myocarditis over a median follow-up of 3.9 years[46].

4. Immune checkpoint inhibitor-associated myocarditis

a) Clinical aspects

ICIs have revolutionized the treatment landscape and clinical history of several tumor types and now are widely employed as standard of care in medical oncology. Their mechanism of action is different from the one of chemotherapy or targeted agents, since ICIs do not exert a direct cytotoxic activity on cancer cells but rather reinvigorate a preexisting, spontaneous immune response directed against the tumor. Inhibitory immune checkpoints are physiological molecules that negatively regulate the immune response, maintain the self-tolerance, and minimize immune-mediated damages to healthy tissues. By blocking these immune checkpoints, ICIs “release the break” of the immune system and activate its response against the tumor. Of note, ICI-related adverse events are typically irAEs that can affect any organ, including the cardiovascular system[51].

ICI-linked fulminant and lethal myocarditis, usually associated with myositis (rhabdomyolysis is diagnosed by elevated creatine phosphokinase (CPK)) were first described in 2016 in patients treated with the anti-programmed cell death 1 (anti-PD-1) nivolumab (1 mg/kg) and the anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) ipilimumab (3 mg/kg)[52]. Besides myositis, ICI-linked myocarditis can be associated with myasthenia gravis[10,53]. A retrospective series conducted over 4 years in 8 sites detected a myocarditis incidence of 1% with a median onset of 13-65 days after the start of ICIs[10,54]. The American Society of Clinical Oncology Clinical Practice Guideline for the management of irAEs graded the severity of myocardial toxicity into 4 categories, from asymptomatic (grade 1) to severe degree of presentation (grade 4), as summarized in Table 1[5].

Myocarditis has been reported with all types of ICIs and is the irAE associated with the highest mortality (40%)[8]. It accounts for 8% of immune related fatal events linked to anti-PD-1/PD-L1 therapy, 25% following the combination of an anti-CTLA-4 *plus* an anti-PD-1[8]. Patients with diabetes undergoing ICIs in combination (ipilimumab *plus* nivolumab) experience more frequent and severe myocarditis[55,56]. Myocarditis with ipilimumab *plus* nivolumab therapy arose at a median of 17 days following the first treatment (range 13–64 days). The precise incidence of myocarditis in cancer patients undergoing ICIs is unknown because, so far, no clinical trials testing nivolumab +/− ipilimumab routinely screened patients for myocarditis, either using cardiac biomarkers (e.g., troponin), electrocardiogram (ECG), or cardiac imaging[55]. While the currently reported incidence of myocarditis is around 1%, it is possible that this value could increase in time due to higher awareness and better reporting of this toxicity[52].

The specific pathophysiological mechanisms underlying ICI-related myocarditis are not fully understood, with few case series reporting myocardial biopsy or autopsy results. It is known that myocarditis occurs due to T-cell infiltration and expansion on the cardiomyocyte, and this can occur due to several causes. Some of the hypothesized mechanisms are: 1) binding of ICIs to target molecules on non-lymphocytic cells with downstream immune activation; 2) cross-reaction of (new or reactivation of exhausted) T lymphocytes against tumor antigens with off-target tissues; and 3) generation of autoantibodies and production of pro-inflammatory cytokines (Figure 1)[57].

Indeed, autopsies in patients with ICI-associated myocarditis demonstrated $CD3^+$ (with predominant $CD8^+$-cytotoxic) T lymphocyte infiltration of cardiac and skeletal muscles, whereas no infiltration was seen in smooth muscles. This infiltration leads to myocyte destruction. Further, abundant $CD68^+$ cells (macrophages) and no $CD20^+$ cells (B lymphocytes) nor antibody deposits were observed. Patients shared high-frequency T-cell receptor sequences among cardiac, skeletal muscle, and tumor infiltrates, signifying that epitopes present in myocardium, skeletal muscle, and perhaps tumor cells were recognized by the same T-cell clones[52]. Similar findings were observed in another case report[55]. These observations support the hypothesis of a common (shared) epitope between the tumor and striated muscle that is at the basis of the immune-mediated reaction affecting myocardium after ICI treatment[52].

This type of cardiomyopathy, characterized by an infiltration of the myocardium, has also been defined as a type III cancer-related cardiomyopathy by *Herrmann et al.*, namely a non-toxic or non-reactive primary inflammatory myocarditis that requires an immediate immunosuppressive treatment[56].

b) <u>CMR and ICI-associated myocarditis</u>

CMR is gaining a central role in the diagnosis and monitoring of cardiovascular damage in cancer patients[58], and CMR is now considered a major diagnostic tool across international cardiology and oncology guidelines. In the recent position paper of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI), and the Cardio-Oncology Council of the European Society of Cardiology (ESC), CMR was recommended as a powerful tool for cancer patients with suspected ICI-related myocarditis[59]. Similarly, the European Society of Medical Oncology suggested CMR as an important piece of the diagnostic work-up for patients who develop cardiovascular symptoms while undergoing or after recent completion of ICI therapy[60].

CMR features of ICI-associated myocarditis are various and unpredictable, ranging from a lack of CMR findings with no edema and/or scars to diffuse myocardial inflammation[61]. A clinical example of ICI-associated myocarditis is reported in Figure 2.

Zhang et al. described the CMR finding from an international registry of patients with ICI-associated myocarditis, reporting that 42% of patients had LGE, and 28 % had elevated T2-STIR[62].

The pattern of LGE is variable with different extension and localization, including sub-endocardial, sub-epicardial, intramyocardial, and diffuse pattern, and it is more common in patients with a reduced LV ejection fraction (LVEF) in comparison with patients with a normal LVEF[62]. In addition, the authors demonstrated that CMR abnormalities were not associated with MACE, suggesting caution in ruling out ICI-associated myocarditis from CMR data (LGE and T2-STIR)[62]. These results may be explained by the limited sensitivity of T2-weighted STIR imaging. Indeed, T2-weighted STIR imaging and LGE depend on regional changes in inflammation or scar/fibrosis to be technically apparent[62].

On the other hand, *Escudier et al.* reported that LGE was present in only 23% of patients, and 33 % had myocardial edema assessed using T2-STIR sequence[63]. Conversely, *Mahmood et al.* described the presence of LGE in 74% of patients who developed ICI-associated myocarditis, especially with a mid-myocardial pattern[54]. A possible explanation for the discrepancy of LGE detection between the cohort studies may be related to the timing of CMR examinations and the onset of symptoms. *Zhang et al.* demonstrated that LGE presence increases with time; when a CMR was performed on day 4 of the onset of the symptomatology or later, the LGE detection increased from 21.6% to 72.0% ($p<0.001$)[62].

Alternative and innovative CMR techniques, including parametric mapping and myocardial strain, have already been shown to be useful in the diagnosis and prognosis of non-ICI myocarditis[13,37,64], and recent reports emphasized their validity in clinical decision-making, even in ICI-associated myocarditis[61,65–69]. *Thavendiranathan et al.* investigated the value of T1 and T2 mapping in 136 patients with ICI-associated myocarditis, reporting that native T1 and T2 were increased in 78% and 43% of patients, respectively[67]. The authors applied the modified LLC in their cohort of patients, finding that 95% of patients met the nonischemic myocardial injury (T1-based criterion) criteria, 53% met the myocardial edema (T2-based criterion) criteria, and 48% met both these main criteria with at least 1 of the main modified LLC for myocarditis present in 100% of the patients[67]. MACE outcomes were also investigated, reporting that T1 mapping was an excellent predictor of MACE with an AUC of 0.91 (95% confidence interval: 0.84 to 0.98)[67]. Conversely, T2 mapping was not independently associated with MACE, suggesting that the high prevalence of T1 abnormalities may reflect the extensive myocardial injuries from myocarditis and the presence of early myocardial fibrosis[67]. On the other hand, the lower prevalence of native T2 abnormalities may be explained by an intrinsic limitation of the study due to the delay of the CMR examination with 72% of patients treated with corticosteroids before the CMR examinations[67].

In the prospective study by *Faron et al.*, oncological patients with planned ICI treatment underwent CMR prior to starting the cancer therapy, as well as 3 months after the start of the treatment[69]. In the follow-up, the patients showed a diffuse increase of T1 and T2 mapping (972 msec ± 26 *versus* 1006 msec ± 36 ,P<0.001; T2 relaxation time, 54 msec ± 3 *versus* 58 msec ± 4, P<0.001, respectively), as well as an increased T2 signal intensity ratio (1.5 ± 0.3 *versus* 1.7 ± 0.3, P=0.03) and a reduction in LVEF (62% ± 7 *versus* 59% ± 7; P=0.048) in comparison with CMR at baseline[69]. Beyond the T2-STIR and parametric mapping abnormalities, a LV longitudinal strain impairment at CMR follow-up in comparison with baseline CMR (–23.4% ± 4.8 *versus* –19.6% ± 5.1, respectively; P=0.005) was described[69]. In addition, new focal non-ischemic LGE lesions were found in 9% of participants, whereas no significant differences in parametric mapping, LGE, and LVEF were found between patients who received ICI combination treatments and those who were administered ICI monotherapy[69]. Similarly, *Higgins et al.* investigated functional and morphological parameters, parametric mapping, and feature tracking of atrial and ventricular strain in a cohort of 20 patients treated with ICIs using CMR[65]. The authors demonstrated impairment in LV myocardial strain values (−9.8% ± 4.2%) in patients treated with ICIs even in those with normal LVEF values (−12.3% ± 2.4%)[65].

These studies highlighted CMR as a crucial tool in baseline cardiology evaluation, as well as in serial screening monitoring, allowing subclinical myocardial markers of inflammation and of LV impairments. In conclusion, we can speculate that comprehensive CMR imaging, including parametric mapping and myocardial strain analysis, is necessary for investigating and following serial changes in the myocardium over time in patients with suspected ICI-associated myocarditis. A summary of the above-mentioned studies regarding the role of CMR in patients with suspected ICI-associated myocarditis is reported in Table 2.

c) Limitations and future perspectives of CMR

The use of CMR in clinical practice is currently limited by low availability, costs, patient's intrinsic or extrinsic factors (e.g., ability to hold breath, claustrophobia, metallic implants, allergy to contrast media, arrhythmias), and the long time required for acquiring and analyzing imaging[15]. In daily clinical practice, some investigations are not carried out in a short period due to the increasing number of examinations, the length of the protocol, and the lack of experienced personnel. Several of the limitations previously described may be overcome by the application of Artificial Intelligence (AI) in daily clinical practice. AI in cardiovascular imaging is a rapidly evolving field and is ready to make a major impact on clinical practice[70–73]. The application of AI and its subsets, namely Machine Learning and Deep Learning, can help in both CMR imaging pre-processing (e.g., automate heart localization, expedite the process of acquiring data, improve patients positioning)[74–76] and post-processing (e.g., automate measurement of image segmentation, LGE, and parametric mapping)[77,78], saving time in the acquisition and analysis process and overcoming inter-individual and intra-individual variability[71].

Another potential approach to reduce the time of image acquisition and consequently to expand the use of CMR in clinical practice is the application of a "short" protocol. According to the Society for Cardiovascular Magnetic Resonance, a rapid protocol can be used in the evaluation of cardiomyopathies, including myocarditis[79]. Recently, *Nadjiri et al.* investigated the performance of a shortened CMR protocol to distinguish between patients with myocardial abnormalities and healthy subjects using parametric mapping and LV function analysis[80]. The authors reported that in patients with LV dysfunction, parametric mapping achieved an AUC of 82%, 60%, and 79% for T1 mapping, T2 mapping, and ECV, respectively. A shortened CMR protocol comprising of T1 mapping and LV function analysis showed a sensitivity of 98% and a negative predictive value of 90%[80].

The objectives of the application of a rapid protocol can be simplified in 3 major points as suggested by *Menacho-Medina et al.*: (1) reduce lengthy protocol; (2) make CMR more available; and (3) reduce costs[81]. Further studies are warranted to evaluate the diagnostic accuracy of rapid protocol and to compare it with standard protocols to make rapid protocols applicable in daily clinical practice.

d) <u>Role of endomyocardial biopsy</u>

The gold standard technique for the diagnosis of ICI-associated myocarditis is the endomyocardial biopsy (EMB)[26]. Traditional EMB in myocarditis is based on 4 to 6 samples obtained from the right ventricle (RV). *Yilmaz et al.* investigated the diagnostic performance of LV, RV, or biventricular EMB in 755 patients with clinically suspected myocarditis and/or cardiomyopathy of unknown origin, demonstrating that diagnostic EMB results were obtained significantly more often in bi-ventricular EMB in comparison with either selective LV-EMB or selective RV-EMB but with an increased risk of complications[82]. The authors hypothesized that the diagnostic accuracy of EMB may improve if the samples were obtained from the ventricle showing LGE[82]. The myocardial tissue from an affected area in ICI-associated myocarditis was characterized by the presence of inflammatory infiltrates, especially of CD8$^+$ T cells, as well as CD4$^+$ T cells, macrophages, and by the expression of human leukocyte antigens[83,84]. *Escudier et al.* demonstrated a lymphocytic infiltration in 89% of patients[63]. Similar results were also reported by *Zhang et al.* in 56 pathology-proven ICI-associated myocarditis[62]. In patients treated with CTLA-4 inhibitors and PD-1 inhibitors, the biopsy has also shown the presence of PD-L1-positive immunohistochemical stains[84]. Finally, the EMB can also exclude other etiologies for myocarditis, and a negative biopsy may allow resuming ICI treatments in patients without an alternative antitumor treatment[83].

The usual limitations of EMB in diagnosing myocarditis are represented by sampling errors, high inter-observer variability in interpreting the histopathological tissue, as well as its invasive nature with a risk of cardiac perforation[17]. For these reasons, EMB is not performed as a first-line test. In patients with suspected ICI-associated myocarditis, EMB should be considered in unstable patients and/or in case of persistent uncertainty after a normal CMR[84].

e) **Beyond ICI-associated myocarditis: other types of ICI-related cardiotoxicity**

ICI-associated myocarditis is the leading cause of immunotherapy-related cardiotoxicity. However, additional cardiac damage during ICIs has been reported. These include pericarditis, Takotsubo cardiomyopathy, atrial and ventricular arrhythmias, and acute myocardial infarction[83]. Figure 3 demonstrates an example of ICI-associated Takotsubo cardiomyopathy. Cardiotoxicity may be related to a direct association between ICI and atherosclerosis. In a recent study of 2,842 patients treated with ICIs, there was a 3-fold higher risk for cardiovascular events after starting an ICI (hazard ratio, 3.3 [95% CI, 2.0–5.5]; $P<0.001$)[85]. Among patients treated with ICIs, 119 developed a cardiovascular event at 2 years in comparison with 66 in the 2 year-period before the start of ICIs, with a 4-fold higher risk for cardiovascular events from 1.37 to 6.55 at 2 years (adjusted hazard ratio, 4.8 [95% CI, 3.5–6.5]; $P<0.001$)[85]. The authors also demonstrated an increase in the total and noncalcified plaque volumes with a rate of progression of total plaque volume > 3-fold higher after ICI (from 2.1%/year pre- to 6.7%/year post-)[85].

This increased risk of cardiovascular events during ICIs was also confirmed in a pooled data analysis of 59 clinical trials with 21,664 total patients, suggesting a 35% increased risk of coronary artery disease at 6 months follow-up in comparison with patients treated with traditional cytotoxic therapies[86].

f) **Proposed diagnostic work-up**

Given the nonspecific presentation of ICI-associated myocarditis, its diagnosis requires the combination of clinical, ECG, laboratory exams, and imaging data. As suggested by *Spallarossa et al.*, proper monitoring should begin with a baseline cardiology evaluation[87], although there is no clear evidence that a pre-existing cardiac disease stratifies patients at high risk for developing ICI-associated myocarditis[88]. The importance of a baseline cardiology evaluation in patients scheduled to receive cardiotoxic cancer therapy has also been emphasized by the position paper from the Cardio-Oncology Study Group of the HFA of the ESC in collaboration with the International Cardio-Oncology Society[89]. The baseline cardiology evaluation should include previous cardiovascular and cancer treatment history, cardiovascular risk factors, cardiac biomarkers (e.g., troponin, BNP, or N-terminal pro-brain natriuretic peptide (NT-proBNP)), ECG, and echocardiography data[89]. In this scenario, the role of CMR is limited by the cost and lack of widespread distribution. Nevertheless, as shown by *Faron et al.* for its ability to assess tissue characteristics, CMR would allow recognizing any myocardium change during ICI therapy[69]. In addition, the recent position paper of HFA/EACVI/ESC suggests CMR as a baseline assessment in patients with (1) poor quality echocardiographic images and (2) pre-existing heart diseases[89]. Further, the paper recommends stress CMR in patients with suspected angina[59].

ICI-associated myocarditis can have a rapidly progressive and life-threatening course; therefore, an early diagnosis is essential. The American Society of Clinical Oncology Clinical Practice Guidelines recommends a screening troponin measurement, especially in patients receiving dual ICI therapy because cardiotoxicity is more common with combination therapy[5]. *Spallarossa et al.* suggest a screening strategy with troponin measurement weekly for 6 weeks, then at weeks 8, 10, and 12[87]. Troponin is a high sensitivity test, with increased levels reported in over 90% of patients with ICI-associated myocarditis, but it is not specific for myocarditis. For this reason, CPK evaluation is associated to increase specificity, because myocarditis may be associated with myositis during ICI therapy. In the case of a positive troponin and/or a patient in ICI therapy with new onset of cardiovascular symptoms, other potential cardiovascular entities should be considered.

They can be either ICI-associated (e.g., Takotsubo cardiomyopathies and pericardial disease) and non-ICI-associated (e.g., myocardial infarction and MINOCA). In patients with persistent high troponin and no other possible causes, CMR is a useful tool. *Vágó et al.* found that in a cohort of patients with troponin-positive acute chest pain and non-obstructed coronary arteries, CMR performed within a suitably narrow time window can provide a definite diagnosis in around 90% of the patients[90]. The position paper of HFA/EACVI/ESC recommends serial monitoring with CMR in patients with poor quality echocardiographic images or to clarify measurement discrepancy from other modalities[59].

When the diagnosis of ICI-associated myocarditis is suspected, the first step is to discontinue ICI therapy, and the patients should be promptly admitted to a cardiology ward.

The guideline recommends that for any grade of severity of ICI-associated myocarditis, the diagnostic work-up should include ECG, cardiac biomarkers (troponin and BNP), echocardiogram, chest X-ray, and further testing after cardiology consultation (e.g., consideration of stress tests, cardiac catheterization, and CMR)[59]. In light of these recent guidelines, CMR represents a key diagnostic tool in clinically stable patients with suspected ICI-associated myocarditis[59]. A diagnostic work-up in these patients, emphasizing the role of CMR, is summarized in Figure 4.

Bonaca et al. proposed a standardized definition and classification of ICI-associated myocarditis into 3 groups of suspicion, namely definite myocarditis, probable myocarditis, and possible myocarditis, as summarized in Table 3[91].

To summarize, CMR and EMB represent the most specific tests to confirm ICI-associated myocarditis. CMR should be performed as the reference standard in clinically stable patients after ruling out alternative etiologies, such as coronary artery disease. Current literature suggests that normal CMR may not exclude all myocarditis patients; therefore, in the case of persistent suspicion, EMB should be considered. EMB should be performed early in the course of the disease in cases of unstable patients[92].

g. Treatment

Treatment of ICI-associated myocarditis includes an interruption of the anti-cancer treatment *plus* the administration of immunosuppressive therapies, starting with high dose systemic steroids (methylprednisolone pulse dosing 1 g/day for 3-5 days)[93]. In the absence of improvements within the first 24 hours, the administration of additional immunosuppressive drugs is needed[93]. Myocarditis might have a potentially life-threatening presentation, such as severe arrhythmias or heart block owing to presumed myocarditis. A differential diagnosis with pericarditis and an associated cardiac tamponade and acute myocardial infarction or coronary vasculitis on angiography is necessary. These signs/symptoms must be carefully considered by a multidisciplinary team involving cardiologists and oncologists. Some patients might require a rapid escalation of immunosuppressive drugs, such as immunoglobulins, antithymocyte globulin, infliximab (in the absence of heart failure), mycophenolate mofetil, or tacrolimus[94]. Additionally, plasmapheresis could eliminate circulating autoantibodies that foster ICI-induced myocarditis. This approach is crucial because ICIs' half-lives are extremely long: 14.5 days for ipilimumab, 25.0 days for pembrolizumab, 26.7 days for nivolumab, and 27.0 days for atezolizumab. Abatacept, a CTLA-4 agonist, might be used in cases of steroid-refractory myocarditis. Mechanical support, such as extracorporeal membrane oxygenation, can become necessary and life-saving as an additional treatment in case of fulminant myocarditis[95].

5. Conclusions

ICIs have significantly improved survival and quality of life of patients with several tumor types. Although most irAEs are mild and reversible, increasing reports of severe cardiac toxicity events raise important questions for future clinical trials and clinical practice. Systematic and standardized reporting of all rare irAEs should be a priority upon ICI trials publications, where irAEs should be reported as completely as possible, regardless of their rarity. Additionally, the population included in clinical trials is generally highly selected, so it is also necessary to assess the cardiac toxicities of ICIs in real-world patients who might experience more irAEs than those included in clinical trials.

In clinical practice, increasing awareness of the potential cardiac toxicity of ICIs among physicians is sought. Of note, a high level of vigilance is required, given that immune mediated myocarditis may present with non-specific symptoms and may potentially have a fulminant progression.[21] Hence, prompt interruption of ICIs and set up of an appropriate diagnostic work-up are recommended upon the clinical suspicion of an ICI-induced cardiac irAE.

The diagnosis of ICI-induced cardiotoxicity can be challenging, and CMR represents the gold-standard imaging test for the diagnosis of myocarditis. The strengths of CMR for the diagnosis of myocarditis rely on its ability to provide tissue characterization, as well as on its excellent spatial resolution, allowing the identification of sub-clinical myocardial markers of inflammation and of LV impairments. However, the use of CMR in clinical practice is currently limited by low availability, costs, patient’s intrinsic or extrinsic factors, and the long time required for acquiring and analyzing imaging. Nonetheless, several of the above-mentioned limitations may be overcome in the future by the application of AI in daily clinical practice and by new “short” protocols able to reduce the time of image acquisition. This could consequently expand the use of CMR in clinical practice.

Due to the rarity of these cardiac irAEs, the recommendations for their diagnosis and management are based mostly on anecdotal evidence, thus emphasizing the need for more robust and solid evidence-based guidance in this area.

Cardio-oncology dedicated trials are expected to address several open questions, including how to better stratify patients according to their risk of developing cardiac irAEs, how to monitor those at higher risk (e.g., clinical examination only *versus* laboratory tests and/or radiologic exams), and for how long to monitor patients. So far, no validated surveillance pathways exist for patients at higher risk of developing a cardiac irAE, although ECG and/or cardiac troponin could represent useful monitoring strategies.

Collaboration between oncologists, cardiologists, and radiologists should be sought in all phases, from the diagnosis to the follow-up of patients experiencing cardiac irAEs.

Figure legends

Figure 1: Mechanisms of development of immune checkpoint inhibitor (ICI)-induced myocarditis. Administration of ICIs can lead to an autoimmune lymphocytic myocarditis by negatively impacting immune tolerance that is achieved through the presence of the PD-1/PD-L1 inhibitory pathway. This tolerance disruption is mediated by activated T cells that can generate an immune-mediated cardiomyocyte damage.

Figure 2: Cardiac magnetic resonance (CMR) findings in immune-checkpoint inhibitor (ICI)-associated myocarditis. A 51-year-old patient with colon adenocarcinoma is treated with ICI. Given the suspicion of ICI-associated myocarditis, CMR was performed. It met the updated Lake Louise criteria (LLC) with a positive T1-based criterion and T2-based criterion. (a) Short-axis T2-weighted short tau inversion recovery (STIR) CMR images demonstrated an increase in signal in the mid-ventricular septal wall (white arrowheads). (b) Short-axis T2 mapping, and (c) T1 mapping revealed diffusely increased T1 and T2 relaxation time and predominant involvement in the septal wall (white arrowheads). (d) Late gadolinium enhancement short-axis view showed a patchy intramyocardial scar in the mid-ventricular septal wall (white arrowheads).

Figure 3: Cardiac magnetic resonance (CMR) findings in immune-checkpoint inhibitor (ICI)-associated Takotsubo cardiomyopathy. STIR T2 CMR 3-chamber (a) and short-axis (b-c) sequences revealed an increase in signal in relation to oedema from the mid ventricle (b) to the apex (c). T2 mapping short-axis (d-f) views confirmed left ventricular oedema and inflammation, which is worse in the apical left ventricle. T1 mapping short axis views (g-i) revealed diffuse signal. Late gadolinium enhancement 2-chamber (j), 4-chamber (k), 3-chamber (l), and short axis views (m-o) demonstrated no late gadolinium enhancement.

Figure 4: Summarized diagnostic work-up for patients with suspected immune checkpoint inhibitor (ICI)-associated myocarditis that emphasizes the role of CMR in the different steps. Despite CMR being limited by the cost and lack of widespread distribution, it may be an useful tool in baseline cardiology evaluation and screening, allowing the evaluation of a subclinical pre-

existing cardiovascular disease and recognizing any myocardium change during ICI therapy, as well as ruling out other possible causes of cardiac damage. When the diagnosis of ICI-associated myocarditis is suspected in clinically stable patients, CMR is a key tool to confirm the diagnosis of myocarditis.

Diagnostic CMR * = 2 out of 3 2009 LLC or at least one positive T1-based criterion and one T2-based criterion in the updated LLC

Suggestive CMR ** = does not entirely meet the 2009 LLC and/or updated LLC

BNP = circulating brain natriuretic peptide; CMR = cardiac magnetic resonance; ECG = electrocardiogram; EMB = endomyocardial biopsy; ICI = immune checkpoint inhibitors; LLC = Lake Louise Criteria; LVEF = Left Ventricle Ejection Fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide

Tables

Table 1

Grade	Features
Grade 1	Asymptomatic patients with abnormal cardiac biomarkers or ECG
Grade 2	Patients with mild symptoms and abnormal cardiac biomarkers and ECG
Grade 3	Patients with a reduction of LV ejection fraction or with a CMR suggestive or diagnostic for myocarditis
Grade 4	Life-threatening

Table 1: Severity grades of myocardial toxicity, according to the American Society of Clinical Oncology.[7]

Cardiac biomarkers = Troponin, BNP, NT-proBNP; ECG = Electrocardiogram; LV = Left Ventricle; CMR = Cardiac Magnetic Resonance

Table 1: Severity grades of myocardial toxicity according to the American Society of Clinical Oncology.[7] Cardiac biomarkers = Troponin, BNP, NT-proBNP; ECG = Electrocardiogram; LV = Left Ventricle; CMR = Cardiac Magnetic Resonance

Table 2

Authors	Number of patients	Year of publication	Research topic	Cardiac Magnetic Resonance Findings
Escudier et al.[22]	30	2017	Description of the clinical manifestations, management, and outcomes of patients who developed ICI-related cardiotoxicity.	23% of patients with ICI-related myocarditis had LGE, and 33 % had elevated T2-STIR.
Mahmood et al.[44]	35	2018	Evaluation of the presentation and clinical course of ICI-associated myocarditis.	Patients with ICI-associated myocarditis frequently shown CMR abnormalities (LGE in 74% of patients who developed ICI-associated myocarditis, especially with a mid-myocardial pattern).

Zhang et al.[50]	103	2020	Assessment of the CMR findings and its association with cardiovascular events among patients with ICI-associated myocarditis.	42% of patients had LGE, and 28% had elevated T2-STIR. In addition, CMR abnormalities were not associated with MACE.
Higgins et al.[52]	20	2021	Investigation of myocardial strain, LGE, and T2-STIR weight abnormalities in ICI-associated myocarditis.	Abnormal myocardial strain parameters were even found in patients with normal LVEF. LGE did not correlate with LVEF or GLS.

Table 2: Recent studies regarding CMR findings in patients with suspected ICI-associated myocarditis.

Table 3

Definition	Criteria
Definite Myocarditis	a) Tissue pathology (EM or autopsy) consistent with myocarditis.
	b) Diagnostic CMR (2 out of 3 2009 LLC or at least one positive T1-based criterion and one T2-based criterion in the updated LLC), clinical symptoms, and positive cardiac biomarkers or ECG evidence of myocarditis.
	c) Echocardiography wall motion abnormality, clinical symptoms, positive cardiac biomarkers, ECG evidence of myocarditis, and exclusion of coronary artery disease.
Probable myocarditis	a) Diagnostic CMR (2 out of 3 2009 LLC or at least one positive T1-based criterion and one T2-based criterion in the updated LLC) without clinical symptoms, positive cardiac biomarkers, and ECG evidence of myocarditis.
	b) Suggestive CMR findings (does not entirely meet the 2009 LLC and/or updated LLC) and clinical symptoms or positive cardiac biomarkers or ECG evidence of myocarditis.
	c) Echocardiography wall motion abnormality and clinical symptoms with either positive cardiac biomarker or ECG evidence of myocarditis.

	d) Clinical symptoms of myocarditis with fluorodeoxyglucose positron emission tomography imaging evidence and no alternative diagnosis.
Possible myocarditis	a) Suggestive CMR findings (does not entirely meet the 2009 LLC and/or updated LLC) without clinical symptoms, positive cardiac biomarkers, and ECG evidence of myocarditis. b) Echocardiography wall motion abnormality and clinical symptoms or ECG evidence of myocarditis. c) Positive cardiac biomarker with clinical symptoms or ECG evidence of myocarditis and no alternative diagnosis.

Table 3: Proposed standardized classification of ICI-associated myocarditis according to *Bonaca et al*.[76]

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The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Conflict of Interests

M.L. acted as consultant for Roche, AstraZeneca, Eli Lilly, Exact Sciences, MSD, Seagen, Pfizer, Gilead, and Novartis and received speaker honoraria from Roche, Sandoz, Takeda, Pfizer, Eli Lilly, Ipsen, Libbs, Knight and Novartis outside the submitted work. M.S acted as consultant for MSD, BMS, Astra-Zeneca, Merck, Amgen and Servier and received speaker honoraria from MSD, Mercks, Amgen, Eisai, Servier outside the submitted work.

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