



Cardiovascular toxicity of checkpoint inhibitors: review of associated toxicity and design of the Spanish Immunotherapy Registry of Cardiovascular Toxicity

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Abstract

Immune checkpoint inhibitors (ICI) have changed the prognosis of many tumors. However, concerning associated cardiotoxicity has been reported. Little is known about the real-life incidence-specific surveillance protocols or the translational correlation between the underlying mechanisms and the clinical presentation of ICI-induced cardiotoxicity. The lack of data from prospective studies led us to review the current knowledge and to present the creation of the Spanish Immunotherapy Registry of Cardiovascular Toxicity (SIR-CVT), a prospective registry of patients receiving ICI that aims to examine the role of hsa-miR-Chr8:96, (a specific serum biomarker of myocarditis) in the early diagnosis of ICI-induced myocarditis. An exhaustive prospective cardiac imaging study will be performed before and during the first 12 months of treatment. The correlation between clinical, imaging, and immunologic parameters may improve our understanding of ICI-induced cardiotoxicity and enable simpler surveillance protocols. We assess ICI-induced cardiovascular toxicity and describe the rationale of the SIR-CVT.

Keywords Cardio-oncology · Cardiotoxicity · Immune checkpoint inhibitors · Myocarditis · miRNA

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Introduction

Immunotherapy has changed the prognosis of many solid tumors, and the number of drug approvals for various indications is continuously expanding. Cardiovascular toxicity induced by immune checkpoint inhibitors (ICI) is a major concern owing to the high fatality rate reported [1].

ICI-induced cardiovascular toxicity has a wide spectrum of presentations, although knowledge on its underlying mechanisms and definitive diagnosis is lacking. While immune-related adverse events (irAE) have been related to better outcomes [2], mortality associated with cardiovascular toxicity and the heightened awareness thereof among physicians treating affected patients may prompt treatment interruptions that can seriously impact survival after small increases in cardiac biomarker levels or unspecific symptoms such as chest pain or palpitation. The lack of prospective registries and surveillance protocols means that decisions must be made based on expert consensus with little scientific evidence.

We aim to review the cardiovascular toxicity of ICI and to describe the design of a novel prospective registry of ICI cardiotoxicity, the Spanish Immunotherapy Registry of Cardiovascular Toxicity (SIR-CVT).

Clinical spectrum of ICI-induced cardiovascular toxicity

A wide range of clinical syndromes classified as irAE can affect the heart and vessels, from the myocardium to the endothelium. Supraventricular and ventricular arrhythmias, conduction disorders, myocardial inflammation, transient cardiac dysfunction, arterial thrombosis, and pericardial inflammation can all lead to acute heart failure and shock, sudden death, myocardial infarction, and cardiac tamponade [3]. These acute toxicities are mainly expected during the first months after initiation of treatment, although there is increasing concern over late vascular toxicity presenting as accelerated atherosclerosis, which may increase the frequency of major cardiovascular events (MACE), namely, myocardial revascularization, myocardial infarction, and stroke [4]. The main types of cardiovascular toxicity of ICIs are shown in Fig. 1. In addition, wide retrospective cohort studies have reported a higher incidence of heart failure, acute coronary syndrome, and cerebrovascular disease than in non-ICI controls, with an incidence of around 10% in ICI patients [5, 6], suggesting a specific immune-related mechanism underlying the toxicity leading to these cardiovascular events, which are also prevalent in patients with cancer. The evidence for this broad cardiotoxicity has been accumulated from the publication of clinical cases and patient series addressing a specific type of toxicity, as well as from retrospective studies aiming to cover the whole spectrum of ICI-induced cardiotoxicity (Table 1). The most specific cardiotoxicities are described below.

Fig. 1 Schematic representation of cardiovascular toxicities of ICI. **A** Hematoxylin–eosin-stained sample of the myocardium with lymphocytic infiltrate. **B** Ventriculogram typical of Takotsubo syndrome

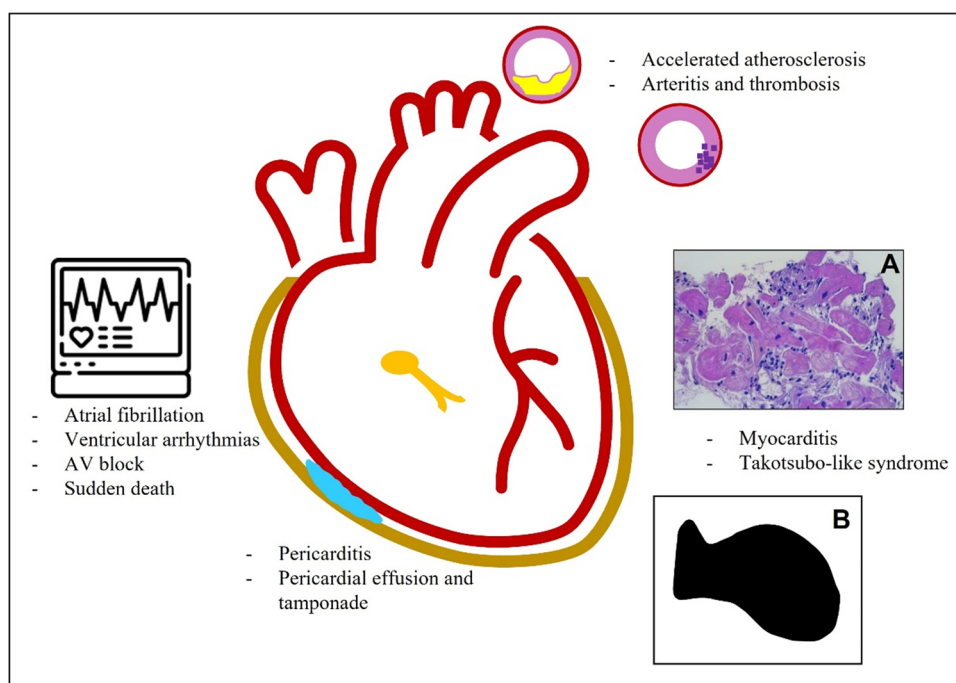


Table 1 Main studies describing the cardiovascular toxicity of ICI

Study	Number of patients, cancer type	Design	Type of toxicity	Main findings
Heinzerling L. et al. [29]	8, melanoma	Case series, multicenter, retrospective	CV toxicity	Description of myocarditis (4 patients), non-ischemic cardiomyopathy (2), heart failure (1), and cardiac arrest (1)
Johnson D. B. et al. [50]	2, melanoma	Case series, single-center, retrospective	Fulminant myocarditis	Clinical description of fulminant myocarditis and myocardium post-mortem findings
Zimmer L. et al. [51]	8, any cancer	Retrospective registry, multicenter	Immune-related toxicity	8 cardiac irAE in 496 patients with irAE: Angina pectoris (1), high BP (1), arrhythmias (3, sinus tachycardia, atrial flutter, ventricular arrhythmias), asystole (1), myocarditis (1), LV dysfunction (1)
Escudier M. et al. [26]	30, any cancer	Retrospective, two-center case series, and literature-reviewed cases	CV toxicity	Clinical spectrum (arrhythmias, non-inflammatory LV dysfunction, myocarditis) and predictors of 27% CV mortality (conduction disorders and combination of anti-CTLA4 and anti-PD-1)
Mostle J. J. et al. [11]	101, any cancer	VigiBase analysis	Myocarditis	Description of clinical features: early time of onset, concurrent irAE (e.g., myositis, myasthenia), mortality (46%), proposed risk factors (combination of anti-CTLA4 and anti-PD-1)
Mahmood S.S. et al. [13]	35, any cancer	Retrospective, international, multi-center, case series	Myocarditis	Clinical, biomarkers (rise in troponin and NT-proBNP) and imaging features (normal EF in almost half of patients). High fatality rate
Salem J.E. et al. [32]	31,321 total adverse events, any cancer	Retrospective VigiBase analysis (comparison of CV adverse events between ICI and non-ICI treatments)	CV toxicity	ICI treatment is associated with the occurrence of myocarditis, pericardial disease (especially in lung cancer), and vasculitis (temporal arteritis and rheumatic polymyalgia). Mortality rate in CV irAE of 50%
Altan M. et al. [35]	3, NSCLC	Retrospective case series	Pericardial disease	Description of clinical presentation and histopathologic findings in the pericardium (2 autopsies and 1 biopsy sample)
Chitturi K.R. et al. [52]	252, lung cancer (135 received ICIs)	Retrospective, single-institution, cohort study	MACE*	Biomarkers (troponin and BNP) and ITK and VEGF1 were associated with an increased risk of MACE in the ICI cohort

Table 1 (continued)

Study	Number of patients, cancer type	Design	Type of toxicity	Main findings
Bar J. et al. [53]	1215, any cancer	Retrospective, single-institution, cohort study	AVE	AVEs were more frequent during the first 6 months
Ederhy S. et al. [28]	13,188,920, any cancer	Retrospective VigiBase analysis	Takotsubo syndrome (TTS)	13 TTS were identified. ICI may be related to a higher incidence of TTS
Saade A. et al. [34]	3, NSCLC	Retrospective, 2-center, case series of nivolumab-treated patients	Pericardial disease	Review of literature with a total of 16 cases describing the time of onset, clinical manifestations (dyspnea, tachycardia, chest pain, shock), high incidence of malignant etiology in pseudo-responsive patients, treatment summary (most of the patients treated with corticosteroid-free regimen)
Zamami Y. et al. [54]	1,979,157 adverse events, any cancer (13 096 cases received ICIs)	Retrospective FAERS database analysis	Myocarditis	Myocarditis more frequent in patients treated with ICI (as with each drug: atezolizumab, avelumab, pembrolizumab, ipilimumab, and nivolumab). Old age (over 75) and female sex were associated with myocarditis in patients taking ICI
Champion S.N. et al. [55]	10, any cancer	Retrospective, single-center, case series	Myocarditis	Defines high- and low-grade myocarditis at biopsy and correlates with the clinical syndrome. Compares ICI-induced myocarditis with heart transplant, acute cellular rejection (2R), lymphohistiocytic infiltrate with increased CD68/CD3 ratio and increased PD-L1 ⁺ macrophages and myocytes
Cautela J. et al. [23]	60, any cancer	Retrospective, single-center, and literature-reviewed cases	Myocarditis	Description of immunosuppressive therapy (IST), clinical profile of patients requiring IST compared with those who do not
Drobni S. et al. [4]	8543, any cancer (2842 received ICIs)	Retrospective, single-center, cohort study, historically controlled	MACE**	ICI cohort of patients had a higher incidence of MACE (overall and for each event) than non-ICI patients at 2 years. Progression of aortic atherosclerosis was demonstrated in imaging sub-analysis
Cautela J. et al. [56]	5, any cancer	Retrospective, single-center, and pharmacovigilance database review	ACS	Probable causality of ICI treatment on ACSs

Table 1 (continued)

Study	Number of patients, cancer type	Design	Type of toxicity	Main findings
Dolladille C. et al. [57]	634, any cancer (38 cases from French cardio-oncology centers and 596 from Vigibase)	Retrospective, multicenter and Vigibase analysis	Cardiac adverse events	Differences in clinical profile and mortality in patients with early vs. late (> 90 days) cardiac adverse events. Myocarditis and arrhythmia occur earlier while HF and pericardial disease occur later
D'Souza M. et al. [5]	25 573 lung cancer, (746 received ICIs) and 13,568 melanoma (357 received ICIs)	Retrospective, nationwide registry, cohort study	CV events (arrhythmia [both tachyarrhythmia and bradyarrhythmia], myocarditis or pericarditis, heart failure, and cardiovascular death)	The absolute risk of CV events is 7–10% in this cohort of ICI-treated patients, higher than in pharmacovigilance studies. The relative risk for CV events was increased at 6 and 12 months after initial treatment vs. the non-ICI cohort
Finke D. et al. [58]	26, any cancer	A retrospective, single-center, cohort of patients with ICI and CT/PET performed	Myocarditis	3 cases of ICI-related myocarditis were compared with 23 patients receiving ICI. 68 Ga-FAPI PET/CT showed a higher signal in patients with ICI-induced myocarditis
Gong J. et al. [31]	5541, any cancer (2842 received ICIs)	Retrospective, single-center, historically matched controlled	Pericardial disease	The absolute rate of pericardial disease of 1.5%, a higher risk than in the matched control cohort. Pericardial disease showed a trend toward a higher mortality rate
Jain P. et al. [47]	2,687,301, any cancer (12,187 received ICIs)	Retrospective, matched controlled cohort study from IBM MarketScan data (US)	CVAEs (Stroke, AFib, HF, conduction disorders, MI)	Incidence of CVAEs is lower than previous. Specific subgroups of risk (renal and lung cancer, combination therapy, previous radiation, other irAE, such as nephritis, encephalitis, and neuropathy)
Ma Z. et al. [33]	705, any cancer	Retrospective, FAERS database analysis	Pericardial disease	Higher prevalence in lung cancer patients and previous chest radiation; anti-CTLA4 and anti-PD-1/PD-L1 combination not related; early occurrence (< 3 months) especially in fatal cases
Palaskas N. L. et al. [59]	28, any cancer	A retrospective, single-center, cohort study	Myocarditis, (EMB of suspected ICI-induced myocarditis patients)	The severity of myocarditis in EMB may stratify patients and guide the intensity of treatment
Waheed N. et al. [60]	424, any cancer	A retrospective, single-center, cohort study	CV events (cardiomyopathy, heart failure, arrhythmia, heart block, pericardial disease, and myocarditis)	CV events cohort associated with higher mortality than non-CV events cohort
Waliany S. et al. [45]	214, any cancer	Prospective, single-center, cohort study	Rise in hs-troponin I	The low rise in troponin has no clear pathological significance (PPV of TnI > 54 pg/ml is 12.5%)

Table 1 (continued)

Study	Number of patients, cancer type	Design	Type of toxicity	Main findings
Wang C. et al. [24]	24, any cancer	Retrospective, single-center, cohort study	Myocarditis	Definition of corticosteroid-resistant myocarditis and potential role of tofacitinib for treatment
Laenens D. et al. [6]	672, any cancer	Retrospective, single-center, matched cohort	Cardiotoxicity (all)	Higher incidence rates of MACE were observed in ICI cohort vs. non-ICI cohort and controls. No myocarditis cases reported

ACS acute coronary syndrome, AVE acute vascular events (stroke, transient ischemic attack, myocardial infarction, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, acute coronary syndrome, embolic event, pulmonary emboli, and deep vein thrombosis), CV cardiovascular, CVAEs cardiovascular adverse events, EMB endomyocardial biopsy, FAERS FDA adverse events reporting system, HF heart failure, ICI immune checkpoint inhibitor, MACE major adverse cardiovascular events, MI myocardial infarction; *pt* patients

*Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure

**Cardiovascular death, myocardial infarction, myocardial revascularization, stroke

Myocarditis

ICI-induced myocarditis is the most worrying immune-related cardiovascular event [7]. The three main drivers of ICI-induced myocarditis described to date are as follows: (1) loss of peripheral immune tolerance, which enhances auto-immune responses; (2) antibody cross-reactivity between tumor antigens and antigens in cardiac tissue or muscle, leading to activation and infiltration of activated T cells, macrophages, and monocytes; and (3) increased blood concentrations of proinflammatory cytokines such as IL-17, which triggers ICI-induced myocarditis [8]. Other proposed mechanisms include elevated autoantibodies against self-antigens or subclinical inflammation driven by regulatory T cell (Treg) infiltration [9]. In their model of autoimmune myocarditis, Cruz-Adalia et al. showed that mice with low expression of CD69 + in Treg experienced exacerbated inflammation and had worse outcomes, including progression to heart failure [10].

Clinically relevant ICI-induced myocarditis is a rare adverse event. It generally affects less than 1% of patients in clinical trials, although its incidence is increasing owing to improved physician awareness and diagnostic protocols [11]. Current guidelines suggest several criteria for identification of high-risk patients in whom cardiac monitoring is advisable, including dual treatment with ICI, combination of ICI with other cardiotoxic agents, development of ICI-related non-cardiovascular events, and pre-existing cardiovascular disease [12].

Myocarditis presents with a variety of clinical manifestations, ranging from non-specific dyspnea to cardiogenic shock, typically within the first 3 months of treatment [13], and is characterized by elevated cardiac biomarkers (troponin and NT-proBNP) and abnormal electrocardiographic findings [14]. However, ejection fraction is preserved in half of patients, making it an insensitive diagnostic tool [15].

If the patient is clinically stable, the diagnosis can be confirmed using non-invasive tools, mainly cardiac magnetic resonance [16]. To improve sensitivity, it is advisable to perform T1 and T2 mapping [17]. While the modified Lake Louis criteria can be applied for imaging-based diagnosis of inflammation, the international consensus definition for ICI-related myocarditis was recently updated [18], with more contemporary definitions of the main toxicities associated with cancer treatment, including ICI-induced myocarditis, defined based on histopathological findings or a combination of biomarkers (high troponin levels), imaging, EKG, and clinical manifestations. These criteria maintain lymphocytic infiltrate in the myocardium as the gold standard for diagnosis, although no consensus has been reached on grading [17] or on the prognostic and therapeutic implications of the histopathological grades of severity [18]. In unstable patients (shock, ventricular tachycardia, or AV block), or when a

non-invasive diagnosis remains doubtful, endomyocardial biopsy is recommended to confirm ICI-induced myocarditis and rule out additional causes of myocarditis [19].

Other biomarkers, such as hsa-miR-Chr8:96 (human homologue of murine miR-721), are specifically related to myocarditis, even in patients with ICI-induced myocarditis (unpublished data from Martin P. et al.). The high specificity of this miRNA for inflammatory myocardial damage has been demonstrated in various cohorts of patients with different types of myocardial damage, including those with ischemia, non-obstructive myocardial infarction, and even autoimmune inflammatory disease not involving the heart and mediated by Th17 lymphocytes [20]. Therefore, this miRNA has the potential to serve as a specific biomarker for ICI-induced myocarditis. However, it has yet to be prospectively validated in patients at risk of developing ICI-induced myocarditis.

Early administration of high-dose corticosteroids is recommended when ICI-myocarditis is suspected [21]. The standard protocol is methylprednisolone 500–1000 mg i.v. for 3–5 days, with subsequent tapering to 1 mg/kg per day for 4–6 weeks. If clinical stability or a 50% reduction in cardiac troponin is not achieved, combination with other immunosuppressive agents should be considered (mycophenolic acid, intravenous immunoglobulins alone or in combination with plasmapheresis, thymoglobulin, tofacitinib, abatacept, or alemtuzumab) [22–24].

Takotsubo-like syndrome

Takotsubo-like syndrome, or stress cardiomyopathy, has been related to many anti-tumor treatments and also to ICI [25, 26]. It is defined as an acute and transient regional dysfunction of the left ventricle in the absence of obstructive coronary artery disease [27]. Its incidence in association with ICI is unknown, although it seems to be more frequent in ICI-treated patients [28]. Clinical manifestations range from chest pain to heart failure or even cardiac arrest [29]. The differential diagnosis with ICI-myocarditis is challenging and requires advanced imaging and, frequently, endomyocardial biopsy to rule out lymphocytic infiltrates [30]. Once myocarditis is reasonably excluded, treatment of heart failure should be sufficient to ensure recovery [12].

Pericarditis

ICI-induced pericarditis has been described as an inflammatory complication affecting the pericardium with frequent clinical manifestations consisting of chest pain, pericardial effusion, and cardiac tamponade. However, patients often remain asymptomatic, and the diagnosis is incidental during routine image testing [31]. There are no clinical predictors or well-recognized risk factors, although pericarditis seems

especially frequent in lung cancer patients [31–33]. It is unclear whether this relationship found in epidemiological studies can be related to concomitant treatments (radiotherapy, other chemotherapies) or infiltration of the pericardium by cancer [34, 35]. In contrast with ICI-induced myocarditis, clinical onset may be some time after initiation of treatment (median of 153 days), as established in retrospective studies [31], while pharmacovigilance studies report 30 days [32]. Other authors report that ICI-induced pericarditis may even appear months after discontinuation of ICI [36]. Treatment consists of pericardiocentesis or pericardial window in the case of tamponade and anti-inflammatory therapy, mainly non-steroidal anti-inflammatory drugs or corticosteroids. Rechallenge with ICI has been described without recurrence; therefore, after resolution of the initial manifestations, treatment with ICI can be restarted under close monitoring if an anti-tumor benefit is expected [34]. However, the development of ICI-related pericardial disease has been associated with a 62% mortality rate, which is considerably greater than that of pericardial complications in non-ICI-treated patients [31].

Arteritis

Arterial acute inflammatory toxicity presenting as acute coronary syndrome (ACS) or vasculitis has also been described [3]. It is unknown whether ACS corresponds to plaque rupture, inflammatory thrombosis, or vasospasm [37]. Most cases of common ICI-related systemic arteritis are temporal arteritis (TA) and rheumatic polymyalgia (RP). Both are rare irAE, with an estimated frequency of less than 0.3%, although they may cause severe morbidity, especially when TA presents with ophthalmic events, which can lead to blindness in up to 15–20% of cases. The pathophysiology of TA is thought to be related to the expression of PD-L1 in the endothelium, while a milder form of systemic inflammation occurs in RP [32].

Atherosclerosis

The pro-atherosclerotic effect of checkpoint inhibition in the endothelium has been demonstrated in murine models, probably related to the high expression of PD-L1 and PD-L2 in endothelial cells [38]. However, a reduction of the atherosclerotic lesion of the aortic root has been observed in transgenic mice with overexpression of CTLA-4 [39]. Other pathogenic theories support a role for the T cell activation involved in the progression and development of atherosclerosis due to inflammation. The inhibition of other innate immunity pathways such as that of interleukin 1 beta (IL-1 β) or neutrophils by canakinumab and colchicine, respectively, has demonstrated favorable cardiovascular outcomes in humans. Retrospective

observational studies have compared the incidence of MACE, which was shown to be fourfold greater in the ICI cohort than in non-ICI patients and twofold higher when 2-years post- and 2 years-pre-ICI treatment periods were compared. In the imaging sub-study, Drobní et al. demonstrated a more marked progression of aortic atherosclerosis by CT imaging compared with a previous CT scan where patients were not-treated with ICI [4]. This ‘atherogenic’ toxicity, while less striking than irAE, is a growing cause for concern, since it can affect survival in patients who would otherwise have a better cancer prognosis. Whether the aggressive control of cardiovascular risk factors can prevent MACE in these patients remains to be elucidated. The expected beneficial role of statins or anti-inflammatory drugs has yet to be proven [40].

Rationale and design of the Spanish Immunotherapy Registry of Cardiovascular Toxicity (SIR-CVT)

Purpose and objectives

SIR-CVT is a multicenter, competitive, observational registry aiming to describe the incidence, predictors, and daily management of cardiovascular complications that present in adult patients treated with ICI not previously included in clinical trials.

With this purpose, the Cardio-Oncology working group of the Spanish Society of Cardiology (SEC), the Spanish Society of Medical Oncology (SEOM), and the Spanish Centre of Cardiovascular Research (CNIC) agreed to prospectively recruit patients receiving their first ICI treatment. Baseline and follow-up cardiovascular assessment includes clinical, electrocardiographic, analytic, and advanced imaging techniques. The translational work at CNIC evaluates the peripheral inflammatory response of patients and analyzes the specific diagnostic value of hsa-miR-Chr8:96, a lymphocytic micro-RNA that is detected specifically in plasma from myocarditis patients (Fig. 2).

The primary and secondary objectives are described in Table 2.

Centers

All participating centers signed an agreement to participate in the study and declared their capacity to recruit patients and adhere to the protocol. All centers have a cardio-oncology program or unit, and each has provided a principal investigator (PI) from cardiology and oncology. The basic research will be conducted at CNIC.

Patients

To be included in the registry, patients must be over 18 years old and have signed the informed consent before initiation of ICI treatment (anti-CTLA4, anti-PD1, anti-PD-L1, or combination of these). Prior chemotherapy for the current or previous tumor is allowed.

The exclusion criteria are participation in a clinical trial with ICI, a survival estimate of less than 6 months, clinical contraindications to ICI, and previous treatment with ICI.

Sample size has been calculated based on a bilateral contrast with an alpha risk of 0.05 and a beta risk of 0.2. To detect a statistically significant difference of 10% between 2 proportions, we determined that 402 subjects are required in the first group and 40 in the second group, assuming an incidence rate of 10% for cardiac events. A rate of loss-to-follow-up of 5% has been estimated. However, given the observational purpose of the study, we aimed to achieve a sample size of 500 individuals.

Study variables

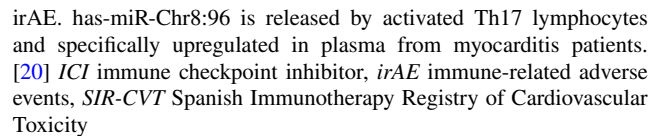
Researchers must include sociodemographic variables, cancer-related variables, laboratory variables, electrocardiographic variables, variables from cardiac imaging examinations and the patient’s medical history, cardiovascular events, and the management of cardiovascular toxicity events.

Data collection and analysis

The study protocol has been approved by the ethical committee at Hospital General Universitario Gregorio Marañón and accomplish with the Declaration of Helsinki and current legislation. The data will be stored in an electronic data capture model to which only the researchers and project managers will have access through a monitored security key. An automatic identification number will be generated in the model for each patient to ensure privacy of personal data.

The participating centers will be monitored through a remote system, and periodic audits of the database will be carried out to optimize quality.

A descriptive analysis of the whole cohort will be carried out. Multivariate logistic regression using mixed models to assess longitudinal data will be applied to identify biomarkers associated with cardiotoxicity events (molecular biomarkers, biomarkers related to treatment, and risk factors). Joint models will also be applied to model time to cardiotoxicity. Previously, we will perform descriptive analyses using heatmaps and univariate models to identify key biomarkers.

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exclusion criteria and must sign the informed consent before inclusion.

All patients included in the study will be followed up until the withdrawal of consent or 12 months after inclusion or loss to follow-up.

The scheduled examinations are shown in Fig. 3. The data to be collected at the baseline visit comprise sociodemographic data, oncologic history, and cardiovascular history. Blood samples will be taken for clinical and translational investigations, and an EKG and advanced cardiac imaging will be performed. During the first 6 months, the schedule will be programmed by the oncologist. The cardiology visits and testing will be coordinated to minimize hospital appointments.

Adverse events and safety concerns

In this non-interventional prospective registry, toxicity will be managed following clinical practice recommendations from international societies [41–43] and local protocols. Cardiovascular events will be treated according to ESC practice guidelines.

An adverse event is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not this is considered related to the medicinal product.

If the adverse event results in death or is considered life threatening or provokes significant disability for the patient or motivates interruption of ICI, it would be classified as a severe adverse event (SAE). The definition of an SAE will be based on the FDA safety reporting recommendations

(<https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event>).

The intensity of an adverse event will be classified according to the Common Terminology Criteria for Adverse Events [44] (CTCAE), version 5 (Table 3).

All cardiovascular toxicity over grade 2 (3 or higher) will be considered an SAE and reported to the registry's safety committee and the Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS) by local investigators, as in routine clinical practice.

Discussion

We present the first prospective registry dedicated to ICI-treated patients that aims to describe cardiovascular toxicity based on a detailed clinical, electrocardiographic, and cardiac imaging assessment before and during treatment. This approach enables us to distinguish clearly between previous cardiovascular damage and ICI-induced cardiotoxicity. Monitoring of biochemical and immunological biomarkers can identify subclinical toxicity and susceptible patients early. Indeed, the second primary objective of SIR-CVT is to validate the use of hsa-miR-Chr8:96 in the early diagnosis of myocarditis, with the secondary objective of analyzing changes in peripheral lymphocyte populations during treatment. These immunological data will be translationally correlated with clinical data for the first time.

Our comprehensive cardiovascular study will enable us to determine the incidence of cardiovascular toxicity in a

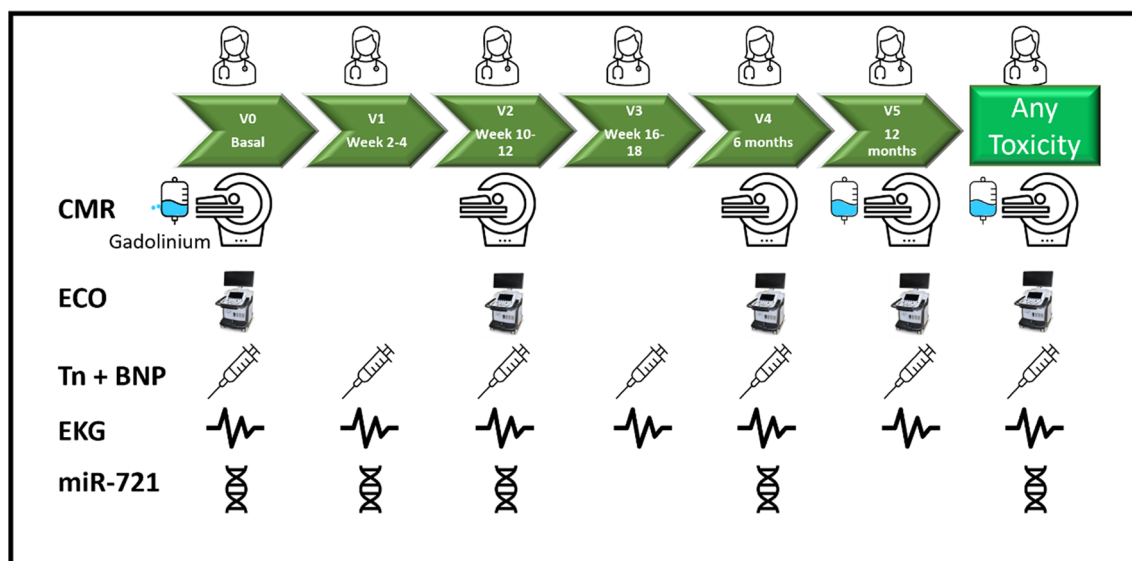


Fig. 3 Scheduled visits and examinations planned in SIR-CVT. *BNP* brain natriuretic peptides, *CMR* cardiac magnetic resonance, *ECO* echocardiogram, *EKG* electrocardiogram, *miR-721*: hsa-miR-

Chr8:96, human homologue of miR-721, *Tn* troponin, Spanish Immunotherapy Registry of Cardiovascular Toxicity

Table 3 Common terminology criteria for adverse events (CTCAE), version 5.0

Grade	Severity	Definition
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)
Grade 3	Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life (bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life threatening	Life-threatening consequences, urgent intervention indicated
Grade 5	Death	Death related to adverse events

real-world cohort. The incidence of ICI-induced myocarditis in clinical trials is low, although most of our knowledge is based on case series and retrospective studies (Table 1). However, reported bias related to non-specific cardiovascular surveillance protocols can also contribute to this infrequent presentation. The combination of hsa-miR-Chr8:96 and high-sensitivity troponin for surveillance of irAE, including myocarditis, has not been previously explored. Measurement and monitoring of hsa-miR-Chr8:96 increase sensitivity and specificity for the diagnosis of myocarditis. In addition, we expect this approach to be able to predict the development of clinically significant ICI-induced myocarditis (Fig. 2). Moreover, we anticipate that the combination of biochemical and immunological biomarkers with cardiac imaging will improve the potential to distinguish clinically relevant toxicity from mild forms of cardiovascular damage (permissive toxicity) and help us to establish new monitoring protocols that will simplify current non-evidence-based surveillance. Especially relevant is the interpretation of isolated elevations of high-sensitivity cardiac troponin, which have a low positive predictive value and, in some cases, may lead to unnecessary interruption of ICI [45].

SIR-CVT will enable us to determine the incidence of cardiovascular disease in a real-world ICI-treated cohort. Epidemiologic studies report an incidence of around 10% of cardiovascular events in ICI-treated patients [5, 6], although a recent meta-analysis and other studies report a much lower frequency of cardiac irAE (around 3%) [46, 47], thus calling into question whether cardiac evaluation and surveillance should be offered to all patients, as recommended by the latest ESC guidelines [12]. This controversy highlights the need for large-scale prospective registries—probably larger than ours—to elucidate the real incidence, predictors, mechanisms of toxicity, and optimal surveillance protocols Fig. 3.

Finally, it is necessary to remark on the relevance of severe toxicity in patients treated in an adjuvant setting, where increased use of ICI [48, 49] constitutes a broad indication that will lead to rare toxicities affecting a high number of patients in the near future. In this context, it is necessary

to develop surveillance protocols that can detect early toxicity, and thus prevent harm.

Limitations

We are aware that the low incidence of myocarditis reported may limit the validation of hsa-miR-Chr8:96 and the explorative intention of our planned analysis. Moreover, since changes in imaging findings over time, especially characterization of myocardial characterization parameters using T1 and T2 mapping, have not been previously evaluated, our data may prove to be of limited relevance or difficult to interpret. We are also aware that our cohort is not completely representative of the whole cohort of ICI-treated patients, since many younger patients with fewer comorbid conditions are enrolled in clinical trials, which is an exclusion criterion for participation in our registry and can represent a selection bias. The absence of a specific adverse event committee to evaluate potential toxicity may constitute another limitation; however, diagnosis is assigned by local investigators. The follow-up period may not be sufficiently long to detect very late toxicity presenting later than 12 months after initiation of ICI.

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Data Availability There is no Data Availability Statement for this review.

Declarations

Conflict of interest Every author has communicate his/her conflicts of interest.

Ethical approval (Research involving human participants and/or animals), Informed consent The study protocol has been approved by the

ethical committee at Hospital General Universitario Gregorio Marañón and accomplish with the Declaration of Helsinki and current legislation.

References

- Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol.* 2018;4(12):1721–8.
- Fan Y, Xie W, Huang H, Wang Y, Li G, Geng Y, et al. Association of immune related adverse events with efficacy of immune checkpoint inhibitors and overall survival in cancers: a systemic review and meta-analysis. *Front Oncol.* 2021;11:633032.
- Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol.* 2018;19(9):e447–58.
- Drobni ZD, Alvi RM, Taron J, Zafar A, Murphy SP, Rambarat PK, et al. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. *Circulation.* 2020;142(24):2299–311.
- D'Souza M, Nielsen D, Svane IM, Iversen K, Rasmussen PV, Madelaire C, et al. The risk of cardiac events in patients receiving immune checkpoint inhibitors: a nationwide Danish study. *Eur Heart J.* 2021;42(16):1621–31.
- Laenens D, Yu Y, Santens B, Jacobs J, Beuselinck B, Bechter O, et al. Incidence of cardiovascular events in patients treated with immune checkpoint inhibitors. *J Clin Oncol.* 2022;40(29):3430–8.
- Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med.* 2018;378(2):158–68.
- Jiménez-Alejandro R, Ruiz-Fernández I, Martín P. Pathophysiology of immune checkpoint inhibitor-induced myocarditis. *Cancers.* 2022;14(18):4494.
- Baik AH, Oluwole OO, Johnson DB, Shah N, Salem JE, Tsai KK, et al. Mechanisms of cardiovascular toxicities associated with immunotherapies. *Circ Res.* 2021;128(11):1780–801.
- Cruz-Adalia A, Jiménez-Borreguero LJ, Ramírez-Huesca M, Chico-Calero I, Barreiro O, López-Conesa E, et al. CD69 limits the severity of cardiomyopathy after autoimmune myocarditis. *Circulation.* 2010;122(14):1396–404.
- Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet.* 2018;391(10124):933.
- Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J.* 2022;43(41):4229–361.
- Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol.* 2018;71(16):1755–64.
- Zlotoff DA, Hassan MZO, Zafar A, Alvi RM, Awadalla M, Mahmood SS, et al. Electrocardiographic features of immune checkpoint inhibitor associated myocarditis. *J Immunother Cancer.* 2021;9(3):e002007.
- Awadalla M, Mahmood SS, Groarke JD, Hassan MZO, Nohria A, Rokicki A, et al. Global longitudinal strain and cardiac events in patients with immune checkpoint inhibitor-related myocarditis. *J Am Coll Cardiol.* 2020;75(5):467–78.
- Zhang L, Awadalla M, Mahmood SS, Nohria A, Hassan MZO, Thuny F, et al. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. *Eur Heart J.* 2020;41(18):1733–43.
- Thavendiranathan P, Zhang L, Zafar A, Drobni ZD, Mahmood SS, Cabral M, et al. Myocardial T1 and T2 mapping by magnetic resonance in patients with immune checkpoint inhibitor-associated myocarditis. *J Am Coll Cardiol.* 2021;77(12):1503–16.
- Herrmann J, Lenihan D, Armenian S, Barac A, Blaes A, Cardinale D, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J.* 2022;43(4):280–99.
- Zhang L, Reynolds KL, Lyon AR, Palaskas N, Neilan TG. The evolving immunotherapy landscape and the epidemiology, diagnosis, and management of cardiotoxicity: JACC: cardiooncology primer. *JACC CardioOncol.* 2021;3(1):35–47.
- Blanco-Dominguez R, Sanchez-Diaz R, de la Fuente H, Jimenez-Borreguero LJ, Matesanz-Marin A, Relano M, et al. A Novel circulating microRNA for the detection of acute myocarditis. *N Engl J Med.* 2021;384(21):2014–27.
- Zhang L, Zlotoff DA, Awadalla M, Mahmood SS, Nohria A, Hassan MZO, et al. Major adverse cardiovascular events and the timing and dose of corticosteroids in immune checkpoint inhibitor-associated myocarditis. *Circulation.* 2020;141(24):2031–4.
- Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. Management of immunotherapy-related toxicities, version 1.2019. *J Natl Compr Canc Netw.* 2019;17(3):255–89.
- Cautela J, Zerrouh S, Gaubert M, Bonello L, Laine M, Peyrol M, et al. Intensified immunosuppressive therapy in patients with immune checkpoint inhibitor-induced myocarditis. *J Immunother Cancer.* 2020;8(2):e001887.
- Wang C, Lin J, Wang Y, Hsi DH, Chen J, Liu T, et al. Case series of steroid-resistant immune checkpoint inhibitor associated myocarditis: a comparative analysis of corticosteroid and Tofacitinib treatment. *Front Pharmacol.* 2021;12:770631.
- Geisler BP, Raad RA, Esaian D, Sharon E, Schwartz DR. Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: a case of takotsubo-like syndrome. *J Immunother Cancer.* 2015;3:4.
- Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. *Circulation.* 2017;136(21):2085–7.
- Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo syndrome of the heart failure association of the European society of cardiology. *Eur J Heart Fail.* 2016;18(1):8–27.
- Ederhy S, Dolladille C, Thuny F, Alexandre J, Cohen A. Takotsubo syndrome in patients with cancer treated with immune checkpoint inhibitors: a new adverse cardiac complication. *Eur J Heart Fail.* 2019;21(7):945–7.
- Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, Tawbi H, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J Immunother Cancer.* 2016;4:50.
- Serzan M, Rapisuwon S, Krishnan J, Chang IC, Barac A. Takotsubo cardiomyopathy associated with checkpoint inhibitor therapy: endomyocardial biopsy provides pathological insights to dual diseases. *JACC CardioOncol.* 2021;3(2):330–4.
- Gong J, Drobni ZD, Zafar A, Quinaglia T, Hartmann S, Gilman HK, et al. Pericardial disease in patients treated with immune checkpoint inhibitors. *J Immunother Cancer.* 2021;9(6):e002771.
- Salem J-E, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol.* 2018;19(12):1579–89.

33. Ma Z, Pei J, Sun X, Liu L, Lu W, Guo Q, et al. Pericardial toxicities associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) database. *Front Pharmacol*. 2021;12:663088.
34. Saade A, Mansuet-Lupo A, Arrondeau J, Thibault C, Mirabel M, Goldwasser F, et al. Pericardial effusion under nivolumab: case-reports and review of the literature. *J Immunother Cancer*. 2019;7(1):266.
35. Altan M, Toki MI, Gettinger SN, Carvajal-Hausdorf DE, Zugaza-goitia J, Sinard JH, et al. Immune checkpoint inhibitor-associated pericarditis. *J Thorac Oncol*. 2019;14(6):1102–8.
36. Yun S, Vincelette ND, Mansour I, Hariri D, Motamed S. Late onset ipilimumab-induced pericarditis and pericardial effusion: a rare but life threatening complication. *Case Rep Oncol Med*. 2015;2015:794842.
37. Nykl R, Fischer O, Vykoupil K, Taborsky M. A unique reason for coronary spasm causing temporary ST elevation myocardial infarction (inferior STEMI)—Systemic inflammatory response syndrome after use of pembrolizumab. *Arch Med Sci Atheroscler Dis*. 2017;2:e100–2.
38. Gotsman I, Grabie N, Dacosta R, Sukhova G, Sharpe A, Lichtman AH. Proatherogenic immune responses are regulated by the PD-1/PD-L pathway in mice. *J Clin Investig*. 2007;117(10):2974–82.
39. Matsumoto T, Sasaki N, Yamashita T, Emoto T, Kasahara K, Mizoguchi T, et al. Overexpression of cytotoxic T-lymphocyte-associated antigen-4 prevents atherosclerosis in mice. *Arterioscler Thromb Vasc Biol*. 2016;36(6):1141–51.
40. Poels K, Neppelenbroek SIM, Kersten MJ, Antoni ML, Lutgens E, Seijkens TTP. Immune checkpoint inhibitor treatment and atherosclerotic cardiovascular disease: an emerging clinical problem. *J Immunother Cancer*. 2021;9(6):e002916.
41. Haanen J, Carbone F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl_4):iv119–42.
42. Majem M, García-Martínez E, Martínez M, Muñoz-Couselo E, Rodríguez-Abreu D, Alvarez R, et al. SEOM clinical guideline for the management of immune-related adverse events in patients treated with immune checkpoint inhibitors (2019). *Clin Transl Oncol*. 2020;22(2):213–22.
43. Bonaca MP, Olenchock BA, Salem JE, Wiviott SD, Ederhy S, Cohen A, et al. Myocarditis in the setting of cancer therapeutics: proposed case definitions for emerging clinical syndromes in cardio-oncology. *Circulation*. 2019;140(2):80–91.
44. Health UDo, Services H. Common Terminology Criteria for Adverse Events. Version 5.0. Published November 27, 2017. 2020.
45. Waliyan S, Neal JW, Reddy S, Wakelee H, Shah SA, Srinivas S, et al. Myocarditis surveillance with high-sensitivity troponin I during cancer treatment with immune checkpoint inhibitors. *JACC CardioOncol*. 2021;3(1):137–9.
46. Rubio-Infante N, Ramírez-Flores YA, Castillo EC, Lozano O, García-Rivas G, Torre-Amione G. Cardiotoxicity associated with immune checkpoint inhibitor therapy: a meta-analysis. *Eur J Heart Fail*. 2021;23(10):1739–47.
47. Jain P, Gutierrez Bugarin J, Guha A, Jain C, Patil N, Shen T, et al. Cardiovascular adverse events are associated with usage of immune checkpoint inhibitors in real-world clinical data across the United States. *ESMO open*. 2021;6(5):100252.
48. Mittendorf EA, Burgers F, Haanen J, Cascone T. Neoadjuvant immunotherapy: leveraging the immune system to treat early-stage disease. *Am Soc Clin Oncol Educ Book*. 2022;42:189–203.
49. Eggermont Alexander MM, Kicinski M, Blank Christian U, Mandal M, Long Georgina V, Atkinson V, et al. Five-year analysis of adjuvant pembrolizumab or placebo in stage III melanoma. *NEJM Evid*. 2022;1(11):EVIDoa2200214.
50. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375(18):1749–55.
51. Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:210–25.
52. Chitturi KR, Xu J, Araujo-Gutierrez R, Bhimaraj A, Guha A, Hussain I, et al. Immune checkpoint inhibitor-related adverse cardiovascular events in patients with lung cancer. *JACC*. 2019;1(2):182–92.
53. Bar J, Markel G, Gottfried T, Percik R, Leibowitz-Amit R, Berger R, et al. Acute vascular events as a possibly related adverse event of immunotherapy: a single-institute retrospective study. *Eur J Cancer*. 2019;120:122–31.
54. Zamami Y, Niimura T, Okada N, Koyama T, Fukushima K, Izawa-Ishizawa Y, et al. Factors associated with immune checkpoint inhibitor-related myocarditis. *JAMA Oncol*. 2019;5(11):1635–7.
55. Champion SN, Stone JR. Immune checkpoint inhibitor associated myocarditis occurs in both high-grade and low-grade forms. *Mod Pathol*. 2020;33(1):99–108.
56. Cautela J, Rouby F, Salem JE, Alexandre J, Scemama U, Dolladille C, et al. Acute coronary syndrome with immune checkpoint inhibitors: a proof-of-concept case and pharmacovigilance analysis of a life-threatening adverse event. *Can J Cardiol*. 2020;36(4):476–81.
57. Dolladille C, Ederhy S, Allouche S, Dupas Q, Gervais R, Madelaine J, et al. Late cardiac adverse events in patients with cancer treated with immune checkpoint inhibitors. *J Immunother Cancer*. 2020;8(1):e000261.
58. Finke D, Heckmann MB, Herpel E, Katus HA, Haberkorn U, Leuschner F, et al. Early detection of checkpoint inhibitor-associated myocarditis using 68Ga-FAPI PET/CT. *Front Cardiovasc Med*. 2021. <https://doi.org/10.3389/fcvm.2021.614997>.
59. Palaskas NL, Segura A, Lelenwa L, Siddiqui BA, Subudhi SK, Lopez-Mattei J, et al. Immune checkpoint inhibitor myocarditis: elucidating the spectrum of disease through endomyocardial biopsy. *Eur J Heart Fail*. 2021;23(10):1725–35.
60. Waheed N, Fradley MG, DeRemer DL, Mahmoud A, Shah CP, Langae TY, et al. Newly diagnosed cardiovascular disease in patients treated with immune checkpoint inhibitors: a retrospective analysis of patients at an academic tertiary care center. *Cardiooncology*. 2021;7(1):10.

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