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# Optimized monitoring for immune checkpoint inhibitor induced myocarditis using high-sensitivity troponin-T

Dirk Tomsitz [a], Ulrich Grabmaier [b], Judith Spiro [c], Leo Nicolai [b,d], Lars E. French [a,e], Steffen Massberg [b], Lucie Heinzerling [a,f,g,*]

[a] Department of Dermatology and Allergy, University Hospital, LMU Munich, Munich, Germany
[b] Department of Medicine I, LMU University Hospital, LMU Munich, Munich, Germany
[c] Department of Radiology, LMU University Hospital, LMU Munich, Munich, Germany
[d] DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany
[e] Dr. Philip Frost, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA
[f] Department of Dermatology, Friedrich-Alexander University Erlangen-Nürnberg (FAU) and University Hospital Erlangen (UKER), Deutsches Zentrum Immuntherapie (DZI) and Comprehensive Cancer Center Erlangen-European Metropolitan Area of Nürnberg (CCC-ER-EMN), Erlangen, Germany
[g] SERIO Registry (www.serio-registry.org), Germany

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ABSTRACT

*Background:* Immune checkpoint inhibitor (ICI)-induced Myocarditis (irMyocarditis) is a rare adverse event with a high mortality rate of 40–50 % and which is mostly not diagnosed until clinical symptoms emerge.
*Objectives:* This study aims to screen patients for irMyocarditis using high-sensitivity cardiac troponin-T (hs-TnT) before and regularly during therapy with ICI.
*Methods:* A cohort of 280 cancer patients were prospectively screened for levels of hs-TnT at baseline and prior to every ICI infusion. In case of elevation of hs-TnT, patients were referred for further work-up.
*Results:* In total, 196 patients exhibited a baseline hs-TnT $\leq$ 14 ng/l (99th percentile concentration for general population; group A) and 84 patients a hs-TnT $>$ 14 ng/l at baseline (group B). An increase of hs-TnT during ICI-treatment was observed in 56 out of 196 (27.6 %) and 56 out of 84 patients (66.7 %) in group A and B. Cardiovascular assessment was performed in 11.2 % and 27.4 % of patients, respectively, and 4.1 % and 9.5 % of patients were diagnosed with irMyocarditis and treated with corticosteroids. No fatalities occurred in any of the 16 irMyocarditis patients. Defining a threshold with the highest sensitivity and maximum specificity in receiver-operating characteristics curves, identified a limit of 22 ng/l (group A) and 60 ng/l (group B) hs-TnT, associated with a sensitivity of 100 % in both and a specificity of 91.0 % and 89.6 %, respectively, to detect irMyocarditis.
*Conclusion:* Screening of hs-TnT can identify irMyocarditis early and lead to reduction of MACE and mortality risk through interruption of ICI-treatment and prompt therapy with corticosteroids.

## 1. Introduction

Immune checkpoint inhibitors (ICI) are a mainstay of therapy for many tumor entities. In cutaneous melanoma, ICI-treatment is moving to earlier stages in the adjuvant setting and to operable disease in the neoadjuvant setting [1–5]. However, severe immune-related adverse events (irAE) have been observed and even fatalities occur [6]. ICI-induced Myocarditis (irMyocarditis) is observed in 1.14 % of patients with a high mortality rate of 40–50 % [7,8]. Of note, in these patients a major adverse cardiac event (MACE) was documented in 46 % of cases [9,10].

A multicenter retrospective analysis recently suggested this could be improved by earlier detection and prompt treatment with corticosteroids in case of diagnosis since otherwise cases of irMyocarditis are only diagnosed at the onset of clinical symptoms [11]. Screening for myocarditis during treatment with ICI is recommended but cardiac

*Abbreviations:* ICI, immune checkpoint inhibitor; Hs-TnT, high sensitivity carciac troponin-T; Hs-TnI, high sensitivity cardiac troponin-I; IrAE, immune-related adverse event; MACE, major adverse cardiac event; CK-MB, Creatine phosphokinase-MB; NT-proBNP, n-terminal pro-brain natriuretic peptide; ECG, electrocardiogram; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; ROC, receiver operating characteristic; AUC, area under the curve.

* Correspondence to: Department of Dermatology, LMU University Hospital Munich, Frauenlobstrasse 9-11, Munich D-80337, Germany.
*E-mail address:* lucie.heinzerling@med.uni-muenchen.de (L. Heinzerling).

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biomarker thresholds and frequency of biomarker elevation have not been defined [12]. In a clinical trial which included 126 patients treated with ICI, a prospective screening for myocarditis using high-sensitivity cardiac troponin-I (hs-TnI) revealed an elevation of hs-TnI in 18 patients (14.3 %), of whom myocarditis was diagnosed in 13 patients (10.3 %) [13]. Another trial which included 214 ICI-treated cancer patients also monitored hs-TnI. Of these patients, 24 (11.2 %) developed an increase of hs-TnI above the upper limit of normal (ULN) and were further evaluated by a cardio-oncology team. The final diagnosis of an ICI-associated myocarditis was made 3 patients (1.4 %) [14].

In this clinical trial we present data from a large prospective cohort of skin cancer patients receiving ICI-treatment who were consistently screened for myocarditis using high-sensitivity cardiac troponin-T (hs-TnT) before and regularly during therapy.

## 2. Methods

This analysis included all patients with either metastatic or unresectable skin cancer or patients with resected cutaneous melanoma stages IIB – IV (according to AJCC 2017) who started treatment with ICI at our skin cancer center between 01/2021 and 12/2023. All patients who received at least one dose of ICI were included and patients without available cardiac biomarkers before treatment start were excluded. The analysis was part of a project to investigate immune-related events which occur during ICI therapy (MelAutim). The study was approved by the institutional review board of the medical faculty of the LMU Munich University Hospital (reference number 20–1122) and was conducted in accordance with the principles of the Helsinki Declaration. All patients gave their written informed consent.

All patients were screened for myocardial disorders using the Elecsys® Troponin T-high sensitive assay (Roche Diagnostics, Switzerland) at baseline (defined as before the onset of ICI-treatment) and prior to each ICI infusion. Elevated hs-TnT was defined as > 14 ng/l, defined as the 99th percentile concentration for general population. Further cardiac biomarkers that were used were serum activity of creatine phosphokinase-MB (CK-MB) and n-terminal pro-brain natriuretic peptide (NT-proBNP) with the age-adjusted values for the ULN.

At baseline, patient demographics, clinical data regarding tumor, comorbidities, and medication were assessed. Patients with elevated baseline hs-TnT (>14 ng/l) or preexisting cardiac morbidities were referred for cardiologic evaluation.

During the course of ICI-therapy, patients with a normal baseline hs-TnT (≤14 ng/l) were referred to the cardiology department for further evaluation if hs-TnT-level increased > 14 ng/l and at least one of the following occurred: i) presence of clinical symptoms, ii) no normalization or no significant decrease of hs-TnT-level upon short-term control within 2 days, and iii) additional elevation of CK-MB-serum activity and/or NT-proBNP. Patients with elevated baseline hs-TnT (>14 ng/l) were referred to the cardiology department for further evaluation if hs-TnT-levels increased significantly (defined as elevation of 20 % compared to baseline) and at least one of the following: i) presence of clinical symptoms, ii) no significant decrease of hs-TnT-level upon short-term control, and iii) additional elevation of CK-MB serum activity and/or NT-proBNP. Further cardiologic examination was determined individually and included electrocardiogram (ECG), echocardiography, cardiac magnetic resonance (CMR), coronary angiography, and endomyocardial biopsies (EMB).

Diagnosis of irMyocarditis was based on the definition published by the International Cardio-Oncology Society [15] (Table 1) and the case definition [16]. For patients diagnosed with irMyocarditis ICI-therapy was suspended and high dose corticosteroids initiated. Additionally, monitoring and symptomatic treatment was employed as indicated in each individual case.

Statistical analyses were conducted with the statistical software SPSS Version 29. Continuous data is presented as median and interquartile ranges and categorical data is presented as percentages. Receiver operating characteristic (ROC) curves and area under the curve (AUC) measurements for the prediction of irMyocarditis were performed. Cutoff was calculated to depict the highest sensitivity and specificity for irMyocarditis.

## 3. Results

### 3.1. Patients

A total of 280 skin cancer patients were included in this study before ICI-treatment onset. Of these, 196 patients (70.0 %) had normal hs-TnT at baseline (group A) and in 84 patients (30.0 %) baseline hs-TnT was > 14 ng/l (group B) with a median hs-TnT of 21 ng/l (IQR 17–29 ng/l). The patients in group B had a higher median age (81 vs. 61 years) and a higher percentage of male patients (71.4 % vs. 50.5 %). Among the different tumor types, there were more patients with squamous cell carcinoma in group B (28.6 % vs. 9.7 %) receiving treatment with cemiplimab (28.6 % vs. 10.7 %, Table 2). Patients without elevation of hs-TnT did not develop irMyocarditis.

### 3.2. Patients with normal hs-TnT at baseline

Of the 196 patients with normal baseline hs-TnT, 28.6 % (56 patients) experienced an increase above 14 ng/L after initiation of ICI-therapy with a median peak concentration of 21.5 ng/l (IQR 16–31 ng/l) after a median duration of 101 days (IQR 59–207 days). Among those, an additional elevation of CK-MB serum activity and an increase of NT-proBNP above the ULN occurred in 23.2 % (13 patients).

Clinical symptoms were present in 17.9 % (10 patients), including shortness of breath (n = 6), fatigue (n = 2), lower extremity edema (n = 1), and palpitations (n = 1). Further diagnostic evaluation by the cardiology department was performed in 24 patients. No additional diagnostic investigations were performed in 32 clinically asymptomatic patients due to either normalization of hs-TnT levels in short-term

**Table 1**
Diagnostic criteria of irMyocarditis according to Herrmann et al. [15].

| |
|---|
| **Either pathohistological diagnosis:** |
| Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples |
| **Or clinical diagnosis:** |
| A troponin elevation (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion |
| **Major Criterion** |
| CMR diagnostic for acute myocarditis (modified Lake Louise criteria) |
| **Minor Criteria** |
| Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock) |
| Ventricular arrhythmia and/or new conduction system disease |
| Decline in cardiac (systolic) function, with or without regional wall motion abnormalities in a non-Takotsubo pattern |
| Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis |
| Suggestive CMR (meeting some but not all of the modified Lake Louise criteria) |

**Table 2 –**
Patient characteristics. The total cohort included 280 cancer patients and was subdivided according to baseline hs-TnT value. Percentages are given in parentheses. hs-TnT = high-sensitivity troponin-T; ICI=immune checkpoint inhibitor; ECG=electrocardiogram.

| | hs-TnT ≤ 14ng/l at baseline (group A) n = 196 | hs-TnT > 14ng/l at baseline (group B) n = 84 |
|---|---|---|
| **Age – years** | | |
| median | 61 | 81 |
| interquartile range | 52.8 – 71.5 | 73.0 – 84.5 |
| **sex – no. (%)** | | |
| male | 99 (50.5) | 60 (71.4) |
| female | 97 (49.5) | 24 (28.6) |
| **documentation of medical condition with impact on hs-TnT** | | |
| present | 57 (29.1) | 76 (90.0) |
| absent | 139 (70.9) | 8 (10.0) |
| **tumor type** | | |
| cutaneous melanoma | 148 (75.5) | 49 (58.3) |
| mucosal melanoma | 7 (3.1) | 3 (3.6) |
| uveal melanoma | 19 (9.7) | 7 (8.3) |
| squamous cell carcinoma | 19 (9.7) | 24 (28.6) |
| basal cell carcinoma | 2 (1.0) | 0 (0) |
| Merkel cell carcinoma | 6 (3.1) | 1 (1.2) |
| Kaposi's sarcoma | 1 (0.5) | 0 (0) |
| **treatment indication – no. (%)** | | |
| neoadjuvant | 12 (6.1) | 2 (2.4) |
| adjuvant | 41 (20.9) | 10 (11.9) |
| metastatic | 143 (73.0) | 72 (85.7) |
| **ICI-treatment (%)** | | |
| ipilimumab + nivolumab | 114 (58.2) | 43 (51.2) |
| nivolumab | 18 (9.2) | 8 (9.5) |
| pembrolizumab | 37 (18.9) | 8 (9.5) |
| cemiplimab | 21 (10.7) | 24 (28.6) |
| avelumab | 6 (3.1) | 1 (1.2) |
| **irMyocarditis** | 8 (4.1) | 8 (9.5) |
| median onset after ICI-start - days | 83.5 | 125.5 |
| with clinical symptoms – no. (%) | 4 (50.0) | 5 (62.5) |
| with ECG abnormalities – no. (%) | 3 (37.5) | 4 (50.0) |

controls (n = 25), loss to follow-up of the patients (n = 4) or death of the patients due to disease progression (n = 3).

ECG was normal in 16 out of 24 patients. The abnormalities detected in 8 patients were atrial fibrillation (n = 2), right bundle branch block (n = 2), sinus tachycardia (n = 1), sinus bradycardia (n = 1), and a first-degree atrioventricular block (n = 1). Cardiac echocardiography was abnormal in 5 out of 18 patients suffering from: pericardial effusion (n = 2), left ventricular hypertrophy (n = 2), and akinesia of the posterior wall (n = 1).

An acute coronary syndrome was ruled out by coronary angiography in six patients and a new diagnosis of coronary heart disease was made in three patients.

According to modified Lake Louise criteria CMR was compatible with myocarditis in six out of 12 patients. An EMB was taken in five patients and showed typical histopathological signs for ICI-induced myocarditis with acute lymphocytic inflammation in three patients and no signs of acute myocarditis in two patients.

The definite diagnosis of irMyocarditis was made in 4.1 % of all patients (eight patients) with normal baseline hs-TnT, corresponding to 14.3 % of those with an hs-TnT increase. ICI-treatment was discontinued permanently in all irMyocarditis patients and treatment with high dose corticosteroids was started in six patients. No death or other MACE occurred in this group. In patients where myocarditis was excluded, ICI-treatment was continued without any further cardiac issues.

### 3.3. Patients with elevated hs-TnT at baseline

Altogether, 84 skin cancer patients had elevated hs-TnT (>14 ng/l) before initiation of ICI-treatment. Underlying medical conditions with potential impact on troponin T levels included arterial hypertension (n = 49), atrial fibrillation (n = 16), coronary heart disease (n = 12), diabetes (n = 11), heart valve diseases (n = 9), chronic renal insufficiency (n = 8), and heart failure (n = 1). Median hs-TnT-level at baseline was 21 ng/l (IQR 17–29 ng/l). After ICI-treatment onset, a significant increase in hs-TnT (defined as elevation of 20 % compared to baseline) with a median peak level of 37 ng/l (IQR 26–58 ng/l) was detected in 66.7 % (56) of patients after a median duration of 70 days (IQR 27–169 days). In these patients, elevated CK-MB serum activity and NT-proBNP above the ULN was detected in 23.2 % and 25.0 % (13 and 14) of patients, respectively.

At the time of hs-TnT increase, clinical symptoms were present in 35.7 % (eight) of patients. These included shortness of breath (n = 5), fatigue (n = 2), and cardiogenic shock (n = 1).

In 23 patients a further cardiologic evaluation was performed, whereas in 31 patients without any clinical symptoms hs-TnT-levels dropped significantly in short-term controls and therefore additional diagnostic procedures were not performed. Two patients died due to non-cardiac causes: one symptomatic patient with shortness of breath succumbed to acute COVID19-infection and one asymptomatic patient died after rapid tumor progression.

ECG was normal in 13 out of 22 patients. In 9 patients the following abnormal findings were detected: left anterior fascicular block (n = 3), atrial fibrillation (n = 2), right bundle branch block (n = 1), first-degree atrioventricular block (n = 1), combined right bundle branch block and first-degree atrioventricular block (n = 1), and sinus tachycardia (n = 1).

Cardiac echocardiography was performed in 22 patients with 14 normal results. Abnormal findings related to irMyocarditis were decreased left ventricular function (n = 5), left ventricular hypertrophy (n = 2), abnormal left ventricular relaxation (n = 1). Coronary angiography was performed in 11 patients and coronary heart disease was diagnosed in six patients. In CMR, criteria for the diagnosis of myocarditis were completely fulfilled in 3 patients, and partly fulfilled in 3 patients. There were no radiologic signs for the diagnosis of myocarditis in 5 patients.

EMB revealed histopathologic proof of acute lymphocytic myocarditis in two patient biopsies, chronic lymphocytic myocardial damage in two patients and no sign of myocardial damage in another two patients.

Based upon consensus criteria, the definite diagnosis of irMyocarditis was made in 9.5 % (eight) of all patients with elevated hs-TnT. In all irMyocarditis patients ICI-treatment was discontinued permanently and treatment with high dose corticosteroids initiated. One patient developed ventricular fibrillation and needed resuscitation prior to diagnostic evaluation for irMyocarditis. There was no other MACE or death observed in this group. Patients without diagnosis of irMyocarditis continued ICI-treatment without further cardiac problems (Fig. 1).

### 3.4. Characteristics of patients with irMyocarditis

Patients with the definite diagnosis of irMyocarditis had a median age of 66.6 years (IQR 56–75.5 years) with 8 male and 8 female patients. Median onset after start of ICI-therapy until diagnosis of irMyocarditis was 91 days (IQR 40–147 days) with asymptomatic patients showing an even later onset after a median of 125 days compared to symptomatic patients with 84 days after ICI-therapy onset. The median peak level of troponin T was 142.0 ng/l (IQR 38.5–200.8). In addition to elevation of hs-TnT, there was an increase of CK-MB-serum activity and NT-proBNP in 62.5 % and 31.3 % of patients, respectively.

ECG showed conduction pathologies in 37.5 % and decline in cardiac systolic function was detectable in echocardiography in 18.6 % of patients. CMR was abnormal in 68.7 % of which modified Lake Louise criteria were completely fulfilled for diagnosis of myocarditis in 72.7 %

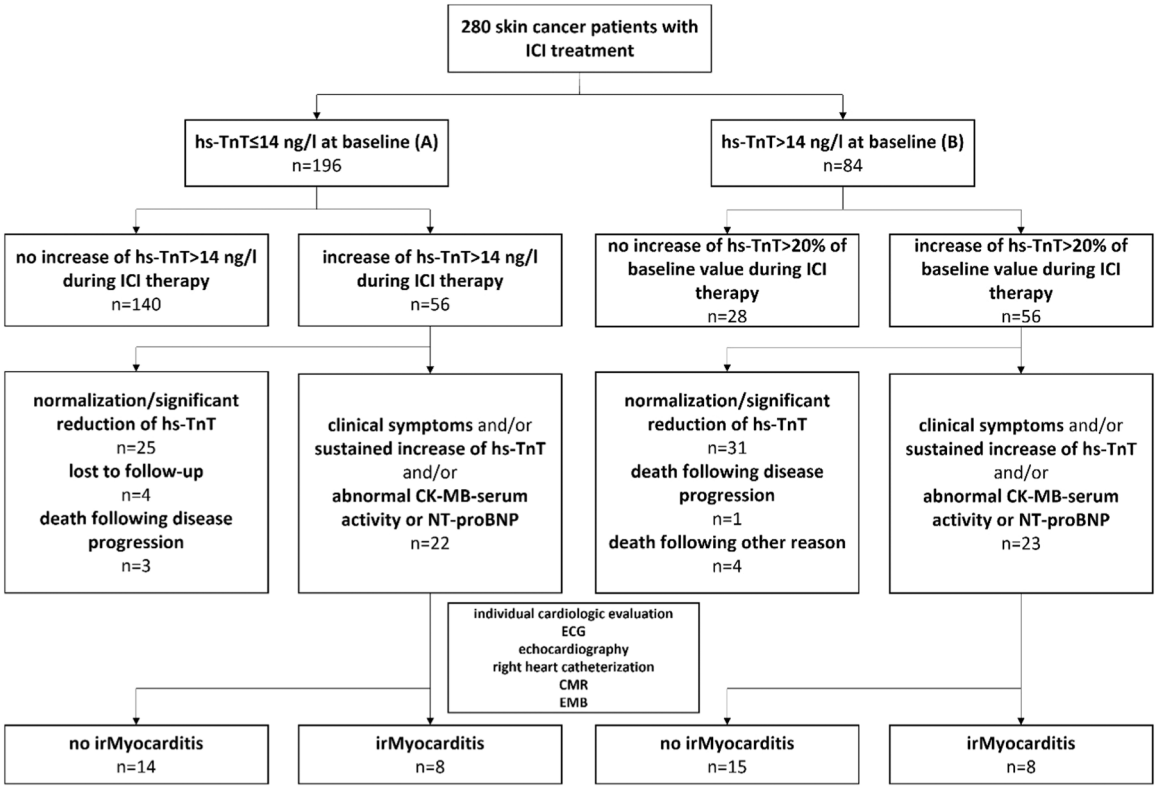


**Fig. 1.** Flow diagram. ICI=immune checkpoint inhibitor, hs-TnT=high-sensitivity troponin-T, CK-MB=creatine phosphokinase-MB, NT-proBNP=n-terminal pro-brain natriuretic peptide, irMyocarditis=immune-related myocarditis.

and partly fulfilled in 27.2 % of abnormal cases. EMB showed acute lymphocytic inflammation in 57.1 % of cases where a biopsy was performed. In the seven patients who underwent both, EMB and CMR, diagnosis of myocarditis was consistent in both examinations in two patients only, while the results were compatible with myocarditis in either EMB or CMR in two and three patients, respectively (Table 3). Among all assessments performed in patients with elevation of hs-TnT, EMB showed the highest positive and negative predictive value, as well as sensitivity and specificity of 100 % for detecting irMyocarditis (Fig. 2). After treatment, ECG pathologies disappeared in 42.9 % of patients during follow-up in the cardiology department.

### 3.5. *Definition of the optimal threshold value*

ROC curves to determine an optimal threshold for the detection of irMyocarditis were generated and assessed. The predictive accuracy of hs-TnT-screening for irMyocarditis as quantified by the AUC was 0.958 (95 % CI 0.928–0.989) for patients without elevated baseline hs-TnT and 0.961 (95 % CI 0.920–1.000) for patients with elevated baseline hs-TnT. Defining a threshold of 22 ng/l (1,57 times the ULN in patients without elevated baseline hs-TnT resulted in a sensitivity of 100 % and specificity of 91.0 %. For patients with elevated baseline hs-TnT a threshold of 60 ng/l (4.29 times the ULN) was associated with a sensitivity of 100 % and specificity of 89.6 % (Fig. 3).

## 4. Discussion

This clinical study is the first to determine threshold values of serum levels of hs-TnT for the detection of immune checkpoint inhibitor induced Myocarditis in a large cohort of cancer patients. Depending on baseline hs-TnT this threshold proved to be 22 ng/l for patients with normal baseline hs-TnT, and thus able to predict irMyocarditis with a specificity and sensitivity of 91.0 % and 100 %, respectively. In patients with elevated baseline hs-TNT a threshold of 60 ng/l had a specificity of 89.6 % and a sensitivity of 100 % to predict irMyocarditis.

In our trial investigating 280 skin cancer patients, 28.6 % experienced an increase of hs-TnT compared to 11.2 % with an increase in hs-TnI in a mixed patient cohort with mainly non-small cell lung cancer and renal cell carcinoma [14]. Since Troponin-I was considered to be more cardio-specific in comparison to Troponin-T, hs-TnI has previously been used for screening [17,18]. However, in a biomarker study of 60 patients with ICI-induced myocarditis, an increase of hs-TnT was observed in 98 % of patients whereas an increase of hs-TnI was documented in only 88 % of cases, making hs-TnT likely a more suitable and sensitive cardiac biomarker to detect irMyocarditis [19]. Furthermore, this trial also included patients who had already started ICI-therapy and baseline hs-TnI was therefore not available in half of the patients [14].

Surprisingly, our cohort documented irMyocarditis in 5.7 % of cases, which is much higher than the to date reported 1–1.5 % of cases. This could be due to a failure to detect asymptomatic patients in the absence

**Table 3 –**
Frequency of diagnostic results in patients with irMyocarditis. Percentages are given in parentheses. CK-MB=creatine phosphokinase-MB, NT-proBNP=n-terminal pro-brain natriuretic peptide, ECG=electrocardiogram, CMR=cardiac magnetic resonance, EMB=endomyocardial biopsy.

| | CK-MB serum activity | NT-proBNP | ECG | echocardiography | CMR | EMB |
|---|---|---|---|---|---|---|
| normal | 6 (37.5) | 11 (68.7) | 10 (62.5) | 13 (81.3) | 3 (18.6) | 3 (18.6) |
| abnormal | 10 (62.5) | 5 (31.3) | 6 (37.5) | 3 (18.6) | 11 (68.7) | 4 (25.0) |
| not done | - | - | - | - | 2 (12.5) | 9 (56.3) |

| | irMyocarditis | no irMyocarditis | |
|---|---|---|---|
| test outcome positive | true positive | false positive | positive predictive value |
| CK-MB | 10 | 7 | 58.8% |
| NT-proBNP | 5 | 16 | 23.8% |
| ECG | 7 | 7 | 50.0% |
| TTE | 8 | 7 | 53.3% |
| CMR | 9 | 0 | 100% |
| EMB | 5 | 0 | 100% |
| test outcome negative | false negative | true negative | negative predictive value |
| CK-MB | 6 | 22 | 78.6% |
| NT-proBNP | 9 | 12 | 57.1% |
| ECG | 9 | 20 | 69.0% |
| TTE | 8 | 16 | 66.7% |
| CMR | 4 | 9 | 69.2% |
| EMB | 0 | 6 | 100% |
| | Sensitivity | Specificity | |
| CK-MB | 62.5% | 75.9% | |
| NT-proBNP | 35.7% | 42.9% | |
| ECG | 43.8% | 74.1% | |
| TTE | 50.0% | 69.6% | |
| CMR | 69.2% | 100% | |
| EMB | 100% | 100% | |

**Fig. 2.** Specificity, Sensitivity and predictive values CK-MB=Creatine phosphokinase-MB, NT-pro-BNP=n-terminal pro-brain natriuretic peptide, ECG=electrocardiogram, TTE=transthoracic echocardiogram, CMR=cardiac magnetic resonance, EMB=endomyocardial biopsy.

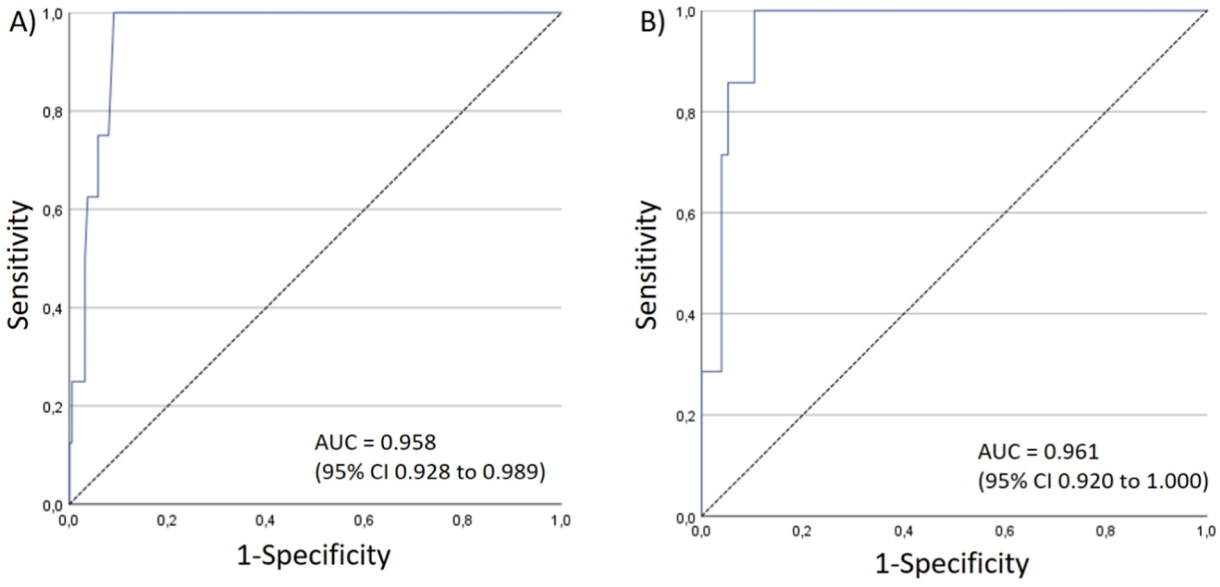


**Fig. 3.** Receiver-operating characteristics (ROC) curves for prediction of irMyocarditis patients treated with immune checkpoint inhibitors. A) Patients with normal baseline high-sensitivity troponin T (hs-TnT). B) Patients with elevated baseline hs-TnT.

of stringent monitoring. This was also observed in another trial in 126 cancer patient that monitored hs-TnI and suspected myocarditis in 10.3 % of patients after initiation of ICI-therapy. Diagnosis was limited solely to serum biomarkers, ECG and echocardiography without performing coronary angiography to rule out coronary heart disease or more specifically CMR or EMB. Thus, myocarditis may have been

misdiagnosed in this patient-population [13].

Importantly, in contrast to the high MACE and irMyocarditis mortality of 46 % and 50 %, respectively, reported in earlier studies [7,10], we observed only one MACE (12.5 %) without any fatalities. This is most likely due to optimized medical therapy, early ICI-interruption and prompt treatment with high dose systemic steroids [11]. Additionally, our cases occurred much later (median 91 days) than in other studies (34 days [10]) which could be due to our different patient cohort which only included skin cancer patients.

The limitations of our study are that the evaluation was set in a population consisting of skin cancer patients only. Furthermore, baseline ECG or echocardiography was only performed in a small fraction of patients with cardiovascular risk or preexisting cardiovascular disease.

This study determines the optimal threshold for hs-TnT to diagnose even asymptomatic patients with irMyocarditis, with a limit of 22 ng/l (1,57 times the ULN) in patients with normal baseline hs-TnT and 60 ng/l (4,29 times the ULN) in patients with elevated baseline hs-TnT, both with a sensitivity of 100 % and a specificity of 91.0 % and 89.6 % for the detection of irMyocarditis, respectively. These findings need to be validated in an independent cohort.

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## CRediT authorship contribution statement

**Lucie Heinzerling:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Lars E. French:** Writing – review & editing, Supervision, Investigation. **Leo Nicolai:** Writing – review & editing, Validation, Conceptualization. **Steffen Massberg:** Writing – review & editing, Validation, Supervision, Conceptualization. **Dirk Tomsitz:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Judith Spiro:** Writing – review & editing, Investigation. **Ulrich Grabmaier:** Writing – review & editing, Validation, Conceptualization.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dirk Tomsitz reports consultancy, speaker fees or travel grants: BMS, Roche, Novartis, Sanofi, Recordati, Kyowa Kirin, Sun Pharma, Recordati and Pierre Fabre. Lucie Heinzerling reports consultancy, speaker fees, travel grants and/or research funding: BMS, MSD, Merck, Roche, Amgen, Curevac, Novartis, Sanofi and Pierre Fabre; clinical studies: BMS, MSD, Merck, Roche, Amgen, GSK, Curevac and Novartis. All remaining authors have declared no conflict of interest.

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## References

[1] Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. Lancet 2022;399(10336):1718–29.
[2] Kirkwood JM, Del Vecchio M, Weber J, et al. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial [published correction appears in Nat Med. 2023 Nov 3;:] [published correction appears in Nat Med. 2024 Mar;30(3):906] Nat Med 2023;29(11):2835–43.
[3] Eggermont AMM, Blank CU, Mandala M, et al. Longer Follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 Trial. J Clin Oncol 2020;38(33):3925–36.
[4] Larkin J, Del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III/IV melanoma: 5-year efficacy and biomarker results from CheckMate 238. Clin Cancer Res 2023;29(17):3352–61.
[5] Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. N Engl J Med 2024.
[6] Tajmir-Riahi A, Bergmann T, Schmid M, Agaimy A, Schuler G, Heinzerling L. Life-threatening autoimmune cardiomyopathy reproducibly induced in a patient by checkpoint inhibitor therapy. J Immunother 2018;41(1):35–8.
[7] Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 2018;19(12):1579–89.
[8] Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol 2018;4(12):1721–8.
[9] Heinzerling L, Ott PA, Hodi FS, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer 2016;4:50. Published 2016 Aug 16.
[10] Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol 2018;71(16):1755–64.
[11] Wang Y, Ertl C, Schmitt C, et al. Stringent monitoring can decrease mortality of immune checkpoint inhibitor induced cardiotoxicity. Front Cardiovasc Med 2024;11:1408586. Published 2024 Jun 10.
[12] Thuny F, Bonaca MP, Cautela J. What is the evidence of the diagnostic criteria and screening of immune checkpoint inhibitor-induced myocarditis? JACC Cardio Oncol 2022;4(5):624–8. Published 2022 Dec 20.
[13] Furukawa A, Tamura Y, Taniguchi H, et al. Prospective screening for myocarditis in cancer patients treated with immune checkpoint inhibitors. J Cardiol 2023;81(1):63–7.
[14] Waliany S, Neal JW, Reddy S, et al. Myocarditis surveillance with high-sensitivity troponin I during cancer treatment with immune checkpoint inhibitors. JACC Cardio Oncol 2021;3(1):137–9.
[15] Herrmann J, Lenihan D, Armenian S, 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.
[16] Bonaca MP, Olenchock BA, Salem JE, 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.
[17] Schmid J, Liesinger L, Birner-Gruenberger R, et al. Elevated cardiac troponin T in patients with skeletal myopathies. J Am Coll Cardiol 2018;71(14):1540–9.
[18] Rittoo D, Jones A, Lecky B, Neithercut D. Elevation of cardiac troponin T, but not cardiac troponin I, in patients with neuromuscular diseases: implications for the diagnosis of myocardial infarction. J Am Coll Cardiol 2014;63(22):2411–20.
[19] Lehmann LH, Heckmann MB, Bailly G, et al. Cardiomuscular biomarkers in the diagnosis and prognostication of immune checkpoint inhibitor myocarditis. Circulation 2023;148(6):473–86.