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ORIGINAL RESEARCH

Severe vs Nonsevere Immune Checkpoint Inhibitor-Induced Myocarditis

Contemporary 1-Year Outcomes

Osnat Itzhaki Ben Zadok, MD, MSc,[a,b] Amos Levi, MD,[b,c] Sanjay Divakaran, MD,[a] Anju Nohria, MD, MSc[a]

ABSTRACT

BACKGROUND The long-term contemporary outcomes of patients with immune checkpoint inhibitor (ICI) myocarditis, spanning the spectrum of clinical severity, are undetermined.

OBJECTIVES We sought to investigate the characteristics and cardiovascular outcomes of patients with severe and nonsevere ICI myocarditis.

METHODS This was a retrospective cohort study of patients with suspected ICI myocarditis at Massachusetts General Brigham Health System conducted between 2015 and 2022. Cases were classified as severe, nonsevere, and negative based on the International Cardio-Oncology Society criteria. One-year cardiovascular mortality, all-cause mortality, and cardiovascular readmissions were evaluated. We also evaluated 1-year ICI resumption and left ventricular ejection fraction over a median follow-up of 18 (Q1-Q3: 8-67) weeks.

RESULTS The study included 160 patients: 28 severe, 96 nonsevere, and 36 negative cases. Patients with severe myocarditis had an increased risk of 1-year cardiovascular mortality, particularly in the early post-myocarditis period (29% vs 5%; HR: 6.52; 95% CI: 2.2-19.6; $P < 0.001$). Patients with nonsevere myocarditis had a cardiovascular mortality rate similar to negative cases (HR: 0.61; 95% CI: 0.14-2.54). One-year all-cause mortality did not differ between severe, nonsevere, and negative cases ($P = 0.74$). Rates of 1-year cardiovascular readmissions and long-term left ventricular ejection fraction were also similar among the 3 groups. ICI resumption was low, even in negative cases.

CONCLUSIONS In a contemporary analysis of patients with suspected ICI myocarditis, severe ICI myocarditis was associated with increased 1-year cardiovascular mortality, which was lower than previously reported. Patients with nonsevere ICI myocarditis had outcomes similar to negative cases. The optimal management strategies for nonsevere ICI myocarditis need to be re-evaluated. (J Am Coll Cardiol CardioOnc 2023;5:732-744) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [b]Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; and the [c]Cardiology Department, Rabin Medical Center, Petah-Tikva, Israel.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Immune checkpoint inhibitors (ICIs) have been approved for the treatment of more than 20 types of cancers, including melanoma, renal cell carcinoma, and lung cancer, leading to substantial improvement in oncologic outcomes. However, these drugs can trigger off-target inflammatory reactions, increasing the risk of immune-related adverse events affecting other organ systems, including the heart. The occurrence of ICI-induced acute myocarditis was first described in 2012,[1] and although the reported incidence of this condition is low, ranging from 0.06% to 1.7% of treated patients,[2,3] it has been associated with a significantly increased risk of mortality, with rates as high as 46%.[4] Due to this poor prognosis, both cardiology and oncology societies have recommended the immediate discontinuation, and in the majority of cases, permanent cessation, of ICI therapy once the diagnosis of myocarditis is confirmed, regardless of its severity.[5-9] However, with the ever-expanding use of ICI agents for treating both solid and hematologic malignancies and the rapid evolution of therapeutic options for ICI myocarditis, it is imperative to re-evaluate the long-term cardio-oncologic management of patients with ICI myocarditis. This necessitates an evaluation of the contemporary prognosis of patients with ICI myocarditis across the spectrum of clinical severity.

In this study, we aimed to describe the characteristics of patients with severe ICI myocarditis and nonsevere ICI myocarditis and to evaluate their cardiovascular (CV) and all-cause mortality, as well as other CV outcomes in the contemporary era.

METHODS

STUDY DESIGN. This was a retrospective cohort study of patients with a suspected diagnosis of ICI myocarditis at the Massachusetts General Brigham (MGB) Health System conducted between January 2015 and June 2022.

STUDY POPULATION. We searched the MGB research patient data registry for adult patients (age ≥18 years) who received at least 1 ICI agent (pembrolizumab, nivolumab, durvalumab, ipilimumab, cemiplimab, avelumab, and/or atezolizumab) between January 2015 and June 2022. In this search, we used additional criteria, which included documentation indicating an ICD-10 code for myocarditis (specifically I40, I41, I51), evidence of an abnormal troponin level, or the performance of a cardiac magnetic resonance (CMR) imaging study.

After this initial search, electronic medical records of identified patients were subjected to review by a cardio-oncologist (O.I.B.Z.) who was blinded to patient outcomes during this process. Patients were included in the study cohort if their medical records contained documentation suggesting suspected ICI myocarditis and if additional testing had been performed to confirm the diagnosis. The tests used for confirmation included troponin measurement, echocardiography, CMR, or endomyocardial biopsy (EMB). Subsequently, all clinical, laboratory, imaging, and histopathology data were reviewed, and patients were categorized in accordance with the criteria set forth by the International Cardio-Oncology Society (ICOS) for ICI myocarditis.[6,10]

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CV = cardiovascular

EMB = endomyocardial biopsy

ICI = immune checkpoint inhibitor

ICOS = International Cardio-Oncology Society

LVEF = left ventricular ejection fraction

MGB = Massachusetts General Brigham

The study protocol was approved by the MGB Institutional Review Board. Given the retrospective nature of the study, the requirement for informed consent was waived.

STUDY DEFINITIONS. ICI myocarditis. For the definition of ICI myocarditis, we adhered to the 2022 ICOS consensus criteria.[6,10] In brief, patients were diagnosed with ICI myocarditis based on any of the following criteria: 1) the presence of histopathological findings consistent with myocarditis in an endomyocardial biopsy; 2) an elevated troponin with 1 major criterion (CMR findings confirming acute myocarditis based on the presence of both nonischemic myocardial injury and myocardial edema modified Lake Louise criteria)[11]; or 3) an elevated troponin with 2 minor criteria, which include a clinical syndrome (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, a decline in cardiac systolic function (defined as a reduction in left ventricular ejection fraction [LVEF] from baseline by ≥5% to <55% in the presence of signs or symptoms of HF, or a reduction in LVEF by ≥10% to <55% without signs or symptoms of HF, or LVEF <50% in cases where baseline transthoracic echocardiograms were unavailable),[10] other immune-related adverse events, or suggestive CMR with 1, but not both, of nonischemic myocardial injury and myocardial edema of the modified Lake Louise criteria. In our laboratory, the normal reference ranges for high-sensitivity troponin T and troponin T were 0 to 14 ng/L and <0.01 ng/mL, respectively.

Severity of myocarditis. According to the ICOS criteria,[6,10] we categorized a severe presentation of ICI myocarditis as myocarditis accompanied by hemodynamic instability, heart failure requiring noninvasive or invasive ventilation, complete or

high-grade heart block, and/or significant ventricular arrhythmias. All patients who met the criteria for ICI myocarditis but did not exhibit these severe features were classified as having nonsevere disease. Patients with suspected myocarditis who did not fulfill the ICOS criteria were classified as negative cases.

ICI resumption. This was defined as administration of an ICI agent, which could involve either the same drug suspected to have caused myocarditis or a different ICI agent, following the index presentation with suspected ICI myocarditis.

STUDY ENDPOINTS. The primary endpoint of our study was the assessment of 1-year CV mortality among patients with suspected ICI myocarditis. Secondary endpoints included one-year all-cause mortality, readmissions related to CV issues, the most recent documented left ventricular ejection fraction (LVEF) after the index presentation with suspected myocarditis, and the proportion of patients who resumed ICI therapy after the index presentation. Mortality status and cause of death were determined from the electronic medical record or death certificates.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or median (25th-75th percentiles: Q1-Q3), whereas categorical variables are expressed as counts (%). The Shapiro-Wilk test was used to determine whether the data were normally distributed. For comparisons across all 3 groups (severe, nonsevere, and negative myocarditis), the 1-way analysis of variance or Kruskal-Wallis tests were used for parametric and nonparametric parameters, respectively. In cases of significance, further comparisons between any 2 groups were carried out using the *t*-test or the Mann-Whitney *U* test for parametric and nonparametric variables, respectively. Fisher's exact test was used to compare categorical variables between groups. To account for type I error in multiple-pairwise comparisons, *P* values were adjusted using the post hoc Bonferroni correction.

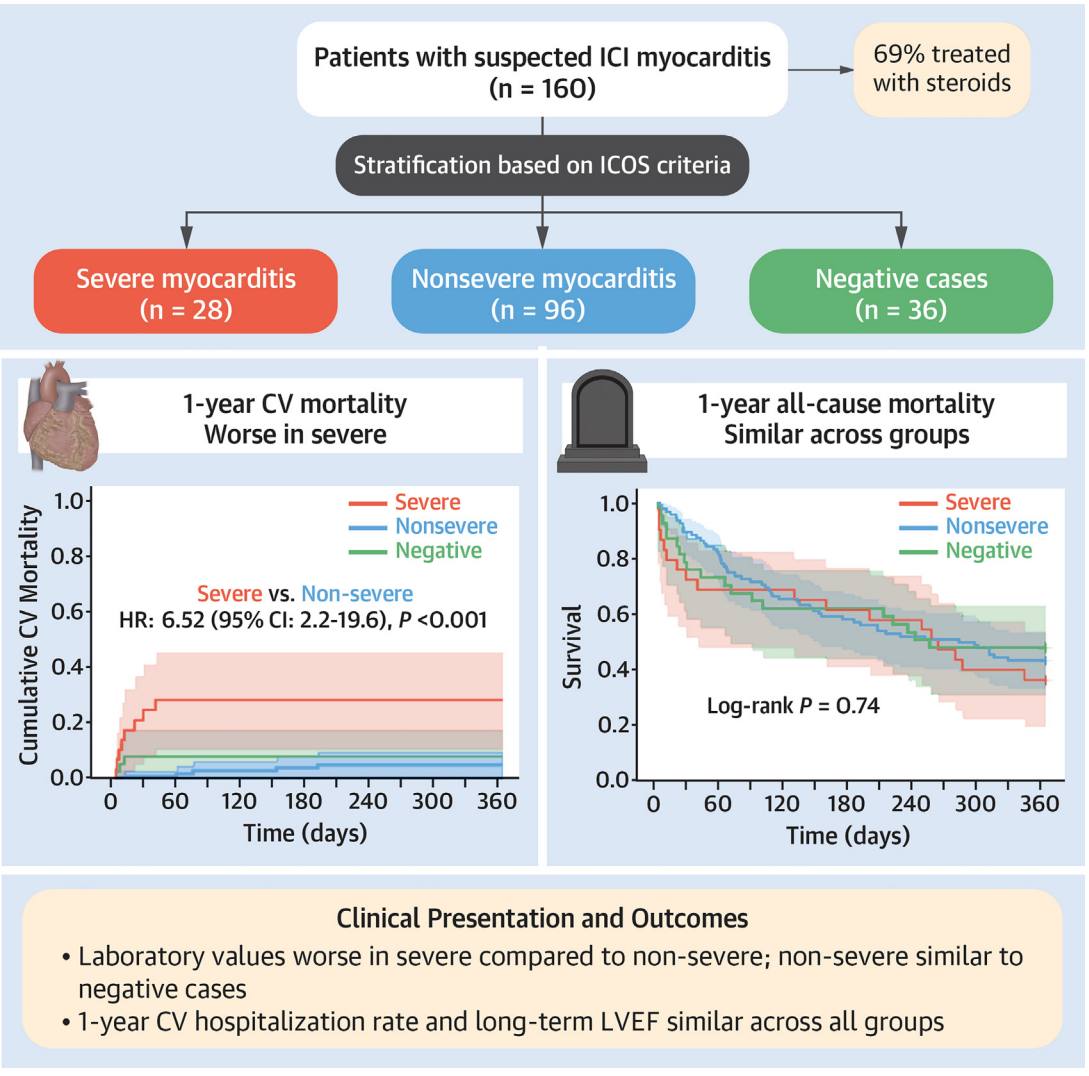
The 1-year all-cause mortality, starting from the time of the initial presentation with suspected ICI myocarditis, was graphically displayed using Kaplan-Meier curves. A comparison between the 3 study groups was made using the log-rank test (unadjusted analysis). Cumulative incidence curves were used to display rates of endpoints other than all-cause death. Cumulative probabilities of various endpoints (CV mortality, CV-related admissions, and ICI drug resumption) during the study follow-up, along with HRs, were assessed using the Cox proportional hazards model and presented as HR with 95% CI. The assumption of proportional hazards for log-rank tests was evaluated using scaled Schoenfeld residuals, based on both statistical and graphical diagnostics. In cases involving competing risk of non-CV death or overall death, Fine and Gray methodology was used as needed. Also, a sensitivity analysis for the endpoints of all-cause mortality and CV mortality was conducted, limited to patients who had undergone an EMB or CMR as part of their evaluation. Two-sided *P* values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS Statistical Software, Version 28 (IBM), R (R-studio, V.4.0.0), and Python (V 3.11.3).

RESULTS

STUDY POPULATION. Between January 2015 and June 2022, a total of 10,046 cancer patients with a diagnosis of cancer received ICI therapy. Of this cohort, 160 patients were suspected of having ICI myocarditis and subsequently underwent diagnostic investigations. Notably, 70% of the cohort had their index presentation after January 2019. The final study population comprised 124 patients with a positive diagnosis of ICI myocarditis (Supplemental Tables 1 and 2), whereas 36 patients received a negative diagnosis of ICI myocarditis, based on the 2022 ICOS criteria.[6,10] Among those diagnosed positively with ICI myocarditis, 28 patients exhibited a severe clinical presentation (23% of positive cases), while 96 patients presented with nonsevere findings (77% of positive cases). Within the severe cases, 3 patients experienced hemodynamic instability, 3 required invasive ventilation for pulmonary edema, 14 exhibited high-degree heart block, and 11 had sustained ventricular arrhythmias (Supplemental Table 3, **Central Illustration**). Presumed diagnoses for the negative cases were determined through detailed chart review and are available in Supplemental Table 4.

BASELINE CHARACTERISTICS OF PATIENTS WITH SUSPECTED ICI MYOCARDITIS. The baseline characteristics of study patients, categorized by a positive or negative diagnosis of ICI myocarditis, are presented in Supplemental Table 5. Among patients with a positive diagnosis of myocarditis, the median age was 72 (Q1-Q3: 66-76) years, and the most prevalent underlying cancer types were malignant melanoma (28%), renal cell carcinoma (25%), and lung cancer (19%). A full list of cancer types is presented in Supplemental Table 6. ICI agents were administered as first-line therapy in both positive and negative cases (61%; $P = 0.28$). The distribution of ICI monotherapy and combination therapy regimens was similar, with a nonsignificant

CENTRAL ILLUSTRATION **1-Year Outcomes in Patients With Severe vs Nonsevere Immune Checkpoint Inhibitor Myocarditis**



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Patients with severe immune checkpoint inhibitor (ICI) myocarditis exhibit increased 1-year cardiovascular (CV) mortality, but they demonstrate similar 1-year all-cause mortality when compared with patients with nonsevere ICI myocarditis. Cardiovascular readmissions and long-term left ventricular ejection fraction (LVEF) were similar among patients with severe and nonsevere ICI myocarditis, as well as those with negative cases. ICOS = International Cardio-Oncology Society.

increase in the use of combination therapy in patients with positive ICI myocarditis compared with negative cases (22% vs 8%; $P = 0.089$). Baseline CV comorbidities were comparable between patients with positive and negative ICI myocarditis diagnoses, except for a higher prevalence of a prior history of atrial fibrillation in positive patients (27% vs 8%; $P = 0.023$). There were no significant differences in the baseline characteristics of patients presenting with severe vs nonsevere ICI myocarditis (Table 1).

THE CLINICAL PRESENTATION OF PATIENTS WITH SUSPECTED ICI MYOCARDITIS. The clinical presentation, complications, and management of patients with a positive vs negative diagnosis of ICI myocarditis are presented in Supplemental Table 5. Patients with a positive diagnosis of ICI myocarditis were more likely to present with myalgia (24% vs 3%; $P = 0.003$), diplopia and/or ptosis (22% vs 0%; $P < 0.001$), or other concomitant immune-related adverse events (56% vs 11%; $P < 0.001$). At presentation, higher levels of

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TABLE 1 Baseline Characteristics of Patients Stratified by Diagnosis and Severity of ICI Myocarditis

	Severe Myocarditis (n = 28)	Nonsevere Myocarditis (n = 96)	Negative Cases (n = 36)	*P* Value Across Groups
Patients' characteristics				
Age at presentation, y	73 (64-79)	72 (67-76)	68 (59-77)	0.39
Sex, female	9 (32)	34 (34)	14 (39)	0.84
Past smoker	15 (54)	52 (54)	18 (50)	0.91
Active smoker	2 (7)	4 (4)	2 (6)	0.81
Hypertension	17 (61)	61 (64)	19 (53)	0.53
Diabetes mellitus	6 (21)	28 (29)	6 (17)	0.30
Dyslipidemia	12 (43)	47 (49)	15 (42)	0.70
CVA/TIA	3 (11)	6 (6)	0 (0)	0.17
CAD	7 (25)	21 (22)	9 (25)	0.90
Prior history of LV systolic dysfunction	1 (4)	8 (8)	2 (6)	0.64
Atrial fibrillation	7 (25)	27 (28)	3 (8)	0.055
Electronic cardiac device	1 (4)	7 (7)	0 (0)	0.22
Hypothyroidism	4 (14)	27 (28)	7 (19)	0.25
Cancer type				
Malignant melanoma	8 (29)	27 (28)	11 (31)	0.93
Lung cancer	3 (11)	21 (22)	4 (11)	
Renal-urethral carcinoma	7 (25)	24 (25)	9 (25)	
Other	10 (36)	24 (25)	12 (33)	
Prior antineoplastic therapy				
Anthracyclines	1 (4)	1 (1)	3 (8)	0.10
Thoracic radiation	5 (18)	14 (15)	9 (25)	0.38
Prior ICI[a]	1 (4)	12 (13)	4 (11)	0.40
Tyrosine kinase inhibitors	1 (4)	8 (8)	1 (3)	0.41
MEK inhibitors	0 (0)	4 (4)	1 (3)	0.53
HER-2 antagonists	1 (4)	0 (0)	0 (0)	0.095
ICI line of cancer therapy				
First	17 (63)	59 (62)	21 (58)	0.80
Second	8 (30)	31 (32)	10 (28)	
Third	2 (7)	5 (5)	3 (8)	
Fourth	0 (0)	0 (0)	0 (0)	
Fifth	0 (0)	1 (1)	2 (6)	
ICI regimen				
Combination therapy	4 (14)	23 (24)	3 (8)	0.10
Pembrolizumab	17 (61)	52 (54)	22 (61)	0.42
Nivolumab	5 (18)	13 (14)	6 (17)	
Ipilimumab	0 (0)	2 (2)	1 (3)	
Durvalumab	1 (4)	2 (2)	3 (8)	
Other monotherapy	1 (4)	4 (4)	1 (5)	
Ipilimumab and nivolumab	3 (11)	22 (23)	3 (8)	
Ipilimumab and pembrolizumab	1 (4)	1 (1)	0 (0)	

Values are median (Q1-Q3) or n (%). [a]Defined as a minimum of 12 months between discontinuation of any prior ICI therapy and initiation of the culprit ICI therapy.

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CVA = cerebrovascular accident; ICI = immune-checkpoint inhibitors; LV = left ventricular; TIA = transient Ischemic attack; TKI = tyrosine kinase inhibitors.

median creatine kinase were observed in patients with positive ICI myocarditis compared to negative cases (397 [Q1-Q3: 52-2,498] U/L vs 93 [Q1-Q3: 38-451] U/L; $P = 0.018$). Seventy-eight percent (n = 97) of patients with positive ICI myocarditis were treated with steroids, and of those, approximately one-third (n = 37) were given additional immunosuppressive agents. Mycophenolic acid and abatacept were administered in 21% (n = 26) and 4% (n = 5) of ICI myocarditis cases, respectively. None of the study patients required temporary mechanical circulatory support or extracorporeal membrane oxygenation.

THE CLINICAL PRESENTATION OF PATIENTS WITH SEVERE VS NONSEVERE ICI MYOCARDITIS. The clinical, laboratory, and imaging findings of patients with severe vs nonsevere ICI myocarditis are presented in Table 2 and Figure 1. Patients with severe myocarditis presented earlier (1.21 ± 3.4 months vs 4.11 ± 6.8 months; $P = 0.001$) and after fewer ICI doses (1.0 [Q1-Q3: 1.0-2.0] vs 2.0 [Q1-Q3: 1.0-4.0]; $P = 0.002$). Although most clinical symptoms were similar in both groups, patients with severe ICI myocarditis had a higher numerical rate of diplopia and/or ptosis (36% vs 18%; $P = 0.077$). At presentation, patients with severe ICI myocarditis had higher median levels of aspartate aminotransferase (127 [Q1-Q3: 28-256] U/L vs 37 [Q1-Q3: 23-93] U/L; $P = 0.046$) and alanine aminotransferase (76 [Q1-Q3: 27-167] U/L vs 31 [Q1-Q3: 17-78] U/L; $P = 0.036$) relative to nonsevere cases. Although not statistically significant, both presenting (280 [Q1-Q3: 26-2,196] ng/L vs 83 [Q1-Q3: 30-355] ng/L; $P = 0.85$) and peak (976 [Q1-Q3: 44-3,482] ng/L vs 126 [Q1-Q3: 41-,441] ng/L; $P = 0.22$) high-sensitivity troponin levels were numerically higher in patients with severe vs nonsevere ICI myocarditis. The levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were also numerically higher in patients with severe vs nonsevere ICI myocarditis (2,537 [(Q1-Q3: 635-9,081] pg/mL vs 955 [Q1-Q3: 390-5,657] pg/mL, respectively; $P = 0.28$). LVEF, as measured by echocardiography and CMR, did not differ between those with a severe or nonsevere presentation. Patients with severe ICI myocarditis were more likely to be treated with intravenous steroids (86% vs 53%; $P = 0.007$) and had a nonstatistical increase in the requirement for additional immunosuppressive agents (46% vs 25%; $P = 0.055$).

To better evaluate the clinical phenotype of patients with severe vs nonsevere myocarditis, we further compared each subgroup of patients with positive ICI myocarditis to negative cases (Table 2, Figure 1). We found that patients with a nonsevere presentation had similar presenting and peak levels of troponin, creatine kinase, hepatic enzymes, and NT-proBNP, as well as LVEF as negative cases.

LONG-TERM OUTCOMES. Using Fine and Gray analysis with non-CV death as a competing risk, patients with severe ICI myocarditis had an increased

TABLE 2 Clinical Presentation and Management of Study Patients Stratified by Diagnosis and Severity of ICI Myocarditis

	Severe Myocarditis (n = 28)	Nonsevere Myocarditis (n = 96)	Negative Cases (n = 36)	*P* Value Across Groups	*P* Value[a]	*P* Value[b]	*P* Value[c]
Number of ICI cycles before presentation	1.0 (1.0-2.0)	2.0 (1.0-4.0)	2.5 (2.0-4.8)	0.001	0.002	0.002	NS
Time from ICI initiation to suspected myocarditis, mo	1.21 ± 3.4	4.11 ± 6.8	4.6 ± 6.6	<0.001	0.001	0.001	NS
Clinical presentation							
Symptom duration before medical contact, d	3.0 (2.0-7.0)	6.0 (3.0-10.0)	5.0 (1.0-14.0)	0.11	–	–	–
Chest pain, angina	1 (4)	16 (17)	4 (11)	0.18	–	–	–
Chest pain, other	3 (11)	7 (7)	4 (11)	0.73	–	–	–
Dyspnea	16 (57)	54 (56)	11 (31)	0.024	NS	NS	0.026
Palpitations	5 (18)	6 (6)	4 (11)	0.17	–	–	–
Syncope	3 (11)	4 (4)	1 (3)	0.30	–	–	–
Peripheral edema	4 (14)	12 (13)	2 (6)	0.46	–	–	–
Myalgias	10 (36)	19 (20)	1 (3)	0.004	NS	0.003	NS
Weakness/fatigue	17 (61)	50 (52)	14 (39)	0.20	–	–	–
Dizziness	3 (11)	8 (8)	2 (6)	0.75	–	–	–
Diplopia and/or ptosis	10 (36)	17 (18)	0 (0)	<0.001	NS	<0.001	0.048
Other concomitant IrAE	14 (50)	55 (57)	4 (11)	<0.001	NS	0.006	<0.001
Laboratory parameters							
Elevated troponin at presentation and/or during the admission	28 (100)	96 (100)	24 (71)	<0.001	NS	<0.001	<0.001
Peak hs-troponin,[d] ng/L	976 (44-3,482)	126 (41-441)	276 (40-1,420)	0.19	–	–	–
Peak troponin,[e] ng/mL	1.68 (0.40-1.89)	0.72 (0.06-2.1)	0.67 (0.11-1.38)	0.50	–	–	–
Peak creatinine kinase, U/L	3,355 (732-5,015)	769 (178-2,804)	467 (128-747)	0.040	NS	0.048	NS
TSH, U/mL	2.46 (1.78-3.60)	1.85 (0.84-3.24)	1.72 (1.00-3.56)	0.22	–	–	–
ECG							
Normal sinus rhythm	14 (52)	72 (77)	28 (82)	0.013	0.024	0.021	NS
New atrial fibrillation	3 (11)	7 (8)	1 (3)	0.46	–	–	–
SVT	0 (0)	1 (1)	3 (9)	0.032	NS	NS	NS
PVCs/bigeminy	2 (7)	2 (2)	4 (12)	0.083	–	–	–
New bundle branch block	7 (26)	4 (4)	0 (0)	<0.001	<0.001	<0.001	NS
High degree AVB	14 (50)	0 (0)	0 (0)	<0.001	<0.001	<0.001	–
Ventricular arrhythmia	11 (39)	8 (8)	0 (0)	<0.001	<0.001	<0.001	NS
ST-segment elevation	1 (4)	4 (4)	1 (3)	0.94	–	–	–
ST-segment depression	6 (22)	23 (24)	4 (12)	0.31	–	–	–
Echocardiography							
LVEF, %	56 (40-64)	60 (37-67)	61 (54-65)	0.26	–	–	–
New decline in LVEF	9 (35)	31 (33)	1 (3)	0.002	NS	0.019	0.002
Pericardial effusion	1 (4)	10 (11)	3 (9)	0.52	–	–	–
CMR							
CMR performed	15 (54)	82 (85)	28 (78)	0.020	0.001	0.062	NS
CMR-LVEF, %	51 (34-59)	55 (43-63)	57 (52-63)	0.20	–	–	–
Myocarditis confirmed[f]	3 (19)	10 (12)	1 (4)	0.27	–	–	–
Myocarditis suggestive[g]	7 (44)	24 (30)	1 (4)	0.005	NS	0.010	0.020
Pericardial effusion	2 (13)	12 (15)	4 (11)	0.91	–	–	–
Pericardial-LGE	1 (7)	5 (6)	2 (7)	0.10	–	–	–
Admission							
Admitted	28 (100)	91 (96)	28 (80)	0.002	NS	0.006	0.005
Coronary/ischemic evaluation	14 (50)	42 (44)	7 (19)	0.018	NS	0.020	0.011

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cumulative incidence of 1-year CV mortality compared with patients with nonsevere ICI myocarditis (29% vs 5%; HR: 6.52; 95% CI: 2.2-19.6; $P < 0.001$). Patients with severe ICI myocarditis also had increased 1-year CV mortality compared with negative cases, but this did not achieve statistical significance (29% vs 8%; HR: 3.71; 95% CI: 0.99-14.0; $P = 0.053$). Patients with nonsevere ICI myocarditis had similar 1-year CV mortality as negative cases (HR: 0.61; 95% CI: 0.14-2.54; $P = 0.49$) (Figure 2). As shown in Figure 2, the increased CV mortality in severe cases of ICI myocarditis was mainly driven by an increased

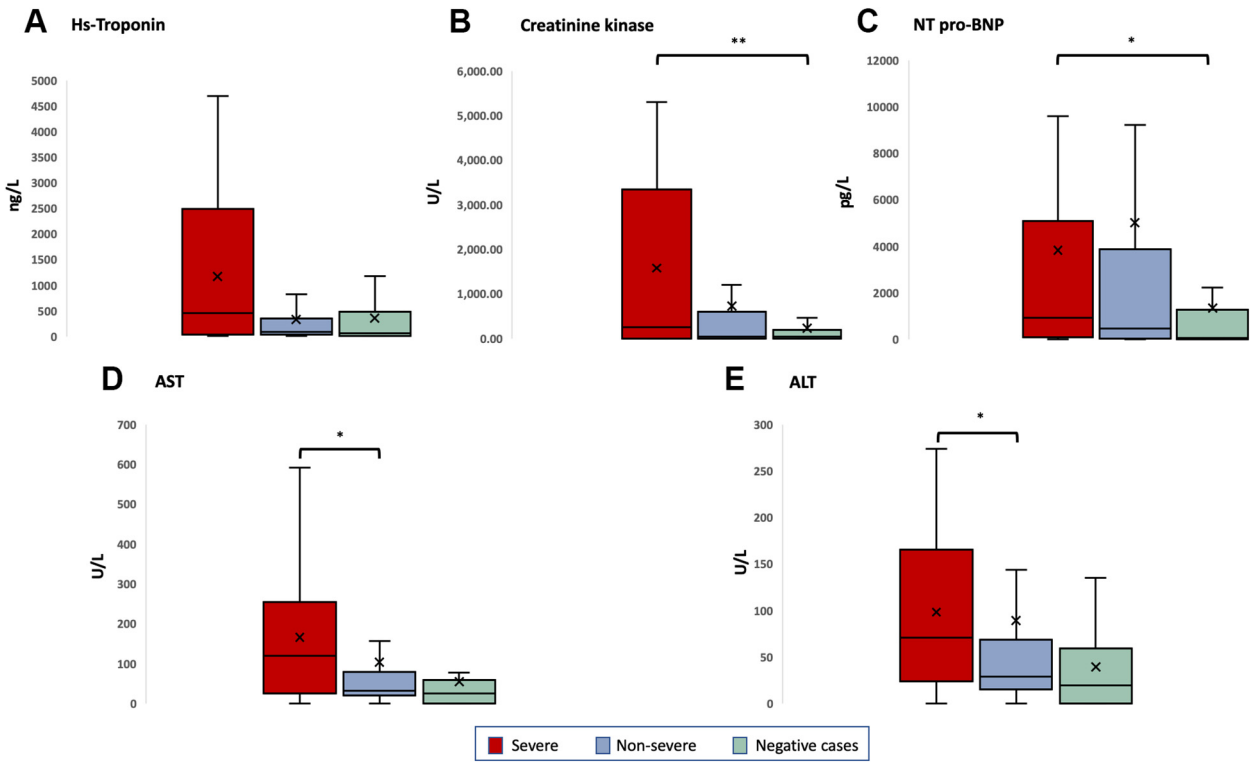
TABLE 2 Continued

	Severe Myocarditis (n = 28)	Nonsevere Myocarditis (n = 96)	Negative Cases (n = 36)	*P* Value Across Groups	*P* Value[a]	*P* Value[b]	*P* Value[c]
Pharmacological management							
Steroids	25 (89)	72 (75)	13 (36)	<0.001	NS	<0.001	<0.001
Intravenous steroids	24 (86)	51 (53)	7 (20)	<0.001	0.007	<0.001	0.002
Time to steroid therapy, d	1.0 (0.75-5.5)	1.0 (1.0-4.5)	1.5 (0.0-5.3)	0.95	–	–	–
Steroid refractory[h]	15 (60)	19 (27)	3 (23)	0.007	0.008	NS	NS
Additional immunosuppressive drugs	13 (46)	24 (25)	0 (0)	<0.001	0.055	<0.001	0.007
Mycophenolic acid	9 (32)	17 (18)	0 (0)	0.002	NS	0.002	0.043
Abatacept	5 (18)	0 (0)	0 (0)	<0.001	<0.001	<0.001	
IVIG	7 (25)	13 (14)	0 (0)	0.010	NS	0.008	NS

Values are median (Q1-Q3), mean ± SD, or n (%). Pair-wise comparisons were conducted only if the across-groups *P* value was significant. *P* values were adjusted for type I error using the post hoc Bonferroni correction. [a]*P* values represent a comparison between patients with severe vs nonsevere ICI myocarditis. [b]*P* values represent a comparison between patients with severe ICI myocarditis vs a negative diagnosis. [c]*P* values represent a comparison between patients with nonsevere ICI myocarditis vs a negative diagnosis. [d]High-sensitivity troponin (hs-troponin) was measured in 124 patients with a normal reference range of 0 to 14 ng/L. [e]Non–high-sensitivity troponin was measured in 36 patients with a normal reference range of <0.01 ng/mL. [f]Presence of both nonischemic myocardial injury and myocardial edema (both modified Lake Louise criteria) on CMR. [g]Presence of either nonischemic myocardial injury or myocardial edema (some of the modified Lake Louise criteria) on CMR. [h]Steroid refractory as a proportion of patients treated with steroid therapy.

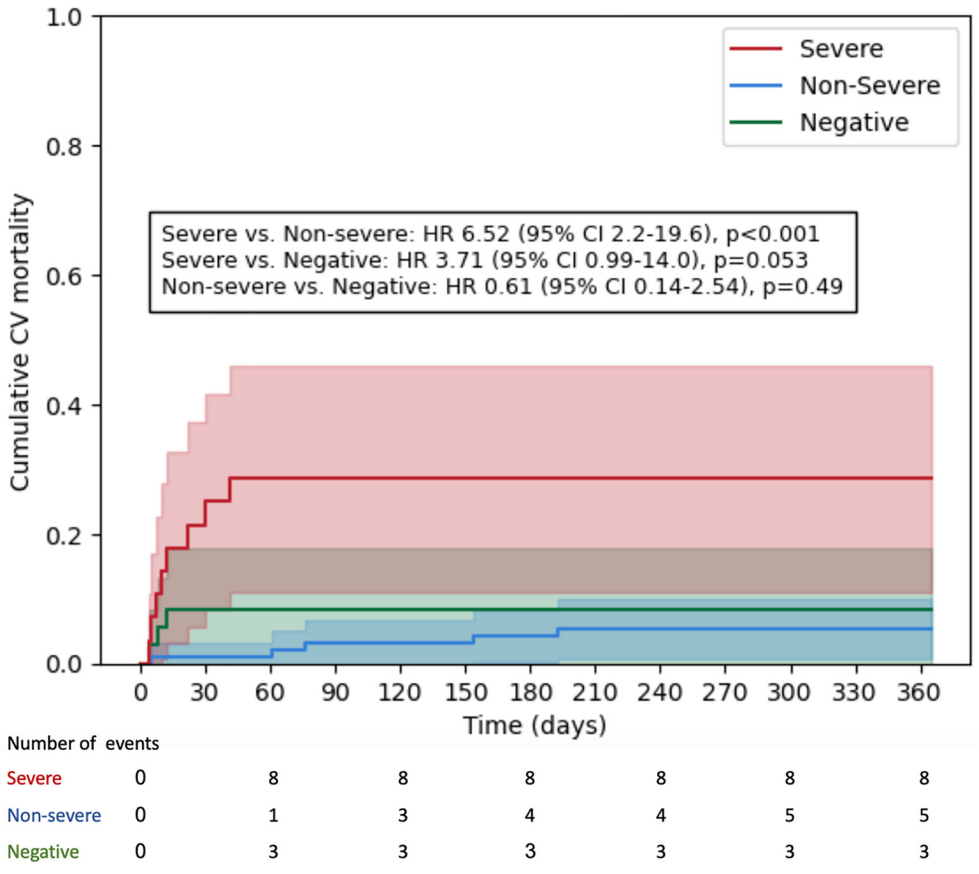
AVB = atrioventricular block; ECG = electrocardiography; HR = heart rate; IrAE = immune-related adverse events; IVIG = intravenous immunoglobulin; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NS = nonsignificant; PVC = premature ventricular contraction; SVT = supraventricular tachycardia; TSH = thyroid stimulating hormone; other abbreviations as in Table 1.

FIGURE 1 Laboratory Parameters at Presentation for Suspected ICI Myocarditis



Comparison of laboratory parameters at the time of presentation for patients with suspected immune checkpoint inhibitor (ICI) myocarditis, categorized as severe, nonsevere, and with a negative diagnosis. *$P < 0.05$, **$P < 0.01$. ALT = alanine transaminase; AST = aspartate aminotransferase; Hs-troponin = high-sensitivity troponin; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

FIGURE 2 1-Year CV Mortality in the Study Cohort



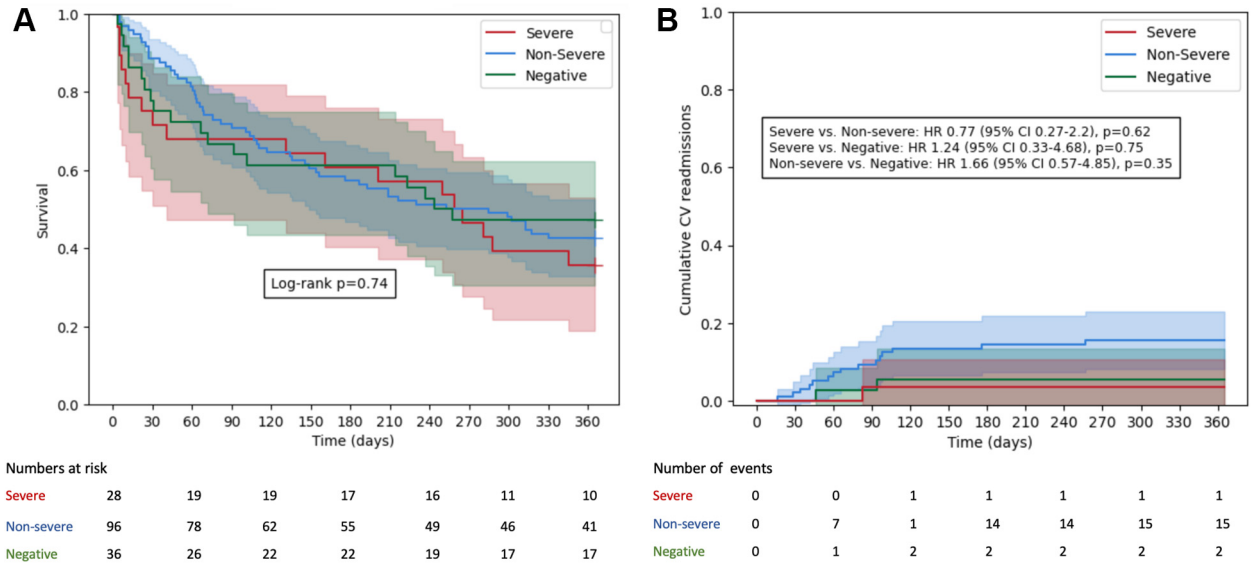
Cumulative incidence curves depict 1-year cardiovascular (CV) mortality in patients with severe, nonsevere, and with a negative diagnosis. Fine and Gray analysis was used to account for non-CV death as a competing risk.

death rate in the first 1 to 2 months following the index presentation.

Of 160 patients, 92 (58%) died within 1 year of the index presentation with suspected ICI myocarditis. One-year all-cause mortality was similar between patients with severe ICI myocarditis, nonsevere ICI myocarditis, and negative cases (64% vs 57% vs 53%, respectively; $P = 0.74$) (**Figure 3A**). Using competing risk analysis, we observed similar cumulative incidence rates of CV-related admissions in the 3 study groups within 1 year after the index admission (4% vs 16% vs 6%; P = NS) (**Figure 3B**). We also investigated long-term median LVEF values (median follow-up of 18 [Q1-Q3: 8-67] weeks) between patients with severe ICI myocarditis, nonsevere ICI myocarditis, and negative cases with available echocardiograms (n = 18/28, n = 45/96, and n = 9/36, respectively). Similar median LVEF values were observed between the 3 study groups (61% [Q1-Q3: 53%-65%] vs 60% [Q1-Q3: 46%-66%] vs 55% [Q1-Q3: 52%-64%]; $P = 0.81$).

We performed a sensitivity analysis limited to patients who underwent either an EMB and/or CMR to diagnose ICI myocarditis (n = 91) (Supplemental Figure 1A). Patients with severe (n = 17) vs nonsevere ICI (n = 46) myocarditis were compared with negative cases (n = 28). Using Fine and Gray analysis with non-CV death as a competing risk, we similarly observed an increased cumulative incidence of 1-year CV mortality in patients with severe vs nonsevere myocarditis (29% vs 7%; HR: 5.21; 95% CI: 1.28-21.2; $P = 0.021$). There were no CV deaths among negative cases. All-cause death was not statistically different between the 3 study groups (log-rank $P = 0.11$) (Supplemental

FIGURE 3 1-Year All-Cause Mortality and CV-Related Readmissions in the Study Cohort



In A, Kaplan-Meier survival curves depict 1-year all-cause mortality in patients with myocarditis categorized as severe, nonsevere, and with a negative diagnosis. Group outcomes were compared using the log-rank test. In B, cumulative incidence curves depict 1-year cardiovascular (CV) readmissions after the index presentation of suspected immune checkpoint inhibitor myocarditis in the 3 study groups. Fine and Gray analysis was used to account for death as a competing risk.

Figure 1B). Patients with severe myocarditis exhibited a nonsignificant increase in all-cause mortality when compared with nonsevere (71% vs 46%; HR: 1.88; 95% CI: 0.92-3.82; $P = 0.083$) or negative cases (71% vs 39%; HR: 2.17; 95% CI: 0.96-4.94; $P = 0.060$). All-cause mortality was comparable between nonsevere myocarditis and negative cases (46% vs 39%; HR: 1.16; 95% CI: 0.56-2.40; $P = 0.69$).

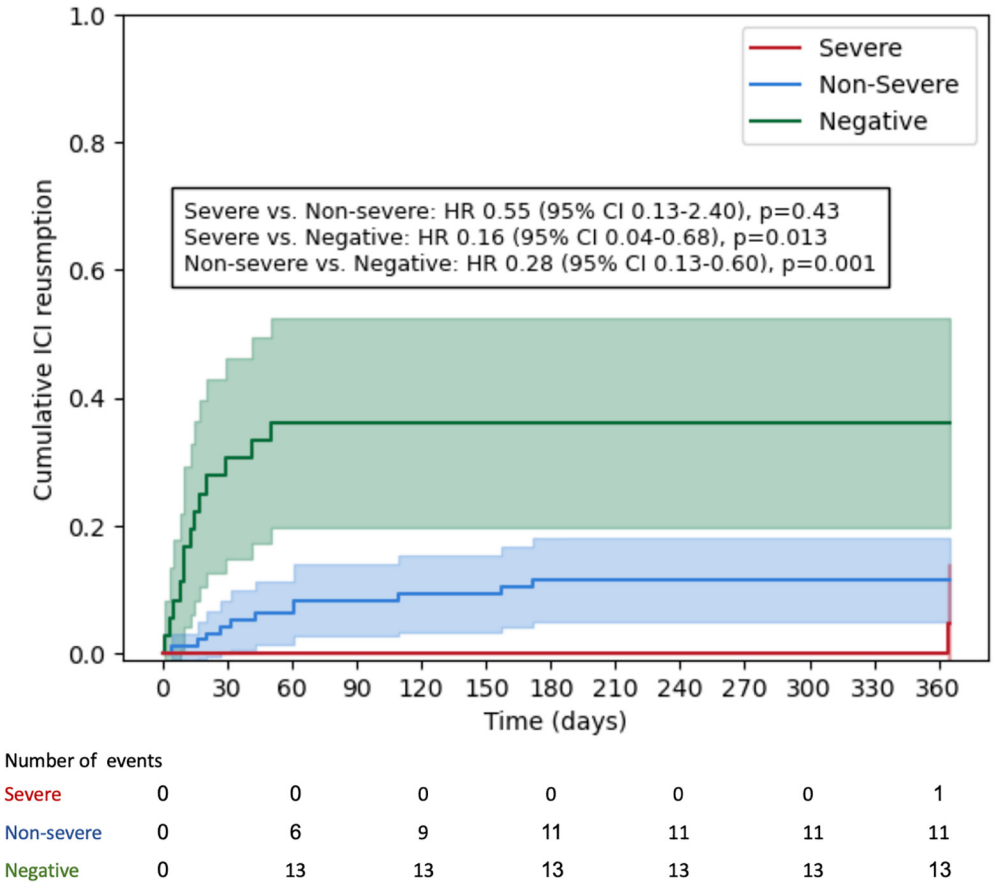
ICI RESUMPTION. ICI resumption was analyzed using the Fine and Gray method accounting for death as a competing risk (**Figure 4**). We found that 2 patients (7%) with severe myocarditis and 12 patients (13%) with nonsevere myocarditis resumed ICI therapy at a median duration of 27 (Q1-Q3: 10-61) days from the index presentation. The reasons for resuming ICI therapy in patients with positive ICI myocarditis are outlined in Supplemental Table 7. Among the 14 patients who were rechallenged, 8 patients had follow-up troponin levels that were abnormal in 7 cases (median 36 [Q1-Q3: 20-45] ng/L). However, none of these 14 patients showed clinical evidence of recurrent myocarditis based on the ICOS criteria. Of the negative cases, 13 of 36 patients (36%) resumed ICI therapy following their index presentation. The reasons for not resuming ICI therapy in negative cases are provided in Supplemental Table 4.

DISCUSSION

In this study, we have analyzed the 1-year outcomes of a contemporary cohort of patients with ICI myocarditis, as defined by the 2022 ICOS criteria. Our results indicate that 1-year CV mortality was higher among patients with a severe presentation compared with those with nonsevere presentation (29% vs 5%). However, these outcomes represent an improvement compared with previous reports on ICI myocarditis.[4] Moreover, the 1-year CV mortality remained low in patients with nonsevere ICI myocarditis and was comparable with the rates seen in negative cases. Rates of CV readmission and the long-term status of LVEF were similar in patients with or without a positive diagnosis of ICI myocarditis. Notably, 1-year all-cause mortality was high in all patients with suspected ICI myocarditis (58%). Lastly, only a minority of patients (17%) resumed ICI therapy, including those with a negative diagnosis.

The advent of ICI agents has significantly changed the landscape of cancer therapy, with almost one-half of all patients with metastatic cancer in high-income countries receiving ICI treatment, and the indications for their use are rapidly increasing.[12,13] However, alongside the benefits of improved patient survival, these therapies come with the significant

FIGURE 4 Cumulative Incidence of ICI Resumption in Patients With Suspected ICI Myocarditis



Cumulative incidence curves depict immune checkpoint inhibitor (ICI) resumption after the index presentation with suspected ICI myocarditis in patients with severe, nonsevere, or with a negative diagnosis. Fine and Gray analysis was used to account for death as a competing risk.

risk of immune-related adverse events, including acute myocarditis. Although ICI myocarditis is an infrequent diagnosis, its prognosis is considered to be more severe than that of other types of myocarditis.[14] An analysis utilizing the World Health Organization pharmacovigilance database revealed that of 122 patients with ICI myocarditis, 61 (50%) died during a median follow-up of 180 days.[4] This dramatic finding has had a significant impact on the acute management of patients with ICI myocarditis. The American Society of Clinical Oncology recommends that for patients with grade 2 or higher ICI myocarditis (myocarditis presenting with mild symptoms), ICI therapy should be permanently discontinued.[5] Similarly, the recent guidelines from the European Society of Cardiology Cardio-Oncology recommend ICI therapy discontinuation for patients with myocarditis, but they also emphasize that resuming ICI therapy should be considered only in select cases of uncomplicated ICI myocarditis and after multidisciplinary discussion.[6]

Although these recommendations appropriately aim to prevent potential CV complications associated with resuming ICI therapy after ICI myocarditis, several factors merit consideration. First, the potential survival benefit of ICI therapy is significant, possibly promoting durable stable disease or even achieving a complete response and "clinical cure" in patients with metastatic cancer.[15-17] Second, evidence suggests that the occurrence of ICI-immune related adverse events reflects a robust immune reaction to ICIs and is modestly correlated with increased antitumor efficacy and greater overall survival.[18] Lastly, we should acknowledge that evidence regarding the

long-term prognosis and outcomes after ICI resumption among patients with ICI myocarditis is scarce and is mostly based on case reports and case series. Therefore, in this study, we explored the contemporary 1-year prognosis and outcomes of patients with ICI myocarditis across the clinical spectrum of severity. Our results demonstrate that the 1-year CV mortality of patients with ICI myocarditis is lower than previously reported and mostly limited to patients with a severe presentation. This is likely due to a heightened clinical awareness for ICI-related adverse events, including myocarditis, and the downstream consequences of rapid diagnosis and early initiation of therapy in these patients.[19] Early initiation of therapy may also explain the low rates of 1-year CV readmission and comparable long-term LVEF among patients with and without a positive diagnosis of ICI myocarditis.

Another important observation from this study is the relatively benign CV course of patients with nonsevere myocarditis. We found a low 1-year CV mortality rate in patients with nonsevere ICI myocarditis that was comparable to negative cases. Moreover, we observed only mild abnormalities in biomarkers associated with ICI myocarditis in patients with a nonsevere presentation. Biomarkers including troponin and creatine kinase have previously been shown to predict adverse outcomes in patients with ICI myocarditis.[3,20] Our results show that transaminase levels, in particular, are significantly elevated in patients with severe ICI myocarditis vs nonsevere ICI myocarditis. Future research should evaluate appropriate cutoff values for these biomarkers to identify high-risk patients with ICI myocarditis.

In-depth evaluation of negative myocarditis cases suggests that the majority of patients who were initially suspected to have ICI myocarditis were ultimately diagnosed with cardiac arrhythmias, acute pericarditis, or not otherwise explained elevated troponin levels. It is important for medical providers to recognize these potential "myocarditis mimickers," particularly in this era of growing use of ICI agents. It is also important to note that 64% of patients with a negative diagnosis and the majority of patients with nonsevere myocarditis (89%) had permanent discontinuation of ICI therapy once ICI myocarditis was suspected. These findings support the need for systematic studies evaluating the consequences of resuming ICI therapy, especially in patients with a nonsevere presentation and in those who do not meet the established ICOS criteria for ICI myocarditis.

This study also provides important insights into the utility of ICOS criteria in patients with ICI myocarditis. A recent study that evaluated the diagnostic value of the ICOS criteria relative to expert clinical opinion demonstrated a sensitivity and specificity of 93% and 70%, respectively.[21] Moreover, the addition of time to presentation of <3 months from initiation of ICI therapy further improved the positive and negative predictive values of the ICOS criteria from 86% to 91% and 85% to 86%, respectively.[21] Similar to this study, our results support the ICOS criteria as a risk stratification tool for determining severe ICI myocarditis and identifying patients at increased risk for adverse CV outcomes. Our real-world data demonstrate that a significant proportion of patients with suspected ICI myocarditis do not undergo EMB or CMR procedures, leaving the diagnosis to be primarily based on clinical criteria. Thus, it is important to acknowledge that given the moderate specificity of the ICOS criteria, inclusion of patients based on a clinical diagnosis, without CMR or EMB, may have misclassified some of the negative cases as nonsevere ICI myocarditis and vice versa. Future studies looking at higher cutoff values for positive troponin (such as in the phase 3 ATRIUM [Abatacept for Immune Checkpoint Inhibitor Myocarditis] trial) or creatine kinase and transaminases may help improve the specificity of the ICOS criteria.

STUDY LIMITATIONS. First, because this study is retrospective in nature, it may be prone to selection bias, potentially limiting its generalizability. Furthermore, it is possible that cases of myocarditis, particularly nonsevere cases, were missed due to the lack of routine screening for myocarditis and troponin testing in all patients treated with ICIs. Second, the definition and severity of ICI myocarditis were based on the recently published ICOS criteria, with only 48 patients (30%) undergoing an EMB for histopathological confirmation. Although 78% (n = 125) of study patients had a CMR as part of their evaluation, the absence of a confirmatory histopathologic diagnosis may have led to overestimation or underestimation of the number of ICI myocarditis cases.[22,23] Similarly, in some cases, the increase in troponin levels was relatively modest, potentially resulting in misclassification of patients across the severity groups. Furthermore, comparisons to a negative myocarditis group, composed of patients suspected to have ICI myocarditis but who did not fulfil ICOS criteria, should be interpreted with caution due to possible inherent bias. Third, our CV mortality estimates may have been influenced by the observation that 22% of

the positive myocarditis cases did not receive steroids. Based on electronic medical chart review, this was mostly due to mild symptoms, clinical recovery by the time the diagnosis was confirmed, or negative CMR or EMB findings. Fourth, cumulative incidence rates were not adjusted for potential confounders associated with CV outcomes, which could have affected the incidence rates observed within the ICI groups. Fifth, we were unable to ascertain cancer stage at the time of presentation as well as non-CV cause-specific mortality in all cases. Furthermore, as demonstrated by our sensitivity analysis, we may have been underpowered to detect differences in all-cause mortality between severe myocarditis and other cases. Lastly, the number of patients in our cohort who resumed ICI therapy was small. Although we observed a safe cardiac course upon ICI resumption in these patients, generalizing these findings is not appropriate in the absence of careful prospective studies evaluating this strategy.

CONCLUSIONS

In a contemporary analysis of patients with suspected ICI myocarditis, we observed a lower than previously reported 1-year CV mortality and reassuring rates of CV-related readmissions and long-term LV systolic function among patients with severe and nonsevere ICI myocarditis. However, 1-year all-cause mortality in this cohort was high and may, in part, be related to permanent discontinuation of ICI therapy, particularly in patients with a nonsevere presentation or negative cases. With increasing use of ICI agents and greater awareness about immune-related adverse events, there is an expected increase in the identification of nonsevere and subclinical cases of ICI myocarditis. Future research efforts should focus on the risk stratification of patients with ICI myocarditis in an effort to identify those patients who may tolerate resumption of ICI therapy to improve cancer outcomes, without increasing adverse CV events.

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ADDRESS FOR CORRESPONDENCE: Dr Osnat Itzhaki Ben Zadok, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 70 Francis Street, Boston, Massachusetts 02115, USA. E-mail: oitzhakibenzadok@harvard.bwh.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with severe ICI myocarditis, defined by the 2022 ICOS criteria, demonstrated a significantly increased 1-year CV mortality rate. However, this rate was lower than previously reported, particularly when compared with patients with a nonsevere presentation. In patients with nonsevere ICI myocarditis, the 1-year CV mortality was low and comparable to that seen in negative cases.

TRANSLATIONAL OUTLOOK: Future studies should prioritize the risk stratification of patients with ICI myocarditis to identify those who may safely resume ICI therapy, aiming to improve cancer outcomes without a concurrent increase adverse CV events.

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KEY WORDS **immunecheckpoint inhibitors, myocarditis, prognosis, severe, severity**

APPENDIX **For supplemental figures and tables, please see the online version of this paper.**