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ORIGINAL RESEARCH

Predictors of Long-Term Survival in Patients With Immune Checkpoint Inhibitor–Associated Myocarditis

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BACKGROUND: Immune checkpoint inhibitor–associated myocarditis (ICIM) carries high rates of morbidity and death, but clinical outcomes vary widely. Little is known about the clinical variables associated with long-term survival.

METHODS: In this case–control study, patients diagnosed with ICIM at Massachusetts General Hospital between 2016 and 2022 were stratified into 3 groups based on length of survival after ICIM diagnosis: short-term (<30 days), intermediate-term (30–365 days), and long-term (>365 days). Baseline characteristics, immune checkpoint inhibitor regimens, laboratory values, ECG parameters, and ICIM treatments were analyzed to identify predictors of long-term survival.

RESULTS: Among 35 patients with ICIM (median follow-up time, 8.3 months), there were 9 (25.7%) in the short-term survival group, 13 (37.1%) in the intermediate-term survival group, and 13 (37.1%) in the long-term survival group. Those in the short-term survival group were older (median age, 82 versus 68 for intermediate-term and 75 for long-term; *P*=0.003). Using logistic regression, long-term survival was associated with an interval from immune checkpoint inhibitor initiation to ICIM diagnosis ≥75 days (odds ratio, 5.4; *P*=0.043) and a troponin T decrement ≥42% by day 8 after immunosuppression initiation (odds ratio, 5.5; *P*=0.042). Using multivariate Cox regression modeling, troponin T≤1000 ng/L (hazard ratio [HR], 4.0; *P*=0.007) and neutrophil/lymphocyte ratio ≤4.4 (HR, 7.9; *P*<0.001) were independently associated with longer survival.

CONCLUSIONS: Time to onset of ICIM, multiple clinical tests, and responsiveness to immunosuppressive therapy were associated with long-term survival after ICIM. Consideration of these variables may help with risk stratification and immunosuppressive therapy individualization.

Key Words: immune checkpoint inhibitor myocarditis ■ immunosuppression ■ survivorship

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment and are increasingly used as first-line treatments for both advanced[1] and early-stage malignancies.[2,3] While rapid expansion of ICI use has extended overall survival across a wide range of cancers,[4] ICIs can trigger off-target toxicities, termed immune-related adverse events (irAEs).[5,6]

ICI-associated myocarditis (ICIM) is a rare but highly morbid irAE, possessing the highest fatality rate among all irAEs.[7] Although the incidence rate among ICI recipients is ≈1%, mortality rates of up to 50% have been described.[8,9] Factors predictive of clinical outcomes remain poorly defined. Risk factors associated with adverse clinical outcomes for ICIM have been proposed,

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CLINICAL PERSPECTIVE

What Is New?

- In a retrospective, observational cohort of 35 cancer patients with immune checkpoint inhibitor myocarditis, multiple variables were associated with longer overall survival, including an increased interval from immune checkpoint inhibitor initiation to myocarditis diagnosis, lower troponin T values and neutrophil/lymphocyte ratios, higher left ventricular ejection fraction, and responsiveness to immunosuppressive therapy.

What Are the Clinical Implications?

- Improved understanding of the variables associated with a more favorable immune checkpoint inhibitor–associated myocarditis clinical course may allow more accurate prognostication and individualization of immunosuppressive therapy.

Nonstandard Abbreviations and Acronyms

ALC	absolute lymphocyte count
EMB	endomyocardial biopsy
ICI	immune checkpoint inhibitor
ICIM	immune checkpoint inhibitor-associated myocarditis
IIST	intensified immunosuppressive therapy
irAE	immune-related adverse event
MACE	major adverse cardiac event
NLR	neutrophil/lymphocyte ratio

although analyses have often relied on limited patient numbers. Clinical factors such as higher troponin levels, prolonged QRS duration, increased neutrophil/lymphocyte ratio (NLR), and receipt of a lower or delayed initial dose of corticosteroids have each been independently linked with an elevated risk of major adverse cardiac events (MACEs) following admission for ICIM.[10–14] Imaging features, such as reduced left ventricular ejection fraction (LVEF) and global longitudinal strain by echocardiography, or increased T1 times by cardiac magnetic resonance imaging (CMR), have also been associated with greater morbidity.[15] However, most studies to date have focused on short-term outcomes during or shortly following the index admission for ICIM; there remains a critical need to define factors that can offer longer-term risk stratification.[10,12,13,16] While a recent case–control study analyzed long-term ICIM cardiovascular outcomes,[17] our intention was to retrospectively identify a diverse array of easily obtainable parameters associated with survival >1 year from the diagnosis of ICIM.

METHODS

Patients and Study Design

This single-center case–control retrospective study included all patients admitted for ICIM at Massachusetts General Hospital between March 2016 and March 2022. Patients who were diagnosed at autopsy or those who did not receive corticosteroid treatment were excluded. Massachusetts General Hospital institutional review board approval was granted under protocol 2017P000501 with waiver of informed consent. Study data are available upon request to the corresponding author.

Adjudication of ICIM Cases

Patients with ICIM were identified by the Massachusetts General Hospital Severe Immunotherapy Complication Service. For this analysis, 3 authors (N.D., C.W., and L.Z.) independently reviewed the charts of all patients who were identified as potentially having ICIM during the target time period. The final diagnosis of ICIM was made per the 2022 International Cardio-Oncology Society consensus criteria.[18] When the 3 reviewers were unable to reach a consensus diagnosis, a cardio-oncologist specializing in cardiac irAEs was consulted (T.G.N. or D.A.Z.). The date of ICIM diagnosis was assigned on the basis of the earliest date at which the patient met the International Cardio-Oncology Society consensus criteria as supported by diagnostic testing.

Clinical Data Collection and Definitions

All clinical information was retrospectively extracted from the electronic medical record. This information included echocardiography, CMR imaging, and endomyocardial biopsy (EMB) results. It also included information on additional irAEs, including preexisting irAEs (defined as those present at least 1 week before admission for ICIM) and co-occurring noncardiac irAEs (defined as those present in the week before or after ICIM was diagnosed). Additional information obtained included baseline demographics, cancer type and stage, history of oncologic surgeries within 1 year before the index admission for ICIM, laboratory values, ECG parameters, ICI regimens received, dates of ICI initiation and death, ICIM treatments, and cause of death. To assess comorbidities, performance status, and concurrent illness, we calculated Charlson Comorbidity Index values,[19] obtained the Eastern Cooperative Oncology Group performance status[20] at the most recent outpatient visit before the index admission, and identified concurrent illnesses during the ICIM index admission by manual chart review, including sepsis upon initial presentation, COVID-19 status (by polymerase chain reaction testing), and Acute Physiology and Chronic Health Evaluation IV scores.[21]

EMB results were given 1 of 3 diagnoses based on the Dallas criteria: (1) active myocarditis (inflammatory infiltrate present along with myocardial damage), (2) borderline myocarditis (inflammatory infiltrate present without evidence of myocardial damage), or (3) negative for myocarditis.[22] All patients underwent a right ventricular endomyocardial biopsy except for 1 patient who had a left ventricular biopsy performed for technical reasons. A CMR was considered diagnostic if it met at least 1 criterion in both the categories listed in the Modified Lake Louise Criteria: (1) T2-based marker for myocardial edema and (2) T1-based marker for associated myocardial injury.[23] If the CMR results met criteria for only 1 of the categories, it was considered suggestive (a minor criterion in the International Cardio-Oncology Society consensus definition).[18]

Based on standardized criteria, a QRS duration >110 milliseconds was considered prolonged, as was a QTc interval (corrected for heart rate with the Bazett formula) >450 milliseconds in men or >460 milliseconds in women.[24,25] Conduction abnormalities were defined as at least 1 of the following: left bundle branch block, right bundle branch block, atrioventricular block, or intraventricular conduction delay. Newly diagnosed heart failure was defined as structural heart disease with the new onset of symptoms of heart failure, while heart failure exacerbation was defined as preexisting heart failure with worsening symptoms or functional capacity.[26] ICI combination therapy was defined as a regimen containing ≥2 ICIs. Consistent with past studies, MACE was defined as cardiovascular death, cardiac arrest, cardiogenic shock, or hemodynamically significant complete heart block.[10,27] Overall survival was defined as the time from ICIM diagnosis to death. Cause of death was adjudicated by a medical oncologist (C.W.) according to the underlying condition that initiated the series of illnesses leading to the death rather than the immediate cause of death. Death from cardiovascular cause or from myocarditis/myositis/myasthenia gravis overlap syndrome was defined as death due to heart failure, arrhythmia, cardiogenic shock, cardiogenic arrest, or respiratory failure thought due to respiratory muscle failure. Cancer death was defined as death due to complications derived from progression of cancer. Death of unknown cause was defined as death of a patient who lacked medical follow-up records within the 2 weeks before death and was not under hospice care.

Serial troponin T (TnT) measurements during index ICIM admissions were obtained from the medical record. Our institutional method of measuring TnT changed during the study period. Before April 4, 2018, the Roche Elecsys Troponin T Short Turn Around Time assay was used (normal reference range, 0–0.03 ng/mL); after that date, the Roche Elecsys Troponin T Gen 5 Short Turn Around Time assay was used (normal reference range, 0–14 ng/L). Values from these 2 assays were directly compared by multiplying the Elecsys Troponin T Short Turn Around Time assay values by a factor of 1000. This study focused on changes in TnT 4 and 8 days after initiation of corticosteroids. ΔTnT was defined as percentage change in TnT from initiation of corticosteroids (day 0); patients on ≥20 mg/d or prednisone-equivalent before admission were excluded from these analyses. If no TnT data were available for day 4 or 8, data within 1 day of these time points were used. NT-proBNP (N-terminal pro B-type natriuretic peptide) values from the initial presentation of index ICIM admissions were also obtained. Before October 31, 2022, the Roche Elecsys proBNP II assay was used; thereafter, the Roche Elecsys proBNP II Short Turn Around Time assay was used. These 2 NT-proBNP assays do not require interconversion. Echocardiography was performed using Phillips Epiq CVx and Epiq 7c machines; LVEF values used in the analysis refer to the nadir value obtained during the index ICIM admission.

Statistical Analysis

Patients were divided into 3 groups based on length of survival after ICIM diagnosis: short-term (<30 days), intermediate-term (30–365 days), and long-term (>365 days). Differences across these groups were analyzed with the Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Categorical data are reported as n (%), and continuous data are reported as median (quartiles 1–3). Missing data points for Eastern Cooperative Oncology Group status and TnT were excluded from the respective analyses. The time course of TnT values after patients were admitted for ICIM was calculated using locally weighted scatterplot smoothing. Univariate analysis using a logistic regression model was used to investigate the association between select variables and survival length. Cutoff points for continuous variables were determined using receiver operating characteristic curves and Youden's index, calculated as sensitivity+specificity − 1. The cutoff point that corresponded to maximal Youden's index were defined as the optimal cutoff point.[28] Due to concerns for confounding, we used multivariate Cox regression modeling using a backward elimination approach. Variables with a P value <0.05 in univariate analysis were included into multivariate analysis. At each step, the predictor with the highest P value (but not <0.05) was sequentially removed, and the model was refitted, until only variables with significant or near-significant associations remained. The associations of laboratory values or diagnostic study results with survival time was assessed using Kaplan–Meier methods and the log-rank test without correcting for multiple comparisons. Time-to-event was defined as the interval between ICIM diagnosis and either the date of death or the last known follow-up. No patient with survival <365 days was lost to follow up; all such patients had documented deaths in the electronic medical record. For patients with survival >365 days, all had a documented death or clinical interaction in the electronic medical record to justify this categorization. Statistical analyses were conducted using IBM SPSS Statistics for Windows version 28.0 (IBM Corporation, Armonk, NY) and GraphPad Prism version 10.2.0 (GraphPad Software, Boston, MA). Two-sided *P* values of <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Between March 2016 and March 2022, a total of 601 patients were admitted for irAEs. Of these, 38 were diagnosed with suspected or confirmed ICIM according to prepublished definitions.[10,18] Three patients were excluded from this study: 1 diagnosed at autopsy and 2 who did not receive corticosteroid treatment after diagnosis (Figure S1). Median follow-up time was 8.3 months (interquartile range [IQR], 0.9–28.9). Among the 35 patients who met the inclusion criteria were 28 men and 7 women, with a median age of 74 years (IQR, 68–78). The most common presenting symptoms were fatigue (n=16 [45.7%]) and dyspnea (n=15 [42.9%]), all patients had a TnT value above the upper reference limit, and a conduction abnormality was observed in 12 patients (34.3%) (Table S1). The median time from initial ICI administration to admission for myocarditis was 42 days (IQR, 26–75). ICI regimens consisted of an anti–programmed death-ligand 1 agent in 28 patients (80.0%), an anti– cytotoxic T-lymphocyte–associated protein 4 agent in 1 patient (2.9%), and ICI combination therapy (anti–cytotoxic T-lymphocyte–associated protein 4 and anti–programmed death-ligand 1 agents) in 6 patients (17.1%). ICIM was diagnosed using histopathology in 19 cases (54.3%), diagnostic CMR in 8 cases (22.9%), and clinical criteria per the International Cardio-Oncology Society definition in 9 cases (25.7%) (Table S2). These diagnostic methods were not mutually exclusive. Non–small-cell lung cancer (n=11 [31.4%]) was the most common cancer type, followed by melanoma (n=9 [25.7%]) and renal cell carcinoma (n=9 [25.7%]) (Table S2). Thirteen patients (37.1%) were diagnosed with an irAE overlap syndrome, presenting with both ICIM and ICI myositis or myasthenia gravis.

Survival Length

Within 1 year of diagnosis of ICIM, 22 patients (62.9%) had died (Table 1 and Figure S2). Among these 22 patients, 10 (45.5%) deaths were attributed to cardiovascular causes and/or overlap syndrome, 6 (27.3%) to cancer, 5 (22.7%) to unknown causes (without evidence of tumor progression in the most recent imaging), and 1 (4.5%) to infection (pneumonia). Among the 6 patients who died from cancer, 2 had not resumed cancer treatment after admission for ICIM because of their fragility and poor performance status after developing the irAE.

To investigate predictors of survival, we stratified patients into 3 groups on the basis of survival time: a short-term group (<30 days; n=9 [25.7%]), an intermediate-term survival group (30–365 days; n=13 [37.1%]), and a long-term survival group (>365 days; n=13 [37.1%]). The selection of 30 days to divide the short-term from the intermediate-term group was based on prior reports indicating that the majority of cardiovascular adverse events and deaths from ICIM occur within the first 30 days.[16,17] The selection of 365 days to divide the intermediate-term group from the long-term group was made because some included patients only had follow up to ≈450 days and hence using longer-term cutoffs (eg, 2 years) was not feasible. Median follow-up time was 30.4 months (IQR, 26.0–42.7) for the long-term survival group. Within the long-term survival group, 10 patients were alive ≥730 days following myocarditis diagnosis. Analysis of baseline characteristics (Table 1) revealed that median age was highest in the short-term survival group (82 years [IQR, 74–88] compared with 68 years [IQR, 62–75] in the intermediate-term group and 75 years [IQR, 69–78] in the long-term group; *P*=0.003). The Charlson Comorbidity Index scores were highest in the short-term survivor group compared with others (*P*=0.014). None of the other baseline characteristics, including malignancy type, significantly differed across groups. Among the 13 patients with overlap syndrome, 5 patients (38.5%) died in ≤30 days, 2 patients (15.4%) died between 30 and 365 days, and 6 patients (46.2%) survived >365 days (*P*=0.151). Of note, the median interval from ICI initiation to ICIM admission exhibited a nonsignificant trend toward longer intervals associating with longer survival: a median interval of 28 days (IQR, 20–42) for the short-term survival group, 42 days (IQR, 30–95) for the intermediate-term group, and 45 days (IQR, 37–162) for the long-term group (*P*=0.080). To ensure the robustness of the 30-day cutoff dividing the short-term and intermediate-term survival groups, we also performed a sensitivity analysis in which the 30-day cutoff was replaced with a 90-day cutoff, with largely similar results (Table S3).

Test Results and Survival

Laboratory parameters previously associated with ICIM outcomes were analyzed. The highest TnT values occurred in the short-term survival group, with a median

Table 1. Baseline Characteristics of Patients Across Short-, Intermediate-, and Long-Term Survival Groups

Survival group	Short-term (<30 d)	Intermediate-term (30–365 d)	Long-term (>365 d)	*P* value
n (%)	9 (25.8)	13 (37.1)	13 (37.1)	
Characteristics				
Median age, y (IQR)	82 (74–88)	68 (62–75)	75 (69–78)	0.003
Male sex, n (%)	6 (66.7)	10 (76.9)	12 (92.3)	0.33
Race				1.00
White, n (%)	9 (100)	12 (92.3)	12 (92.3)	
Non-White, n (%)	0 (0)	1 (7.7)	1 (7.7)	
Malignancy type				0.18
Lung, n (%)	1 (11.1)	6 (46.2)	4 (30.8)	
Genitourinary, n (%)	5 (55.6)	2 (15.4)	4 (30.8)	
Melanoma, n (%)	1 (11.1)	3 (23.1)	5 (38.5)	
Other, n (%)	2 (22.2)	2 (15.4)	0 (0)	
Stage IV malignancy, n (%)	8 (88.9)	13 (100)	10 (76.9)	0.17
Comorbidities				
ECOG status*				0.059
0, n (%)	4/7 (57.1)	3/12 (25.0)	4/12 (33.3)	
1, n (%)	1/7 (14.3)	5/12 (41.7)	8/12 (66.7)	
2, n (%)	1/7 (14.3)	4/12 (33.3)	0 (0)	
3, n (%)	1/7 (14.3)	0 (0)	0 (0)	
Charlson Comorbidity Index (IQR)	12 (10–12)	10 (8–10)	10 (9–11)	0.014
Concurrent COVID-19 infection, n (%)	0 (0)	0 (0)	0 (0)	N/A
Concurrent sepsis, n (%)	1 (11.1)	1 (7.7)	0 (0)	0.72
Cancer treatments				
Treatment intention				0.17
Neoadjuvant/adjuvant, n (%)	1 (11.1)	0 (0)	3 (23.1)	
Palliative, n (%)	8 (88.9)	13 (100)	10 (76.9)	
Recent oncologic surgery, n (%)	3 (33.3)	0 (0)	2 (15.4)	0.098
ICI regimen				0.49
Anti-CTLA4/anti-PD-1, n (%)	1 (11.1)	3 (23.1)	2 (15.4)	
Anti-CTLA4, n (%)	0 (0)	1 (7.7)	0 (0)	
Anti-PD-1, n (%)	8 (88.9)	9 (69.2)	9 (69.2)	
Anti-PD-L1, n (%)	0 (0)	0 (0)	2 (15.4)	
irAEs				
Median time from ICI initiation to myocarditis admission, days (IQR)	29 (20–42)	42 (30–95)	45 (37–162)	0.080
Preexisting irAE, n (%)	1 (11.1)	4 (30.8)	3 (23.1)	0.55
Co-occurring noncardiac irAE, n (%)	5 (55.6)	6 (46.2)	7 (53.8)	1.00
Neurologic, n (%)	5/5 (100)	2/6 (33.3)	6/7 (85.7)	
Hepatic, n (%)	1/5 (20.0)	2/6 (33.3)	0/7 (0)	
Hematologic, n (%)	0/5 (0)	0/6 (0)	1/7 (14.3)	
Endocrine, n (%)	0/5 (0)	1/6 (16.7)	1/7 (14.3)	
Pulmonary, n (%)	0/5 (0)	1/6 (16.7)	0/7 (0)	
Renal, n (%)	0/5 (0)	1/6 (16.7)	0/7 (0)	
Overlap syndrome	5 (55.6)	2 (15.4)	6 (46.2)	0.15
ICIM+myositis, n (%)	3/5 (60.0)	1/2 (50.0)	4/6 (66.7)	
ICIM+MG, n (%)	0/5 (0)	0/2 (0)	0/6 (0)	
ICIM+myositis+MG, n (%)	2/5 (40.0)	1/2 (50.0)	2/6 (33.3)	

Values are n (%) or median (IQR). *P* values were calculated using Fisher's exact test for categorical variables and Kruskal–Wallis test for continuous variables. CTLA4 indicates cytotoxic T-lymphocyte–associated protein 4; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; ICIM, immune checkpoint inhibitor–associated myocarditis; IQR, interquartile range; irAE, immune-related adverse event; MG, myasthenia gravis; N/A, not applicable; PD-1, programmed cell death-1; and PD-L1, programmed death-ligand 1.

*ECOG status at last outpatient visit before the index admission for ICIM; 4 missing data points: 2 in the short-term group, 1 in the intermediate-term group, and 1 in the long-term group.

value of 1316 ng/L (IQR, 858–2490), compared with 180 ng/L (IQR, 32–287) in the intermediate-term group and 233 ng/L (IQR, 36–684) in the long-term group (P=0.001) (Table 2). There was an inverse relationship between NLR values and duration of survival: 8.3 (IQR, 6.1–13.1) in the short-term survival group, 5.4 (IQR, 4.3–6.1) in the intermediate-term group, and 3.6 (IQR, 2.2–5.0) in the long-term survival group (P=0.002). Conversely, absolute lymphocyte count (ALC) values were directly related to length of survival: 0.76 K/μL (IQR, 0.45–1.1) in the short-term survival group, 1.1 K/μL (IQR, 0.81–1.6) in the intermediate-term survival group, and 1.5 K/μL (IQR, 1.2–1.9) in the long-term survival group (P=0.031).

We next examined electrocardiographic features previously reported to be associated with cardiovascular outcome or death in ICIM.[13,29] The QRS duration and QTc interval were each inversely related to duration of survival (Table 2). The QRS duration was 134 milliseconds (IQR, 123–144) in the short-term survival group, 94 milliseconds (IQR, 89–114) in the intermediate-term survival group, and 100 milliseconds (IQR, 89–128) in the long-term survival group (P=0.012); the QTc interval was 480 milliseconds (IQR, 455–534) in the short-term survival group, 458 milliseconds (IQR, 443–480) in the intermediate-term survival group, and 442 milliseconds (IQR, 418–458) in the long-term survival group (P=0.013). Conduction abnormalities including left bundle branch block, right bundle branch block, atrioventricular block, and intraventricular conduction delay were present on the admission ECG more often in the short-term group (n=7 [77.8%]) than in the intermediate-term (n=1 [7.7%]) or long-term (n=4 [30.8%]) groups (P=0.003). Additionally, a nadir LVEF <55% during the index admission was associated with survival length, occurring in 3 patients (33.3%) in the short-term survival group, 7 (53.8%) in the intermediate-term group, and none in the long-term survival group (P=0.010).

EMB was performed in 21 patients (60.0%). Histologically active myocarditis did not associate with survival, as it was noted in all patients in the

Table 2. Associations Between Clinical Data and Survival Length

Survival group	Short-term (<30 d)	Intermediate-term (30–365 d)	Long-term (>365 d)	*P* value
n (%)	9 (25.8)	13 (37.1)	13 (37.1)	
Initial laboratory data				
NT-proBNP, pg/mL (IQR)	2537 (1007–7837)	807 (371–7464)	113 (56–3976)	0.20
CK, U/L (IQR)	2702 (349–6515)	163 (32–582)	397 (62–1207)	0.035
TnT, ng/L (IQR)	1316 (858–2490)	180 (32–287)	233 (36–684)	0.001
NLR (IQR)	8.3 (6.1–13.1)	5.4 (4.3–6.1)	3.6 (2.2–5.0)	0.002
ALC, K/μL (IQR)	0.76 (0.45–1.1)	1.1 (0.81–1.6)	1.5 (1.2–1.9)	0.031
Initial ECG				
PR interval, ms (IQR)	156 (150–161)	150 (146–176)	177 (160–184)	0.32
QRS duration, ms (IQR)	134 (123–144)	94 (89–114)	100 (89–128)	0.012
QTc interval, ms (IQR)	480 (455–534)	458 (443–480)	442 (418–458)	0.013
Any conduction abnormality, n (%)	7 (77.8)	1 (7.7)	4 (30.8)	0.003
Cardiac function				
LVEF <55%, n (%)	3 (33.3)	7 (53.8)	0 (0)	0.010
Diagnostic tests				
CMR, n (%)	3 (33.3)	11 (84.6)	10 (76.9)	
Diagnostic CMR, n (%)	1/3 (33.3)	6/11 (54.5)	1/10 (10.0)	0.09
Supportive CMR, n (%)	1/3 (33.3)	3/11 (27.3)	5/10 (50.0)	0.71
No evidence of myocarditis, n (%)	1/3 (33.3)	2/11 (18.2)	4/10 (40.0)	0.49
Biopsy, n (%)	4 (44.4)	8 (61.5)	9 (69.2)	
Active, n (%)	4/4 (100)	5/8 (62.5)	6/9 (66.7)	0.57
Borderline, n (%)	0/4 (0)	1/8 (12.5)	3/9 (33.3)	0.47
No evidence of myocarditis, n (%)	0/4 (0)	2/8 (25.0)	0/9 (0)	0.16
≥2 minor clinical criteria, n (%)*	4 (44.4)	2 (15.4)	3 (23.1)	0.30

Values are n (%) or median (IQR). *P* values calculated using Fisher's exact test for categorical variables and Kruskal–Wallis test for continuous variables. ALC indicates absolute lymphocyte count; CK, creatine kinase; CMR, cardiac magnetic resonance; ICI, immune checkpoint inhibitor; IQR, interquartile range; LVEF, left ventricular ejection fraction; NLR, neutrophil/lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QTc, heart rate-corrected QT; and TnT, troponin T.

*Minor criteria based on International Cardio-Oncology Society consensus include clinical syndrome, arrhythmia, left ventricular systolic dysfunction, other co-occurring immune-related adverse events, suggestive CMR, and suggestive histopathologic findings.

Table 3. Associations of Clinical Events and Treatments With Survival Length

Survival group	Short-term (<30 d)	Intermediate-term (30–365 d)	Long-term (>365 d)	*P* value
n (%)	9 (25.8)	13 (37.1)	13 (37.1)	
Clinical events				
Heart failure				0.010
None, n (%)	5 (55.6)	6 (46.2)	13 (100)	
Newly diagnosed, n (%)	2 (22.2)	6 (46.2)	0 (0)	
Exacerbation, n (%)	2 (22.2)	1 (7.7)	0 (0)	
Intubation, n (%)	4 (44.4)	1 (7.7)	0 (0)	0.018
ICU admission, n (%)	6 (66.7)	3 (23.1)	0 (0)	0.002
APACHE IV score (IQR)	75 (67–88)	65 (64–70)		0.30
MACEs, n (%)	6 (66.7)	2 (15.4)	0 (0)	0.001
Sudden cardiac arrest, n (%)	1/6 (16.7)	0/2 (0)	0 (0)	
Cardiogenic shock, n (%)	1/6 (16.7)	0/2 (0)	0 (0)	
Complete heart block, n (%)	1/6 (16.7)	1/2 (50.0)	0 (0)	
Cardiovascular death, n (%)	6/6 (100.0)	1/2 (50.0)	0 (0)	
Myocarditis treatment				
Median time from EMB to corticosteroid initiation, hours (IQR)	14 (2 to 25)	23 (22 to 29)	25 (12 to 29)	0.51
Initial corticosteroid dose				1.00
≥500 mg/d, n (%)	8 (88.9)	11 (84.6)	11 (84.6)	
<500 mg/d, n (%)	1 (11.1)	2 (15.4)	2 (15.4)	
Intensified immunosuppression, n (%)	7 (77.8)	5 (38.5)	7 (53.8)	0.20
Mycophenolate mofetil, n (%)	5/7 (71.4)	4/5 (80.0)	5/7 (71.4)	
IVIg, n (%)	3/7 (42.9)	1/5 (20.0)	4/7 (57.1)	
Abatacept, n (%)	4/7 (57.1)	0/5 (0)	1/7 (14.3)	
Infliximab, n (%)	1/7 (14.3)	0/5 (0)	1/7 (14.3)	
Number of additional immunosuppressive agents				0.14
1 agent, n (%)	2/7 (28.6)	5/5 (100)	4/7 (57.1)	
2 agents, n (%)	3/7 (42.9)	0/5 (0)	2/7 (28.6)	
3 agents, n (%)	2/7 (28.6)	0/5 (0)	1/7 (14.3)	
TnT change after corticosteroid initiation				
Median ΔTnT at day 4, % (IQR)*	−23.1 (−37.0 to 11.1)	−38.9 (−43.8 to −11.5)	−44.0 (−69.2 to −24.0)	0.50
Median ΔTnT at day 8, % (IQR)†	−14.8 (−35.3 to 106.9)	−44.7 (−69.2 to −25.5)	−51.2 (−75.2 to −33.7)	0.013

Values are n (%) or median (IQR). *P* values calculated using Fisher's exact test for categorical variables and Kruskal–Wallis test for continuous variables. APACHE indicates Acute Physiology and Chronic Health Evaluation; EMB, endomyocardial biopsy; ICI, immune checkpoint inhibitor; ICU, intensive care unit; IVIg, intravenous immunoglobulin; IQR, interquartile range; MACEs, major adverse cardiac events; and TnT, tropinin T.

*ΔTnT at day 4=(day 4 TnT−day 1 TnT)/day 1 TnT×100; values for 2 patients (1 in the short-term group and 1 in the intermediate-term group) were excluded due to use of ≥20 mg/d prednisone-equivalent before admission for myocarditis.

†ΔTnT at day 8=(day 8 TnT−day 1 TnT)/day 1 TnT×100; 6 missing data points: 2 patients (1 in the short-term group and one in intermediate-term group) were excluded due to use of ≥20 mg/d prednisone-equivalent before admission for myocarditis; 2 patients expired or transitioned to comfort measures (both in the short-term group); 1 patient (in the intermediate-term group) transferred to another hospital; 1 patient (in the long-term group) lacked a TnT measure for day 8.

short-term survival group, 5 of 8 patients (62.5%) in the intermediate-term group, and 6 of 9 patients (66.7%) in the long-term group (*P*=0.57). Histologically borderline myocarditis was found in 0 of 4 patients in the short-term survival group, 1 of 8 patients (12.5%) in the intermediate-term survival group, and 3 of 9 patients (33.3%) in the long-term survival group (*P*=0.47) (Table 2). The presence of cardiomyocyte damage (ie, borderline versus active myocarditis) was not associated with survival length (*P*=0.50).

Cardiac Events, Immunosuppression, and Survival

Cardiac events were reviewed for associations with survival length. Clinical heart failure incidence (newly diagnosed or exacerbation) was correlated with survival length, occurring in 4 patients (44.4%) in the short-term survival group, 7 patients (53.8%) in the intermediate-term survival group, but no patients in the long-term group (P=0.010) (Table 3). Similarly, MACE was also related to survival, occurring in 6 patients (66.7%) in the short-term survival group, 2 patients (15.4%) in the intermediate-term survival group, and no patients in the long-term group (P=0.001). Notably, no patients in the long-term survival group experienced MACE or required intubation or intensive care unit admission.

The majority of all patients (n=30 [85.7%]) were initially treated with pulse-dose corticosteroids (≥500 mg/d methylprednisolone equivalent). After excluding 3 patients on whom ICIM treatment was started before EMB, the median time from EMB to corticosteroid initiation among all patients was 24 hours (IQR, 14–27) and did not differ across the 3 survival groups (P=0.51) (Table 3). Furthermore, 19 patients (54.3%) received other immunosuppressive agents in addition to corticosteroids (intensified immunosuppressive therapy [IIST]) including mycophenolate mofetil, intravenous immunoglobulin, abatacept, and infliximab. The IIST group included nearly all patients with ICIM/myositis/myasthenia gravis overlap syndrome (12/13 [92.3%]). Rates of IIST use did not significantly differ across the groups (P=0.20).

Among the 35 patients in the study, only 1 in the long-term survival group resumed ICI therapy after admission for ICIM. This patient with metastatic melanoma had been treated with ipilimumab and nivolumab and developed ICIM with an initial TnT level of 21 ng/L. Upon resolution of the myocarditis and discontinuation of immunosuppressive therapy, the patient was reinitiated on nivolumab. Ipilimumab was later added due to rapidly progressive tumor burden. The patient did not develop recurrent ICIM but did develop refractory ICI-associated colitis 2 weeks after rechallenge with ipilimumab.

Troponin Response to Immunosuppression

Given the association between survival duration and TnT levels at admission (Table 2), we further investigated the dynamic changes in TnT levels during the hospitalization (Table 3 and Figure 1). A greater decrement of TnT levels at day 8 after initiation of immunosuppressive therapy was associated with survival length: the median ΔTnT was −14.8% (IQR, −35.3 to +106.9), −44.7% (IQR, −69.2 to −25.5), and −51.2% (IQR. −75.2 to −33.7) in the short-term, intermediate-term, and long-term survival groups, respectively (P=0.013). Furthermore, the median ΔTnT among the subset of patients who survived >730 days (n=10) was even greater at −64.4% (−21.7 to −78.2). Additionally, the association between initial TnT levels and MACE was analyzed. Among the 21 patients with TnT <32-fold the upper reference limit, only 1 (4.8%) developed a MACE within 90 days. Conversely, among the 14 patients with TnT ≥32-fold upper reference limit, 6 (42.9%) developed a MACE (P=0.010), hence demonstrating a significant association between initial TnT levels and MACE within 90 days. Finally, we investigated the association between initial TnT levels and use of IIST. Patients receiving IIST had an earlier onset of myocarditis after ICI initiation (median, 33 days [IQR, 22–45] versus 70 days [IQR, 36–157]; P=0.007) and higher initial TnT levels (715 ng/L [IQR, 175–1470] versus 204 ng/L [IQR, 30–271], P=0.007) than those not receiving IIST.

Predictors of Long-Term Survival

To further investigate factors associated with long-term survival, a logistic regression model was generated. Variables introduced into the model included those with P values <0.1 in Tables 1 to 3 and factors with prognostic value as described in prior reports.[10,12,30] Factors found to be significantly associated with long-term survival included time to myocarditis ≥75 days (odds ratio [OR], 5.4 [95% CI, 1.1–28.8]; P=0.043), initial NT-proBNP ≤450 pg/mL (OR, 12.8 [95% CI, 1.8–88.4];

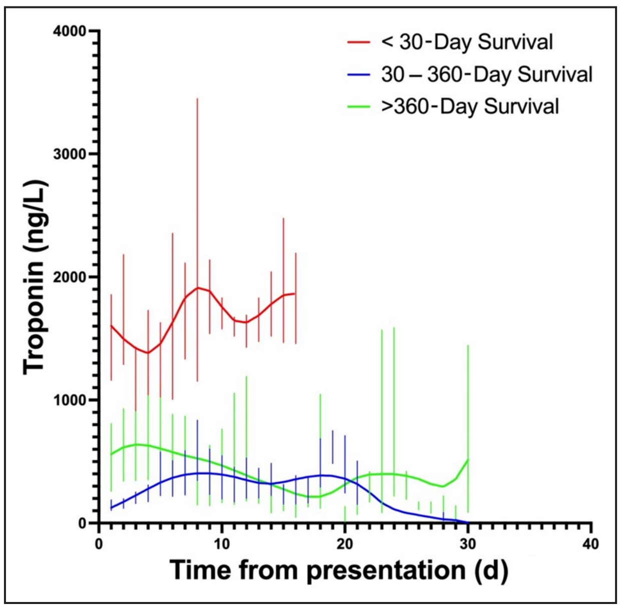

Figure 1. TnT levels during index admission for ICIM.
Troponin values were plotted for patients stratified by survival time: short-term survival (<30 days, n=9; red line); intermediate-term survival (30–365 days, n=13; blue line); and long-term survival (>365 days, n=13; green line). The short-term survival group data are limited to 16 days because n was <3 after this point. Day 1 represents the day of initial presentation. Lines indicate mean values and were smoothed using the locally weighted scatterplot smoothing method. Vertical bars indicate the standard error of the mean. ICIM indicates immune checkpoint inhibitor–associated myocarditis; and TnT, troponin T.

P=0.010), initial NLR ≤4.4 (OR, 13.3 [95% CI, 2.5–72.5]; *P*=0.003), initial ALC ≥1.1 K/μL (OR, 10.2 [95% CI, 1.7–59.7]; *P*=0.010), LVEF (OR, 1.1 [95% CI, 1.0–1.2]; *P*=0.022), and a TnT decrement of ≥42% by day 8 of immunosuppression (OR, 5.5 [95% CI, 1.1–28.4]; *P*=0.042; Table 4). A QTc interval ≤450 milliseconds in men or ≤460 milliseconds in women at admission showed a nonsignificant trend toward association with long-term survival (*P*=0.051). Neither TnT ≤1000 ng/L nor creatine kinase ≤2000 U/L at admission were associated with long-term survival. We performed additional regression modeling to assess variables differentially associated with 30-day death versus 365-day death (Table S4). Variables associated with the 30-day mortality rate but not the 365-day mortality rate included age, an initial creatine kinase >2000 U/L, an initial TnT >1000 ng/L, and the presence of any conduction abnormalities. Conversely, an NLR >4.4 and nadir LVEF were associated with 365-day death but not 30-day death.

Associations between select variables and overall survival were then tested using Kaplan–Meier analysis and the log-rank test. Initial TnT levels ≤1000 ng/L (*P*=0.005), NT-proBNP ≤450 pg/mL (*P*=0.025), LVEF ≥55% (*P*=0.027), NLR ≤4.4 (*P*=0.001), and ALC ≥1.1 K/μL (*P*=0.002) were each found to be associated with improved overall survival after ICIM diagnosis (Figure 2). A trend toward improved overall survival was observed for patients with ≥42% decrement of TnT by day 8 of immunosuppression (*P*=0.060).

To address potential confounders, we generated a multivariate Cox regression model. As a first step, we created a univariate Cox regression model to identify variables significantly associated with survival: this yielded 6 variables (NT-proBNP ≤450 pg/mL, TnT ≤1000 ng/L, NLR ≤4.4, ALC ≥1.1 K/μL, LVEF ≥55%, and QRS interval≤110 milliseconds) (Table 5). Day 8 TnT decrement ≥42% showed a trend toward significance (hazard ratio [HR], 2.2 [95% CI, 0.9–5.0; *P*=0.067), similar to what was seen in the Kaplan–Meier analysis of this variable (Figure 2). We then proceeded to create a multivariate Cox model. To reduce the risk of overfitting the model, we used a backward elimination approach to sequentially eliminate variables with the weakest associations with survival. Starting with the 6 variables that were significantly associated with survival in their respective univariate analyses, the covariate with the highest *P* value (but not <0.05) was sequentially removed (first LVEF ≥55%, then QRS interval ≤110 milliseconds, and then NT-proBNP ≤450 pg/mL); the model was then rerun until only covariates with significant or near-significant associations remained (TnT ≤1000 ng/L, NLR ≤4.4, and ALC ≥1.1 K/μL). We then performed the multivariate Cox regression adjusting for these 3 covariates, finding that TnT ≤1000 ng/L (HR, 4.0 [95% CI, 1.5–10.9]; *P*=0.007) and NLR ≤4.4 (HR, 7.9 [95% CI, 2.7–22.8]; *P*<0.001) were independently positively associated with longer survival. A trend toward improved survival was observed for ALC ≥1.1 K/μL (HR, 3.1 [95% CI, 1.0–10.1]; *P*=0.058).

Table 4. Univariate Logistic Regression Analysis of Factors Associated With Long-Term (>365 Days) Survival

	>365-d survival	
	OR (95% CI)	*P* value
Baseline characteristics		
Age	1.0 (0.9–1.1)	0.52
Male	4.5 (0.5–42.5)	0.19
Charlson Comorbidity Index	1.3 (0.67–2.5)	0.44
Recent oncologic surgery	0.44 (0.03–5.9)	0.53
ICI combination	0.8 (0.1–5.2)	0.83
Time from ICI initiation to myocarditis ≥75 d	5.4 (1.1–27.8)	0.043
Initial laboratory data*		
NT-proBNP ≤450 pg/mL	12.8 (1.8–88.4)	0.010
CK ≤2000 U/L	1.7 (0.3–11.0)	0.56
TnT ≤1000 ng/L	5.6 (0.6–52.0)	0.13
NLR ≤4.4	13.3 (2.5–72.5)	0.003
ALC ≥1.1 K/μL	10.2 (1.7–59.7)	0.010
Initial ECG		
No conduction abnormalities	1.3 (0.3–5.6)	0.74
QRS duration ≤110 msec	2.7 (0.6–11.5)	0.18
QTc interval ≤450 msec (men) or ≤460 msec (women)	4.3 (1.0–18.4)	0.051
Cardiac function		
LVEF (per %)	1.1 (1.0–1.2)	0.022
Myocarditis treatment and TnT response		
Not requiring intensified immunosuppression	1.0 (0.3–4.1)	0.97
Day 8 TnT decrement ≥42%*	5.5 (1.1–28.4)	0.042

ALC indicates absolute lymphocyte count; CK, creatine kinase; ICI, immune checkpoint inhibitor; ICIM, immune checkpoint inhibitor–associated myocarditis; LVEF, left ventricular ejection fraction; NLR, neutrophil/lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; QTc, heart rate-corrected QT; and TnT, troponin T.

*Cutoffs determined using receiver operating characteristic curves and Youden's index.

DISCUSSION

ICIM is associated with a high rate of morbidity and death, but a subset of patients do experience favorable clinical outcomes. This is the first retrospective cohort study to identify several novel predictors of long-term survival to aid in risk stratification of this disease. First, a greater time interval from ICI initiation to ICIM diagnosis was noted among long-term survivors. Second, lower admission NLR and TnT values and higher admission ALC values each held prognostic value for long-term survival. Finally, events after ICIM diagnosis were associated with long-term survival, including the

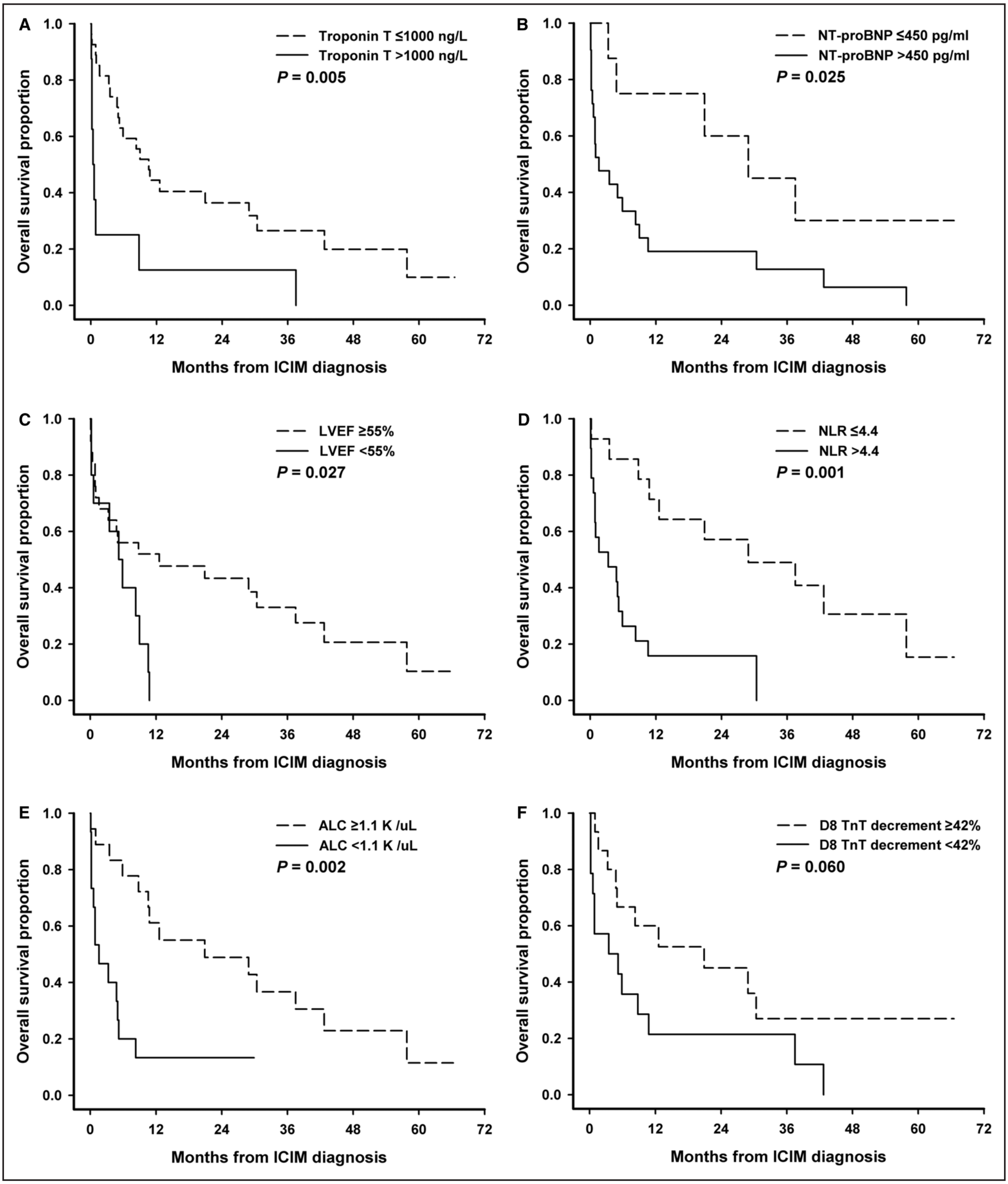

Figure 2. Associations between select variables and overall survival by Kaplan–Meier analysis.
Overall survival over time among 35 patients admitted for ICIM was analyzed on the basis of (**A**) admission TnT, (**B**) admission NT-proBNP, (**C**) nadir LVEF, (**D**) admission NLR, (**E**) admission ALC, and (**F**) decrement in TnT 8 days after initiation of immunosuppressive treatment. Cutoff values were determined by receiver operating characteristic curves and Youden's index. ALC indicates absolute lymphocyte count; ICIM indicates immune checkpoint inhibitor–associated myocarditis; LVEF, left ventricular ejection fraction; NLR, neutrophil/lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and TnT, troponin T.

Table 5. Cox Regression Modeling of Factors Associated With Increased Overall Survival (n=35)

Factors	Univariate analysis		Multivariate analysis*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.1 (0.9–1.2)	0.41		
Charlson comorbidity index	1.1 (0.6–2.0)	0.77		
Initial laboratory data†				
NT-proBNP ≤450 pg/mL	3.0 (1.1–8.0)	0.033	1.9 (0.6–5.7)	0.27
CK ≤2000 U/L	2.0 (0.8–5.2)	0.15		
TnT ≤1000 ng/L	3.1 (1.3–7.3)	0.008	4.0 (1.5–10.9)	0.007
NLR ≤4.4	4.3 (1.7–10.9)	0.002	7.9 (2.7–22.8)	<0.001
ALC ≥1.1 K/μL	3.7 (1.5–8.6)	0.003	3.1 (1.0–10.1)	0.058
Initial ECG and heart function				
QRS interval≤110 ms	2.4 (1.1–5.1)	0.021	1.5 (0.5–4.2)	0.45
QTc interval≤450 ms (men) or ≤460 ms (women)	1.7 (0.8–3.8)	0.16		
LVEF ≥55%	2.5 (1.1–5.9)	0.033	1.2 (0.4–3.9)	0.76
Myocarditis treatment				
Day 8 TnT decrement ≥42%a†	2.2 (0.9–5.0)	0.067		

ALC indicates absolute lymphocyte count; CK, creatine kinase; HR, hazard ratio; ICI, immune checkpoint inhibitor; LVEF, left ventricular ejection fraction; NLR, neutrophil/lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QTc, heart rate-corrected QT; and TnT, troponin T.

*Multivariate regression was conducted using backward elimination approach; final model incorporates adjustments made for TnT ≤1000 ng/L, NLR ≤4.4, and ALC ≥1.1 K/μL. For other covariates, the shown HR and *P* values reflect final values just before removal during the backward elimination process.

†Cutoffs determined using receiver operating characteristic curves.

lack of a depressed LVEF or clinical heart failure, lack of intensive care unit admission, and a greater decrement in TnT by day 8 of immunosuppression.

ICIM clinical courses are highly variable, and it may take days for laboratory trends to appear and for coordination and interpretation of diagnostic tests. We have identified several prognostic variables available at the time of admission that can aid in rapid risk stratification. First, we observed links between both ALC and NLR values and outcomes of ICIM. This finding extrapolates a previous observation that decreases in ALC and increases in NLR at the time of ICIM diagnosis compared with prior baseline values were each associated with an elevated risk of subsequent MACEs.[13] Furthermore, reports have shown symptomatic heart failure is associated with worse overall survival in ICIM.[31] In our study, all 13 patients in the long-term survival group had an LVEF ≥55% during admission and none developed heart failure or MACE. Additionally, higher LVEF was associated with better overall survival in the regression model, consistent with findings among cancer patients without ICIM.[32] Finally, none of the patients in the long-term survival group required intensive care unit admission or mechanical ventilation. All of these findings may be attributable to lower myocarditis severity, increased responsiveness to immunosuppressive treatment among long-term survivors, or both. Further investigation with larger cohorts is required to determine if hematologic parameters provide prognostic information independent of cardiovascular parameters such as LVEF and TnT, and prospective studies are needed to better elucidate the relationship between ICIM and long-term cardiac complications.

TnT levels have known prognostic significance in ICIM with multiple past studies reporting a link between higher TnT levels and poorer outcomes.[10,11] Our results are consistent with these findings, such that higher initial TnT levels were associated with MACEs and worse overall survival. One important new insight is that TnT responsiveness to immunosuppressive treatment predicts long-term survival. While the exact molecular mechanisms of ICIM remain unclear, previous studies have suggested ICIM is, in part, mediated by T-cell–induced myocardial damage.[33] Persistently elevated TnT levels likely indicate ongoing inflammation, which could be due to robust positive feedback loops increasing T-cell activation and infiltration or damage from less corticosteroid-responsive cell types. In contrast, a larger decrement in TnT levels after immunosuppression may indicate an enhanced ability to interrupt the pathways that promote antigen presentation and T-cell activation and infiltration. We hypothesize that the greater decrement in TnT levels indicates reduced ongoing damage to cardiomyocytes, which may translate to the preservation of cardiac structure and function and a lower risk of long-term adverse events. Furthermore, high-dose corticosteroids, the current recommended first-line treatment,[34] have a considerable side effect profile but may also inhibit tumor-directed T cells and may therefore risk accelerated cancer progression.[35] Biomarkers to identify strong responders may allow for a shorter course of high-dose corticosteroids with a more rapid taper to be used in some patients. Additional studies regarding the long-term clinical outcomes of different immunosuppressive treatments are needed.

Median time to onset of ICIM has been reported as 34 to 51 days after initiation of ICI therapy, with ≈80% of cases presenting within the first 3 months.[10,14] Earlier onset has been reported to be associated with fulminant myocarditis,[16] a higher risk of subsequent MACEs,[10] and the use of IIST.[36] Our findings affirm these results, as the median time from ICI administration to admission for ICIM was 42 days (IQR, 26–75). While previous reports have demonstrated the association between time to onset of ICIM and various clinical outcomes, our study is the first to report that a time from ICI start to onset of ICIM ≥75 days predicts long-term survival. It remains unclear why later onset of disease correlates with clinical outcomes; later onset may actually represent delayed and/or incidental detection of more mild, minimally symptomatic ICIM. Moreover, a prior study found that late-onset irAEs (>3 months from ICI initiation) were associated with greater radiographic response and longer overall survival, suggesting that early- versus late-onset irAEs may have differing underlying molecular and cellular drivers;[37] there are currently no data on this topic. Similar to patients with more marked decrements in TnT in response to early immunosuppression, patients with late-onset ICIM may benefit from less intensive immunosuppressive treatment.

Overlap syndrome, in which ICIM is accompanied by myositis and/or myasthenia gravis, has been reported to have poor clinical outcomes.[38] Of the 13 patients in our study with overlap syndrome, 5 patients (38.5%) died in <30 days, which is moderately less than the 60% mortality rate described for this group in a systematic review,[39] but higher than the 30-day mortality rate of 25.8% for the entire 35 patients in our cohort. In addition, 12 of the 13 patients with overlap syndrome in our study received IIST, consistent with prior reports from other centers.[39,40] These findings suggest that while patients with overlap syndrome are at higher risk for poor outcomes, many patients do achieve long-term survival. Interestingly, among patients with and without overlap syndrome, there was no difference in the TnT response to immunosuppression at day 8.[11] In all cases of ICIM, this entity should be evaluated for and excluded, and multidisciplinary care involving experts in cardiology, neurology, and oncology should be involved in the care of this population.

A prior study found that patients with ICIM who received IIST had higher initial TnT levels and were more likely to die than those who did not receive IIST.[36] However, this study pooled data for 28 on-site patients (4 of whom required IIST) with data for 32 patients that required IIST in previously published case reports, complicating interpretation of the results. In our study, roughly half the patients received IIST. Patients who received IIST had earlier onset of ICIM and higher initial TnT levels; however, receipt of IIST was not associated with long-term survival. One challenge with determining the relationship between IIST and outcomes is that the decision to use IIST rests with the treating clinicians, who likely elect to use IIST for patients with more severe ICIM. Furthermore, practice patterns for IIST are not standardized and vary widely between institutions. Prospective randomized studies are eminently needed to decipher the utility of IIST in ICIM.

Our study has several important limitations. First, while associations between different variables and overall ICIM survival were detected, the poor prognosis for patients with this disease is typically multifactorial. Cardiopulmonary complications and discontinuation of potentially lifesaving cancer treatment can contribute to poor prognosis. A competing risk from cancer death could affect our findings. The impact of this competing risk is minimized by the relatively equal distribution of cancer types and stage IV disease, only 1 patient being rechallenged with ICI among our different survival groups, and the multifactorial nature of death caused by ICIM. Second, this study examines several variables without accounting for the testing of multiple hypotheses, increasing the risk of falsely positive results. Third, this was a retrospective study from a single academic medical center, thus limiting generalizability. Fourth, the timing of lab values and serial TnT measurements were not protocolized; to accommodate this, in some cases, TnT results from the day before or after our designated time point of interest were included. Fifth, ICIM is a rare condition, reflected in the small sample size (n=35) of this study, which limited certain analyses such as multivariable regression analysis. Even so, the high mortality rate of ICIM allowed for the use of univariable and multivariable modeling to identify several key predictors of long-term survival. Finally, this study does not address the mechanistic basis for the association of certain laboratory values and ECG parameters with long-term survival; further research into the pathophysiological mechanisms is needed.

CONCLUSIONS

In this study of patients with ICIM, time from ICI initiation to ICIM onset, NLR, ALC, LVEF, and TnT response to immunosuppressive therapy were associated with long-term survival. Further investigations should clarify how these variables can instruct clinical management of ICIM.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S2

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