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Predictors and Risk Score for Immune Checkpoint-Inhibitor-Associated Myocarditis Severity

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Keywords:

Myocarditis; cardio-oncology; immunotherapy; mortality; myositis; risk-score.

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Abstract

Background:

Immune-checkpoint inhibitors (ICI) are associated with life-threatening myocarditis but milder presentations are increasingly recognized. The same autoimmune process that causes ICI-myocarditis can manifest concurrent generalized myositis, myasthenia-like syndrome, and respiratory muscle failure. Prognostic factors for this "cardiomyotoxicity" are lacking.

Methods:

A multicenter registry collected data retrospectively from 17 countries between 2014-2023. A multivariable cox regression model (hazard-ratio(HR), [95% confidence-interval]) was used to determine risk factors for the primary composite outcome: severe arrhythmia, heart failure, respiratory muscle failure, and/or cardiomyotoxicity-related death. Covariates included demographics, comorbidities, cardio-muscular symptoms, diagnostics, and treatments. Time-dependent covariates were used and missing data were imputed. A point-based prognostic risk score was derived and externally validated.

Results:

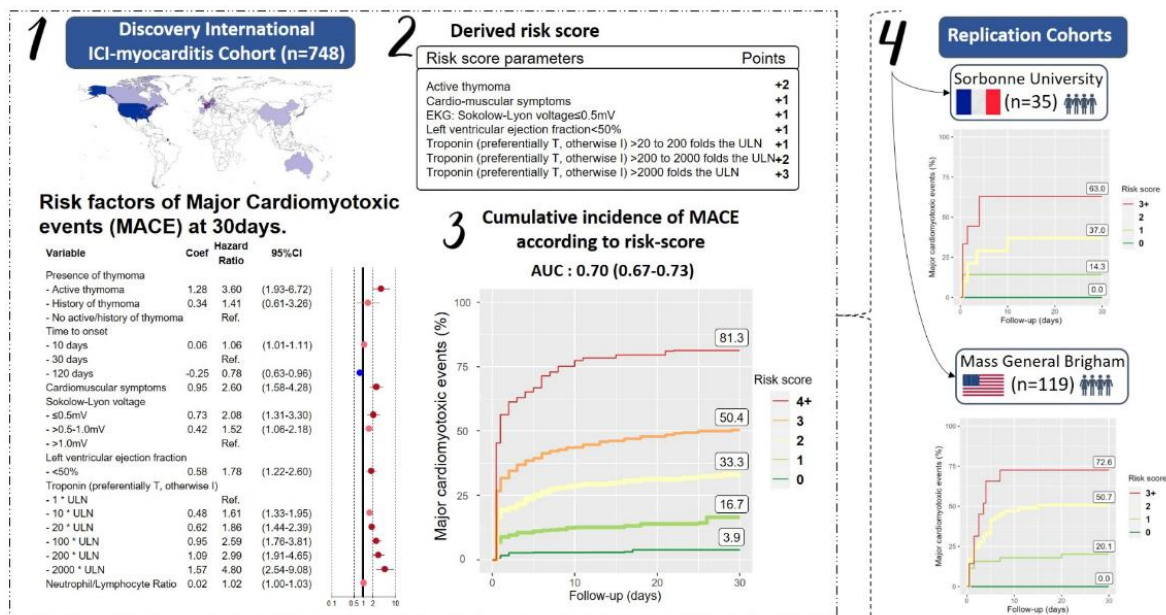
In 748 patients (67% male, age 23-94), 30-days incidence of the primary composite outcome, cardiomyotoxic death, and overall death were 33%, 13%, and 17% respectively. By multivariable analysis, the primary composite outcome was associated with active thymoma (HR=3.60[1.93-6.72]), presence of cardio-muscular symptoms (HR=2.60 [1.58-4.28]), low QRS-voltage on presenting electrocardiogram (HR for $\leq 0.5\text{mV}$ versus $> 1\text{mV}$ =2.08[1.31-3.30]), left ventricular ejection fraction (LVEF) $< 50\%$ (HR=1.78[1.22-2.60]), and incremental troponin elevation (HR=1.86 [1.44-2.39], 2.99[1.91-4.65], 4.80[2.54-9.08], for 20, 200 and 2000-fold above upper reference limit, respectively). A prognostic risk score developed using these parameters showed good performance; 30-days primary outcome incidence increased gradually from 3.9%(risk-score=0) to 81.3%(risk-score ≥ 4). This risk-score was externally validated in two independent French and US cohorts. This risk score was used prospectively in the external French cohort to identify low risk patients who were managed with no immunosuppression resulting in no cardio-myotoxic events.

Conclusions:

ICI-myocarditis can manifest with high morbidity and mortality. Myocarditis severity is associated with magnitude of troponin, thymoma, low-QRS voltage, depressed LVEF, and cardio-muscular symptoms. A risk-score incorporating these features performed well.

Trial registration number:

NCT04294771 and NCT05454527.



Structured Graphical Abstract (39/40)

Key Question: What predicts poor prognosis in ICI-associated myocarditis?

Key Finding: Troponin, thymoma, cardio-muscular symptoms, low QRS-voltage, and LVEF predicted negative outcomes. A risk score containing these features performed well.

Take-Home Message: ICI-myocarditis is part of a generalized myotoxicity and early risk-stratified early is possible.

INTRODUCTION

Immune checkpoint inhibitors (ICI) have emerged as a mainstay of cancer therapy with widespread adoption across multiple tumor types and clinical settings. Almost 50% of patients with cancer are currently eligible for ICI therapy.¹ ICI activate the immune system with anti-tumor effects but cause immune related adverse events (irAE) in 70-90% of patients.²⁻⁴ IrAE can affect any organ including cardio-muscular tissues and range from mild to fatal.^{1,5-8} ICI-myocarditis, which occurs in 0.3-1% of ICI recipients, is the most fatal irAE with mortality estimated at 30-50% in early studies.^{5,7,9} However, ICI myocarditis severity is heterogeneous; while asymptomatic cases are increasingly recognized, others patients experience life-threatening arrhythmias, cardiogenic shock, or severe concomitant myositis with respiratory muscle failure.^{5,10} Triage and management of this rare condition remains a significant challenge even for advanced multidisciplinary teams.

To date, prognostic studies of ICI-myocarditis have used pharmacovigilance datasets or cohorts less than 150 patients, without external validation and with differing results.^{7,9,11,12} Proposed predictors of severity include combination ICI treatment, elevated biomarkers, conduction delays, systolic dysfunction, inadequate immunosuppression, and simultaneous myasthenia or myositis irAE. Since these features often coexist, reconciling these data is challenging. Consequently, major knowledge gaps remain in selecting the appropriate level of care and immunosuppression strategy for ICI-myocarditis. To address this, we leveraged a web-based platform and built a multicenter registry with approximately 750 adjudicated cases of ICI-myocarditis. In this work, we use this cohort to perform a comprehensive multivariable analysis of predictors of severe outcomes in ICI-myocarditis. We then generated and externally validated a risk score to assist clinicians in risk stratification and treatment decisions.

Methods

Data Collection

A retrospective registry spanning 127 institutions across 17 countries containing 757 cases of ICI myocarditis diagnosed by treating clinicians was used as a discovery cohort (Table S1, Figure S1 for collaborators). Clinical data were locally adjudicated and submitted by participating centers via a HIPPA compliant REDCap web-based platform (IRB:181337; NCT04294771). Submissions were reviewed and cases were rejected when evidence did not meet Bonaca's diagnostic criteria for myocarditis, a hierarchical definition incorporating the availability and strength of diagnostic data.¹³ Electrocardiograms (ECG) on presentation were independently interpreted by two cardiologists (B.O. and C.D) blinded to specific cases who performed quantitative measurements (Sokolow-Lyon Index, PR, and QRS length) and identified qualitative features (methods previously published).^{14,15} The primary outcome, major cardio myotoxic events, was defined as any of the following: 1) severe heart failure requiring either intravenous medicines or mechanical circulatory support 2) severe arrhythmia defined as sustained ventricular arrhythmia, complete heart block, sudden cardiac death, use of atropine or isoproterenol, and/or use of pacemaker/defibrillator 3) respiratory failure due to myositis-related respiratory muscles failure requiring ventilation and/or 4) death due to these conditions (henceforth referred to as cardio myotoxicities). Respiratory muscle failure was included to reflect contemporary understanding of ICI myocarditis as part of a generalized skeletal myositis that can impair ventilation.^{5, 8, 16, 17} The study period ended 30 days after clinical presentation with ICI-myocarditis to avoid including unrelated endpoints. Cases were excluded if the primary outcome was met more than 24 hours prior to presentation (n=9), leaving 748 cases for analysis.

Two external independent validation ICI-myocarditis cohorts (using the updated Bonaca's criteria) were obtained from Sorbonne University (SU, Paris, France) (prospective cohort of 35 consecutive cases presenting between April 2023 and April 2024 where the risk score was used to guide treatment; NCT05454527)^{5,18} and Mass General Brigham (MGB, Boston, USA) (retrospective cohort of 119 consecutive cases presenting between January 2015 and June 2022, with enough available elements to compute the replication),¹⁹ both collected after derivation of a risk-score from the discovery cohort. The same inclusion and exclusion criteria, and outcomes definition from the discovery cohort were applied.

Table 1: Discovery cohort characteristics (n=748)

Variable	ICI-Myocarditis Study Cohort	N missing
Administrative data		
World region		
<ul style="list-style-type: none"> North America Europe Asia Australia 	343/748 (46%) 334/748 (45%) 63/748 (8%) 8/748 (1%)	0
Demographics		
Age (years, median, (IQR), [range])	69 (61-77) [23-94]	2
Body Mass Index (kg/m ²)		
<ul style="list-style-type: none"> Underweight (<18.5) Normal weight (18.5-25) Overweight (>25-30) Obese (>30) 	33/690 (5%) 280/690 (41%) 226/690 (33%) 151/690 (22%)	58
Female	249/747 (33%)	1
Patient history		
Diabetes (either type 1 or 2)	160/707 (23%)	41
Coronary artery disease	134/718 (19%)	30
History of heart failure	60/706 (8%)	42
Stroke	29/710 (4%)	38
Chronic obstructive pulmonary disease	88/699 (13%)	49
Obstructive sleep apnea	60/696 (9%)	52
Chronic kidney disease	100/701 (14%)	47
Peripheral vascular disease	43/709 (6%)	39
Prior organ transplant	4/682 (1%)	66
History of autoimmune disease*	62/714 (9%)	34
Seasonal influenza vaccination in the last year	196/462 (42%)	286
Cancer		
Cancer type		
<ul style="list-style-type: none"> Hemopathy Lung Skin Urogenital Other 	15/747 (2%) 180/747 (24%) 231/747 (31%) 164/747 (22%) 157/747 (21%)	1
Presence of thymoma		
<ul style="list-style-type: none"> Active thymoma History of thymoma No active or history of thymoma 	14/748 (2%) 6/748 (1%) 728/748 (97%)	0
Cancer treatments concurrent to ICI		
Vascular Endothelial Growth Factor inhibitors	27/748 (4%)	0
ICI Regimen		
<ul style="list-style-type: none"> Anti-PD1 or anti-PDL1 monotherapies Anti-CTLA4 monotherapy Anti-CTLA4 & anti-PD1/PDL1 combination therapy Other combination regimen 	575/741 (78%) 11/741 (1%) 151/741 (20%) 4/741 (1%)	7
Time from current line 1 st ICI infusion to myocarditis (days)	40 (23-77) [0-953]	48
Clinical examination		
Cardio-muscular symptoms**	625/748 (84%)	0
Heart rate on presentation (beat/minute, median, (IQR), [range])	86 (73-102) [25-220]	55

Variable	ICI-Myocarditis Study Cohort	N missing
Index electrocardiogram (adjudicated blindly from outcomes)		
Heart rhythm on presentation***		
• Sinus rhythm	465/588 (79%)	
• Accelerated junctional rhythm	3/588 (1%)	
• Heart Block, second degree (type I or II)	12/588 (2%)	160
• Supraventricular tachycardia	63/588 (11%)	
• Complete heart block	34/588 (6%)	
• Ventricular arrhythmia	11/588 (2%)	
Presence of pathological Q-waves [#]	77/535 (14%)	213
Sokolow-Lyon QRS voltage [#]		
• ≤0.5mV	42/535 (8%)	
• >0.5-1.0mV	112/535 (21%)	213
• >1.0mV	381/535 (71%)	
QRS duration [#]		
• ≤120ms	425/535 (79%)	
• >120-150ms	80/535 (15%)	213
• >150ms	30/535 (6%)	
Follow-up electrocardiographic features (as assessed by the reporters) ##		
• Ventricular arrhythmias and complete heart blocks	26/699 (4%)	
• Ventricular arrhythmias without complete heart blocks	74/699 (11%)	
• Complete heart blocks without ventricular arrhythmias	69/699 (10%)	
• Other significant conductive disorders, excluding complete heart blocks and ventricular arrhythmias	74/699 (11%)	49
• Other rhythm or repolarization abnormalities, excluding conductive disorders and ventricular arrhythmias	417/699 (60%)	
• None of the above	39/699 (6%)	
Left ventricular ejection fraction assessment, nadir (%), lowest of MRI or echo if both available		
• ≥50%	406/699 (58%)	49
• <50%	293/699 (42%)	
Cardiac magnetic resonance imaging (MRI) and histopathology		
At least one MRI suggestive or consistent with myocarditis	293/459 (64%)	289
Biopsy or autopsy findings at least suggestive of myocarditis	193/290 (67%)	458
Biology (values are expressed as folds of upper limit of normal)		
Creatine Kinase, initial		
• ≤1	204/564 (36%)	
• >1-10	200/564 (35%)	184
• >10-50	135/564 (24%)	
• >50	25/564 (4%)	
Creatine Kinase, peak		
• ≤1	182/564 (32%)	
• >1-10	206/564 (37%)	184
• >10-50	148/564 (26%)	
• >50	28/564 (5%)	
Troponin (preferentially T, otherwise I), initial		
• ≤1	57/673 (8%)	
• >1-20	282/673 (42%)	75
• >20-200	265/673 (39%)	
• >200-2000	64/673 (10%)	
• >2000	5/673 (1%)	
Troponin (preferentially T, otherwise I), peak		
• ≤1	32/675 (5%)	73
• >1-20	236/675 (35%)	
• >20-200	293/675 (43%)	
• >200-2000	100/675 (15%)	
• >2000	14/675 (2%)	
Neutrophil to Lymphocyte Ratio [§]	6 (3-10) [0-76]	391
Estimated glomerular filtration rate (CKD-EPI, mL/min/1.73m ²)	75 (54-92) [9-137]	196

Variable	ICI-Myocarditis Study Cohort	N missing
Myocarditis staging (criteria detailed in ¹³)		
• Possible	179/746 (24%)	2
• Probable	174/746 (23%)	
• Definite	393/746 (53%)	
Myocarditis treatment		
Corticosteroids	619/748 (83%)	0
• Initial daily dose (prednisone equivalent, mg/kg)	2 (1-15) [0-29]	43
• Peak daily dose (prednisone equivalent, mg/kg)	7 (1-16) [0-40]	58
Corticosteroids, initial daily dose (prednisone equivalent, mg/kg)		
• <1	85/576 (15%)	43
• 1-2	171/576 (30%)	
• >2	320/576 (56%)	
Corticosteroids, peak daily dose (prednisone equivalent, mg/kg)		
• <1	67/561 (12%)	58
• 1-2	135/561 (24%)	
• >2	359/561 (64%)	
Immunomodulators (any, but not corticosteroids)	268/748 (36%)	0

* **Prior autoimmune diseases** : Addison's disease (2), Ankylosing spondylitis (1), Antiphospholipid syndrome (1), Autoimmune hepatitis (3), Chronic inflammatory demyelinating polyneuropathy (2), Hashimoto's thyroiditis (6), Immune gastritis (2), Myasthenia gravis (3), Myositis (3), Other (16), Psoriasis (5), Rheumatoid arthritis (12), Sarcoidosis (2), Sjogren (2), Systemic lupus erythematosus (4), Thyroiditis (2), Type 1 diabetes (4); patients with more than one disease (6).

Other autoimmune diseases details (1 patient each): Anti-synthetase Syndrome, Atopic asthma, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, Autoimmune nephritis, Bullous pemphigoid, Chronic cutaneous lupus, Erythema nodosum, Fibromyalgia, Immune thrombocytopenic purpura, Paraneoplastic acrokeratosis, Paraneoplastic limbic encephalitis, Primary generalized osteoarthritis, Raynaud's disease, Ulcerative colitis, Viral myocarditis, Unspecified.

** Any of the following symptoms: Altered mental status, Anorexia / Loss of appetite, Arthralgia / Joint pain, Dyskinetic apical impulse, Dysphagia, Dyspnea, Chest pain or discomfort, Cough, Fatigue, Jugular venous distention, Lower extremity edema, Myalgias, Nausea/vomiting, Ocular symptoms (ptosis, diplopia, vision changes), Orthopnea, Pain other than chest pain (e.g abdominal), Palpitations, Paroxysmal Nocturnal Dyspnea, Pre-syncope, Pulmonary rales, Syncope, Third heart sound gallop or S3 gallop, Weakness, Weight gain

*** For index electrocardiogram description: If patients had more than one ECG available on first day of presentation, sinus rhythm (and supraventricular tachycardia) ECGs were preferred over complete heart block and ventricular arrhythmia ones.

Q-waves, Sokolow-Lyon voltage, QRS voltage and duration were not measured in patients presenting with accelerated junctional rhythm (3), complete heart block (34), and sustained ventricular arrhythmias (11). Additionally, measures were missing for 5 patients without fully interpretable ECG available (e.g ventricular pacing, full 12-lead missing).

Follow-up (median (IQR) in days : 116 (31-331))

EKG features : Ventricular arrhythmias include sustained and non-sustained ventricular tachycardia, Torsade de Pointes, and ventricular fibrillation.

Other significant conduction disorders include first or second-degree heart blocks, fascicular blocks (left anterior or posterior), bundle branch blocks (left, right, or undetermined, including QRS duration >120ms), sinus dysfunction with escape junctional rhythm, sinus arrest/sinus pause.

Other repolarization or rhythm abnormalities include supraventricular arrhythmias (including junctional tachycardias), PR-segment depression, premature atrial and/or ventricular complex(es), left ventricular hypertrophy, ST segment and T-U waves abnormalities, presence of pathological Q-waves, microvoltage or Sokolow-Lyon voltage <0.5mV).

§ Blood count collected within 48 hours before the first dose of immunosuppressant (either steroid or immunomodulator, whichever was first). If no treatment given, first available value.

Abbreviations:

CKD-EPI: Chronic Kidney Disease Epidemiology collaboration (Ann Intern Med. 2009 May 5; 150(9): 604612)

Statistical Analysis

Explanatory model

A univariate cox regression model was used to evaluate the association of clinical variables with major cardio-myotoxic events in the discovery cohort. Independent variables spanned past medical history, objective data collected during the ICI-myocarditis evaluation, and immunosuppressant use. Troponin, creatine-kinase, cardio-muscular symptoms, left ventricular ejection fraction (LVEF), and immunosuppressant use were treated as time-dependent covariates to prevent survivorship bias. Troponin and creatine-kinase were divided by the contributing institution's upper limit of normal (ULN). When both cardiac troponin-T and troponin-I were collected, troponin-T was preferentially used.¹⁸ A multivariable explanatory model tested pre-selected variables based upon available evidence and clinical experience. Multivariable analysis was performed after multiple imputation by chained equations of missing data using 50 imputed datasets. Imputed results were merged according to Rubin's rule.²⁰

Predictive model

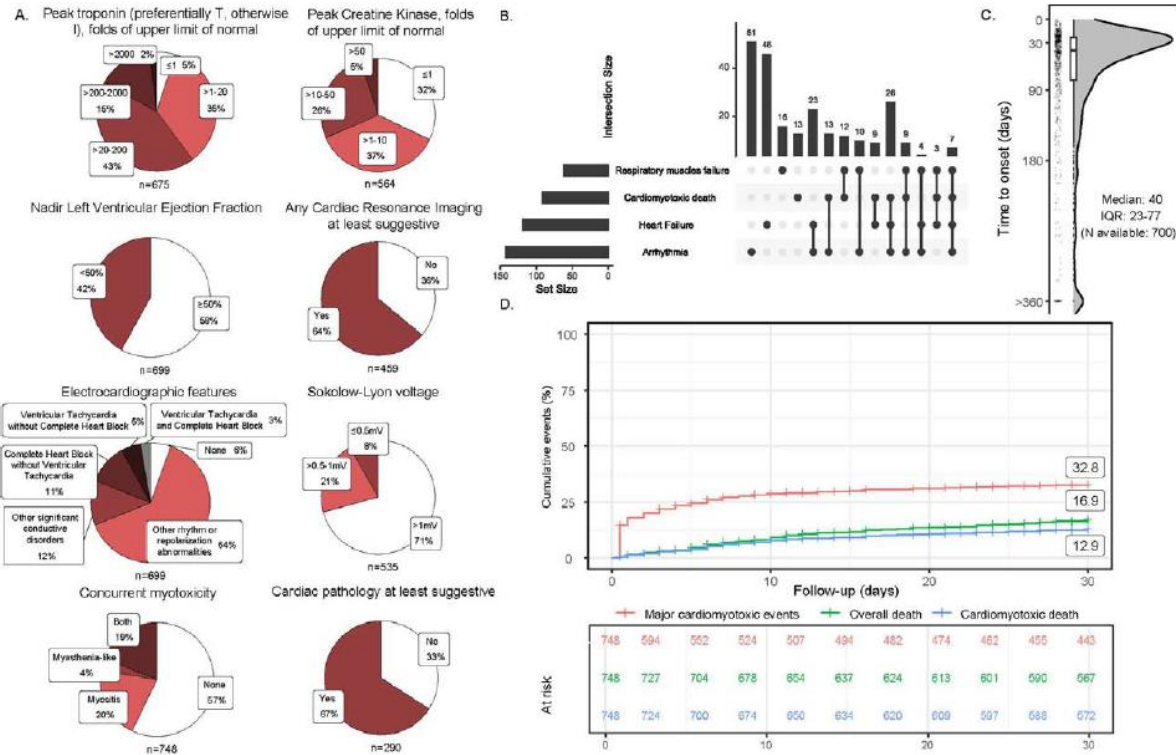
Starting from an empty predictive model, a stepwise selection procedure was performed using Schwartz Criteria to select the most impactful variables. The untransformed coefficients of these variables were used to derive a risk score for predicting the primary outcome with one point assigned for a coefficient of 0.5-1, two points for a coefficient of >1-1.5, and three points for a coefficient >1.5. Internal validation was performed with K-fold cross-validation with k-set of 10. External validation was performed on the two external validation ICI-myocarditis cohorts. For both internal and external validation, Harrell's c-index assessed the risk score's goodness-of-fit using serial models on days 1-3. Confidence intervals were obtained with bootstrap, using up to 1000 bootstrap replicates. Sensitivity analysis was performed with an unimputed dataset as well as a competing risk model to account for death from other causes. Analyses were conducted with R-v.4.2.2 for Windows, and the R-packages survival, mice, boot and rms. A two-sided p-value<0.05 was deemed significant.

Results

Patient Characteristics and Outcomes

Among 748 cases of ICI-myocarditis, median(interquartile-range) age was 69(61-77) and 33% were female (Table-1 for the baseline characteristics). Median time from first ICI dose to myocarditis presentation was 40(23-77) days with 21% patients receiving combination ICI and 79% receiving ICI monotherapy (usually anti-PD-1). The most common primary cancers were skin (31%), lung (24%), and genitourinary (22%); 3% had a thymoma. Half the cohort was classified as definite myocarditis, and one quarter each as probable and possible. Among those who underwent cardiac MRI (n=459), studies were consistent with myocarditis in 64% patients and when endomyocardial biopsy or autopsy was performed (n=290), histopathology was consistent with myocarditis in 67% patients. Patients without supporting MRI or histopathology met myocarditis criteria by other diagnostics; 84% had cardio-muscular symptoms within 72h of presentation, 95% had elevated troponin, 94% had abnormal ECG, 42% had depressed LVEF, and 43% had either concomitant myositis or myasthenia gravis-like syndrome (Figure-1A). Corticosteroids were given to 83% of patients and 36% received non-steroidal immunomodulators.

Figure 1: Cardiac workup and clinical event rate. Results of diagnostics used in myocarditis workup (A), major cardio-myotoxic events overlap (B), time from first ICI dose to onset of myocarditis (C), and event curve of first major cardio-myotoxic event at 30-days (D).

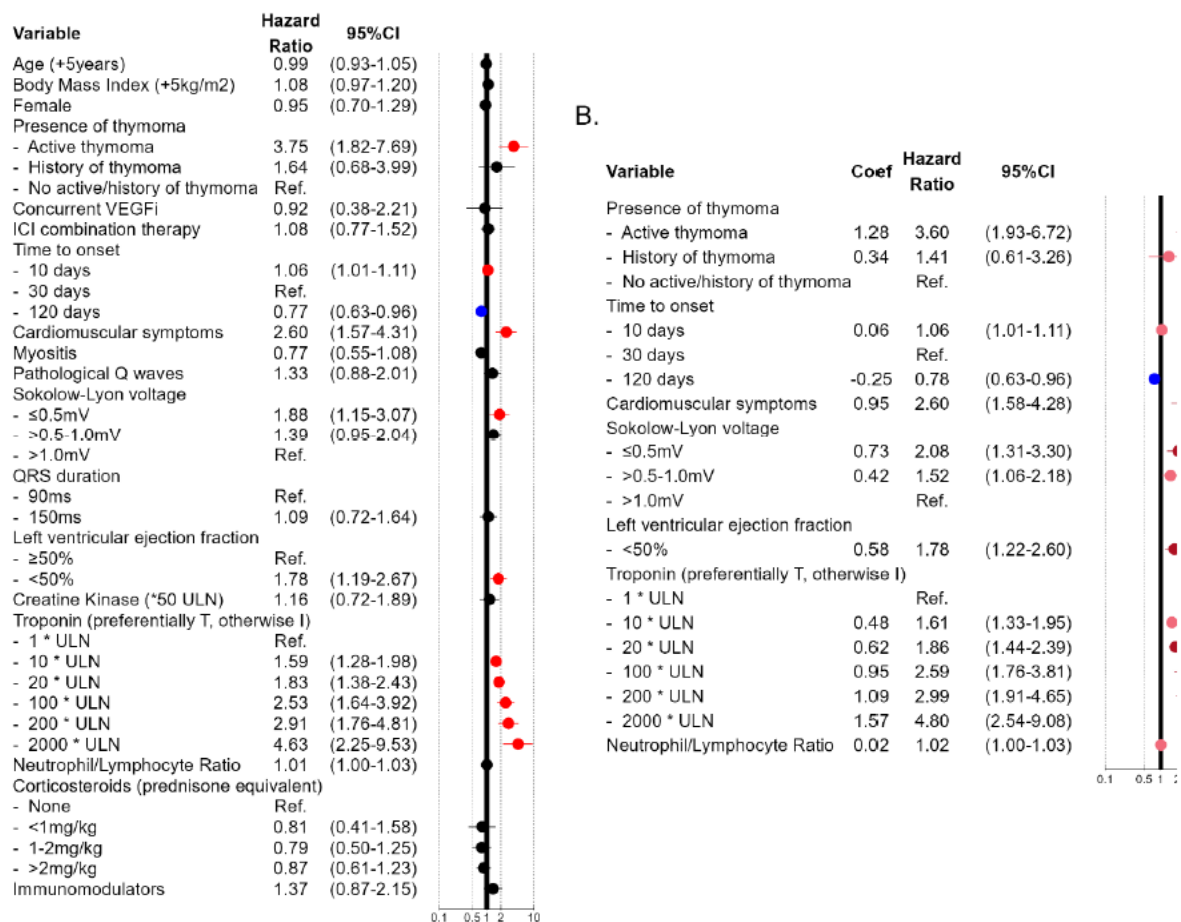


The primary composite outcome of major cardio-myotoxic events occurred in one third of patients within one month of presentation. This included 118/748(16%) patients with heart failure, 143/748(19%) with arrhythmia, 61/748(8%) with respiratory muscle failure, and 92/748(13%) with death due to cardio-myotoxicity (Figure-1B for the intersection of primary outcome components). Most cardiomyotoxicity events and related deaths occurred early in the 30-days study period while overall death (17%) was more evenly distributed (Figure-1D for event curves).

Explanatory Analysis

Multivariable modeling found that major cardio-myotoxic events were associated with active thymoma (HR=3.75[1.82-7.69]), recent ICI initiation (HR for 10 versus 30 days=1.06 [1.01-1.11]), presenting ECG with low QRS-voltage (HR for $\leq 0.5\text{mV}$ versus $>1\text{mV}$ =1.88 [1.15-3.07]), LVEF<50% (HR=1.78 [1.19-2.67]), presence of cardio-muscular symptoms (HR=2.60[1.57-4.31]) and troponin elevation (HR=1.83 [1.38-2.43], 2.91 [1.76-4.81], 4.63 [2.25-9.53] for 20, 200 and 2000-fold increase over upper reference limit (Figure-2A). In this model, notable variables that showed no association with severe cardio-myotoxicity included age, sex, combination ICI therapy, corticosteroid dose, and use of non-steroidal immunomodulators.

Figure 2: Multivariable analysis of association with 30-days major cardio-myotoxic events. Explanatory multivariable model for association with major cardio-myotoxic event (A). Predictive multivariable model for association with major cardio-myotoxic event using a stepwise selection procedure (B).

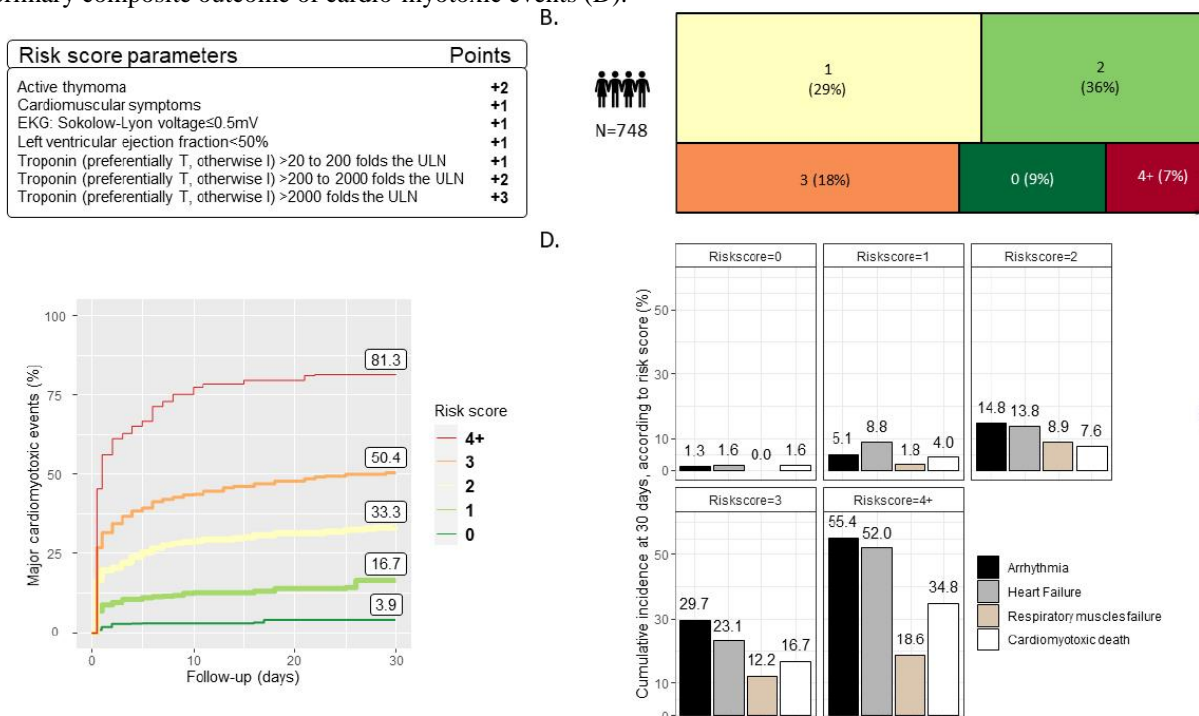


Abbreviations: CI : confidence interval, coef: coefficient, ICI: immune checkpoint inhibitor, ms: millisecond, mV: millivolt, Ref: reference, ULN: upper limit of normal, VEGFi: Vascular Endothelial Growth Factor Inhibitor, Immunomodulator: non-steroidal immunomodulators only

Univariate analysis associated major cardio-myotoxic events with several features, some of which did not meet significance upon multivariable analysis. Those included high body mass index (HR=1.10 [1.00-1.21]), cardio-muscular symptoms (HR=3.44 [2.10-5.63]), pathological Q-waves (HR=1.96 [1.34-2.89]), magnitude of QRS prolongation (HR=1.64[1.18-2.27] for 150ms vs. 90ms), elevated creatine kinase (HR for 50-fold increase over ULN=2.44[1.77-

3.35]), elevated neutrophil-to-lymphocyte ratio (HR=1.03[1.01-1.04]), and treatment with non-steroidal immunomodulators (HR=1.98 [1.34-2.94]) (Figure S2A). The incremental association of severe cardio-myotoxicity with continuous variables on day of presentation including biomarkers, ECG, LVEF, and time to onset are displayed in Figure S3. Similar results were found when multivariable modeling was performed on an unimputed complete dataset (Figure S2B). A competing risk analysis correcting for the effect of death due to other causes had overall unchanged findings and effect size compared to the original multivariable model (Figure S4).

Figure 3: Risk score for major cardio-myotoxic events. Components of the risk score of major cardio-myotoxic events at 30-days (A). Distribution of patients according to risk score (B). Cumulative incidence of major cardio-myotoxic events according to for risk score level (C). Cumulative incidence of components of the primary composite outcome of cardio-myotoxic events (D).



Predictive Analysis and Risk Score

A stepwise variable selection procedure identified the strongest predictors of the composite major cardio-myotoxic event outcome to be active thymoma (HR=3.60[1.93-6.72]), presence of cardiomuscular symptoms (HR=2.60 [1.58-4.28]), low QRS-voltage on presenting electrocardiogram (HR for \leq 0.5mV versus $>$ 1mV=2.08 [1.31-3.30]), LVEF $<$ 50% (HR=1.78 [1.22-2.60]), and elevated troponin (HR=1.86 [1.44-2.39], 2.99 [1.91-4.65], 4.80 [2.54-9.08], for 20, 200 and 2000-fold increase over institution's upper limit respectively) (Figure-2B). A risk score ranging from 0 to 8 was derived by assigning each predictor a value proportional to its respective regression coefficient: +2 for active thymoma, +1 for cardio-muscular symptoms, +1 for low QRS-voltage, +1 for LVEF $<$ 50%, and +1-3 points for degree of troponin elevation (Figure-3A). Classification of the cohort according to risk score on day of presentation showed 9% with 0 points, 29% with 1 point, 36% with 2 points, 18% with 3 points, and 4% with 4 or more points (Figure-3B). 30-days cumulative incidence of major cardio-myotoxic events was low at 3.9% for patients with risk score of 0 and increased proportionally as risk score increased with 16.7% incidence for 1 point, 33.3% for 2 points, 50.4% for 3 points, and 81.3% for 4 or more points (Figure-3C). There was a 1.6% cumulative incidence of cardio-myotoxicity related death for a risk score of 0 compared to

34.8% for a score ≥ 4 . All components of the primary outcome increased incrementally with higher risk scores (Figure-3D).

Risk Score Validation

Internal validation of the risk score showed good performance with a c-index of 0.70[0.67-0.73] on day one and remained unchanged at 0.71[0.66-0.75] by day three (Figure-S5). A score of 0 had a negative predictive value of 97%[90-100] for severe myotoxicity and 98%[91-100] for myotoxicity-related death (Table S3 for predictive properties per risk score value).

The external validation 1 cohorts' characteristics are detailed in Table-S2. Compared to the discovery cohort, the SU cohort had a higher proportion of score 0 (20%), but scores 1, 2, and 3+ were similar (31%, 31%, and 17%, respectively) to the discovery cohort (Figure-S6). The MGB cohort had almost no patients with score 0 (<1%), but more with score 1(37%) and score 2(45%), and fewer with score 3+(18%). For risk score 0, 30-days cumulative incidence of major cardio-myotoxic events was 0% in both cohorts and increased incrementally for score 1(22.1% SU vs 20.1% MGB), score 2(39.8% SU vs 50.7% MGB), and were highest for risk score 3+(63% SU vs 72.6% MGB) (Figure-S6). In the MGB cohort, the risk score had a c-index of 0.63(0.55-0.71) on day 1 which increased to 0.72(0.63-0.80) on day 2 and 0.75(0.65-0.82) on day 3. In the SU cohort, the risk score had c-index of 0.75(0.53-0.86) on day 1 and 0.74(0.52-0.87) on day 2. In both cohorts, a risk score of 0 had 100% negative predictive value (Table-S3, Figure-S5). In the prospective SU validation cohort, all seven patients with risk score of 0 had ICI stopped but no immunosuppression given per a recently published therapeutic protocol.⁵ There was no death or major cardiomyotoxic events in these seven patients over one month.

Discussion

ICI-myocarditis manifests with a wide range of severity. This study used a contemporary multicenter registry to follow 748 patients with ICI-myocarditis for one month after presentation, observing 13% mortality from cardio-myotoxicity. ICI-myocarditis was highly morbid with a primary composite outcome of severe heart failure, arrhythmia, respiratory muscle failure, and cardiomyotoxicity-related mortality occurring in 33% of patients. Multivariable analysis showed this primary outcome was associated with elevated troponin, thymoma, cardio-muscular symptoms, LVEF<50%, and ECG with low QRS-voltage. To avoid over-fitting and favor generalization, a simplified risk score was generated from these features which predicted adverse outcomes with good accuracy and very high negative predictive value. The risk score was externally validated in both a prospective cohort of 35 patients at Sorbonne University (Paris, France) and a retrospective cohort of 119 patients at Mass General Brigham (Boston, USA). In the prospective cohort, all patients with a risk score of zero had ICI withheld and were managed without immunosuppressants with excellent outcomes.

While early reports of ICI-myocarditis estimated a mortality of 50%, this study's lower event rate is consistent with contemporary reports that include cases with less severe disease.^{9, 11, 21, 22} To date, few cohort studies have analyzed ICI-myocarditis outcomes with sample sizes ranging from 33 to 147. All studies used a major adverse cardiac event (MACE) primary outcome, typically including cardiovascular death, complete heart block, ventricular arrhythmias and/or cardiogenic shock.^{9,14,23–28} Over 1-5 month follow-up, 23-64% MACE was observed, similar to our discovery cohort's major cardiomyotoxic event rate of 33% and our validation cohorts' rates of 31% (SU) and 41% (MGB). Our study used a 30-days surveillance period which reduced the cumulative event rate but prevented misattribution of late endpoints in this multimorbid population.

With 748 patients, this is the 1 largest cohort of ICI-myocarditis ever studied. Unlike previous studies, this cohort also included patients with mild or sub-clinical ICI-myocarditis (~20% of the cohort) reflecting contemporary understanding that milder asymptomatic cases exist.^{5, 21} In contrast to previous studies only evaluating a limited number of predictors, our study's size allowed for a large multivariable analysis including variables implicated in previous studies as well as novel predictors. Consequently, previous associations with severe outcomes such as combination ICI therapy or corticosteroid use, were not found to be significant.^{9, 24, 26, 27} These findings reframe combination ICI therapy as a risk factor for developing myocarditis with little prognostic value when other variables are considered.^{11, 29, 30} The lack of benefit with corticosteroids is provocative given their widespread use. In the discovery cohort, it is likely that immunosuppression was prescribed to sicker patients at higher risk for adverse events. On the other hand, the SU prospective validation cohort followed a pre-defined therapeutic algorithm where patients with risk score of 0 were managed without any immunosuppressants and had no major cardiomyotoxic events at one month. It is worth considering these findings in light of ongoing debates over appropriate corticosteroid dosing in ICI-myocarditis, high rates of corticosteroid resistance, and recent evidence of higher mortality in severe cases when corticosteroids are used as first line therapy without non-steroidal immunosuppressants.^{5, 31, 32}

The strongest predictors of adverse outcomes identified in this study – troponin levels, thymoma, low QRS-voltage, LVEF and cardio-muscular symptoms – are logical from a mechanistic perspective. Troponin release is inherent to the inflammatory myocyte necrosis of myocarditis and has been demonstrated as a surrogate for disease severity in smaller studies.^{9, 18, 24} While univariate analysis of creatine kinase showed significant association in this and other studies, the multivariable model did not, suggesting it may be confounded by other biomarkers, namely troponin.^{18, 33} While only 14/748 (2%) of patients in this study received ICI for active thymoma, these patients had nearly 4-fold higher severe cardio-myotoxicity risk after multivariable adjustment. This is consistent with increased autoimmunity seen in thymic neoplasms and fits the leading hypothesis that ICI-myocarditis is associated with thymic dysregulation and generation of auto-reactive T-cells targeting cardio-muscular antigens and unleashed by ICI.^{8,34–36} Similarly, the prognostic value of low QRS-voltage is also based in pathophysiology as immune infiltrates have been shown to directly impact myocyte electrophysiology and induce arrhythmias.^{14, 37}

The results of this analysis are compelling given their clinical utility. Factors such as troponin, symptoms, ECG features, LVEF and thymoma status can be promptly ascertained in

ambulatory and emergency room settings. While advanced imaging or endomyocardial biopsy results have been linked to outcomes in previous studies, the inaccessibility of these resource-intensive diagnostics makes them impractical prognostic tools.^{23, 25, 38} Separately, this study's identification of risk profiles complements ongoing efforts to optimize immunosuppression for the treatment of ICI-myocarditis. For example, while ruxolitinib and abatacept have been effectively used to treat severe ICI-myocarditis, asymptomatic cases without severity infra-clinical surrogates have been managed by simply stopping ICI without steroids or other immunosuppressants with good outcomes.⁵ Two prospective randomized studies are currently testing abatacept treatment in ICI-myocarditis. While one trial only includes patients with suspected mild to moderate ICI-myocarditis without ventricular arrhythmias, high-degree atrioventricular blocks, or cardiogenic shock (NCT05335928), the other aims to optimize abatacept dosing in definite ICI myocarditis with these latter severe features (NCT05195645). Using predictive risk scores like ours in future studies could identify patients with the most potential for positive treatment effect.

There are multiple potential clinical applications of this risk score. A score of 0 in combination with thorough clinical assessment may identify patients who can be managed with minimal or no immunosuppression since cardio-myotoxic events are rare in this group. Since over 14% of patients with a risk score of 1 had major cardio-myotoxic events in the three studied cohorts, inpatient monitoring may be preferred for a score of 1 or higher. Patients with score equal or above 2 may benefit most from empiric immunosuppression due to their >30% event rate. Further studies of this risk score may allow much-needed decision support for clinicians managing this rare and complex disease entity.

This study's limitations should be recognized. The discovery cohort was derived from a multicenter registry wherein treating physicians adjudicated clinical data and outcomes. We attempted to mitigate this variability by excluding cases with no evidence for myocarditis per Bonaca's criteria and by utilizing a core lab for ECG interpretation. Second, this cohort had missing data (detailed in [Table 1](#)) which were imputed. Imputation was necessary to power this analysis and prevented bias linked to potential non-random missingness. Finally, while the model tested known predictor variables, it is possible that unknown confounders were not included. Nevertheless, this risk score performed well in two independent external cohorts suggesting the validity of our model despite the aforementioned limitations.

In conclusion, we used a large multicenter registry to study predictors of severe outcomes in ICI myocarditis and establish a risk score. This risk score was validated in 2 independent cohorts. These contemporary cohorts continue to show a high frequency of severe cardio-myotoxicity, occurring in one third of patients over the first month. A multivariable model showed that magnitude of troponin increase, pre-existing thymoma, presence of symptoms, low LVEF, and low QRS-voltage were associated with severe cardio-myotoxicity. These findings were used to derive a practical risk score which performed well in predicting adverse events in patients who present with ICI-myocarditis. This risk score was applied prospectively and was promising in identifying patients who could be safely managed without corticosteroids or other immunosuppressants.

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Data availability statement.

The international ICI myocarditis registry is open to the entire scientific community based on a ‘reciprocity principle’, i.e., access to the cohort will only be allowed to those entities also willing to share data. Access to the database is granted to researchers and clinicians who are part of the consortium and have been approved by the project’s coordination (Pr Joe-Elie SALEM and Dr Javid MOSLEHI).

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Supplementary Figures Legends

Figure S1: Geographic distribution of study population (discovery cohort)

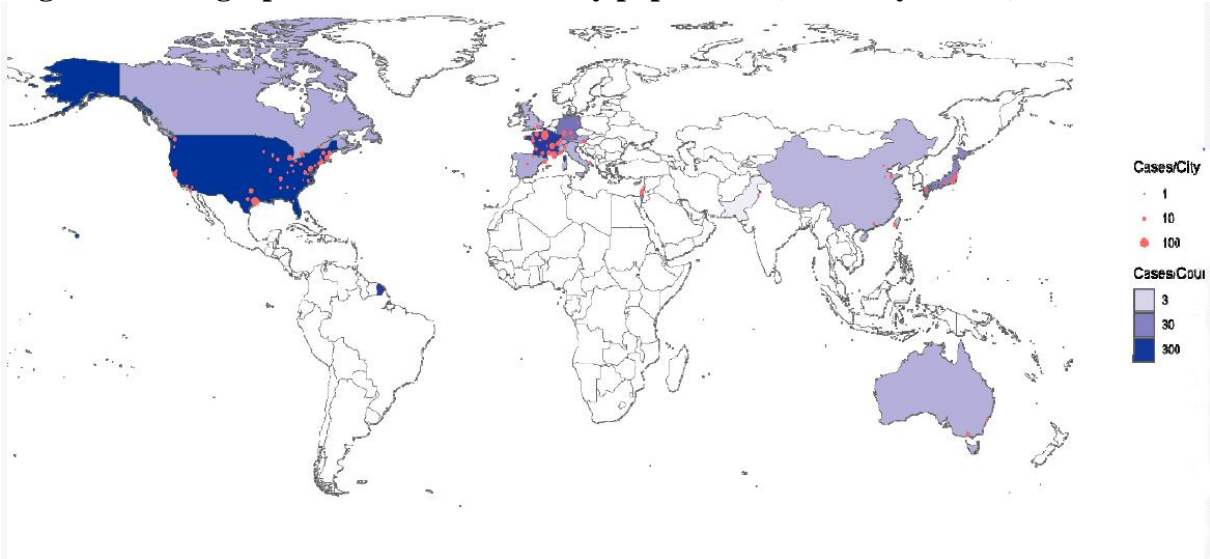
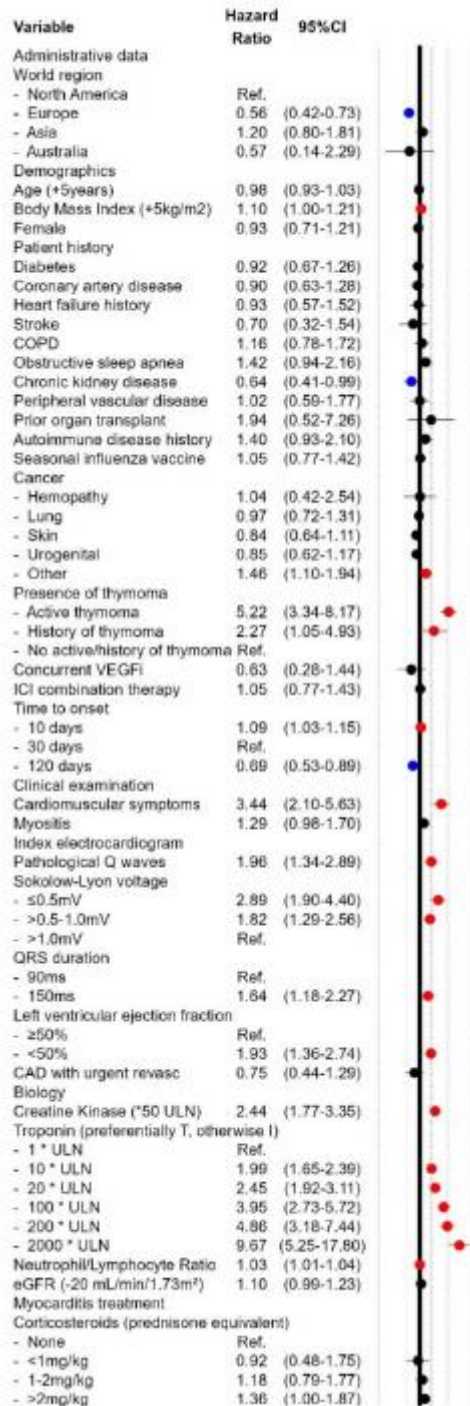
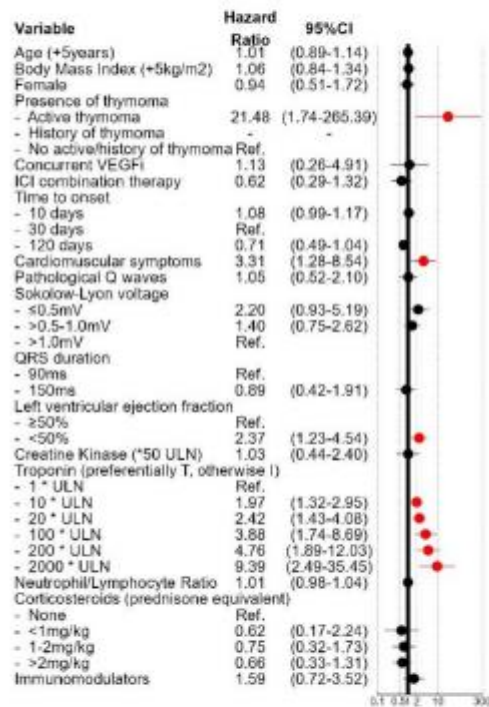


Figure S2: Univariate (A) and Unimputed (B) (n=238) multivariable models for association with major cardio-myotoxic events.

A.



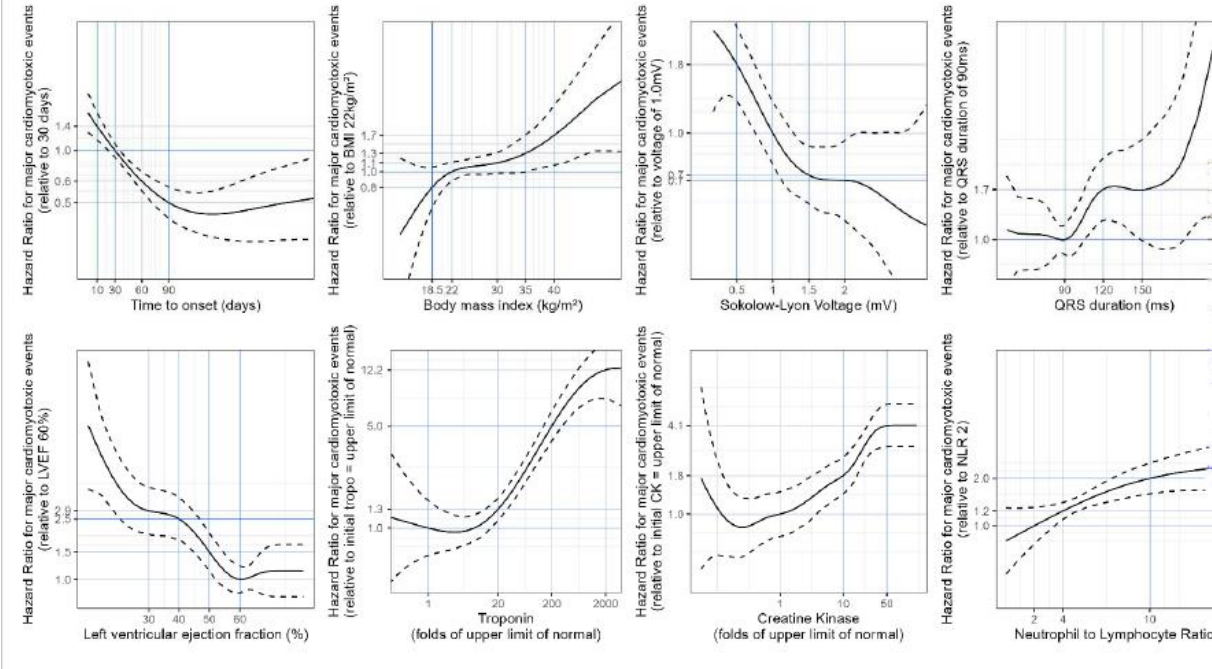
B.



Abbreviations:

CAD: coronary artery disease, CI: confidence interval, COPD: Chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, ICI: immune checkpoint inhibitor, ms: millisecond, mV: millivolt, Ref: reference, ULN: upper limit of normal, VEGFi: Vascular Endothelial Growth Factor Inhibitor, Immunomodulator: non-steroidal immunomodulators only

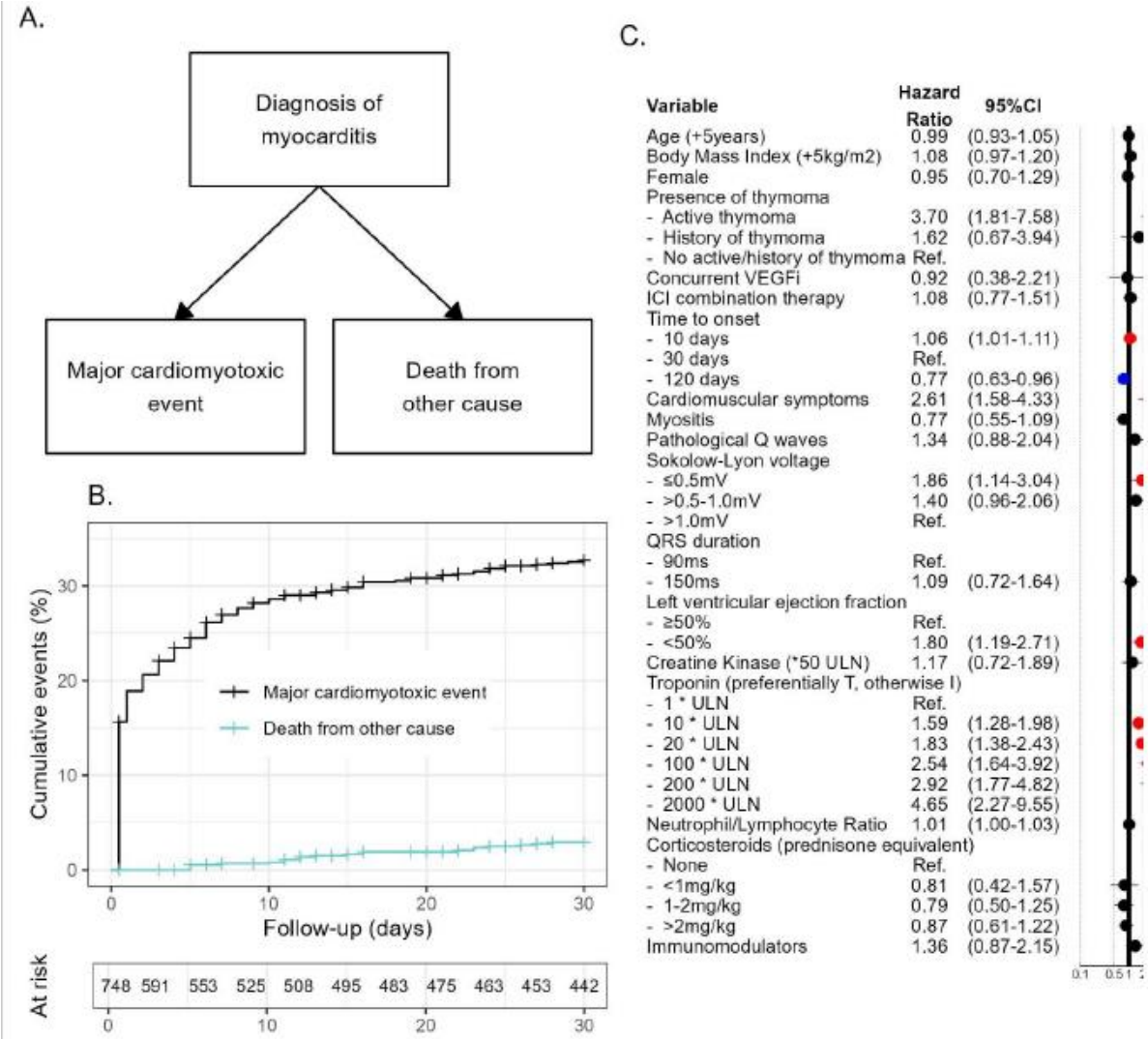
Figure S3: Spline models. Hazard-ratio for major cardio-myotoxic event at 30 days after presentation as a function of continuous variable predictors using data available at initial presentation. Troponin and creatine kinase were log transformed to account for non-linearity.



Abbreviations:

BMI: body mass index, LVEF: left ventricular ejection fraction, CK: creatine kinase, NLR: neutrophil to lymphocyte ratio

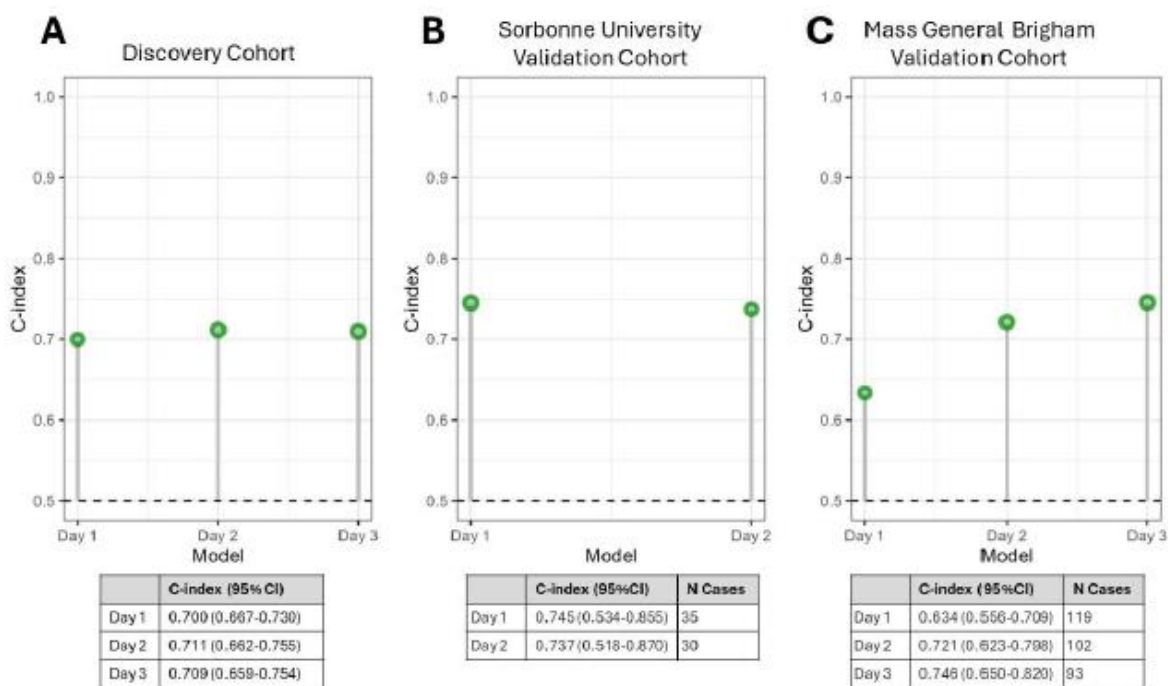
Figure S4: Predictors of 30-days mortality with competing risk approach. Illustration of competing risks for study patients (A). Cumulative incidence of competing risks during study period (B). Explanatory multivariable model for association with major cardio-myotoxic events fitted using Aalen Johanssen approach to account for death from other causes (C).



Abbreviations:

eGFR: estimated glomerular filtration rate, ICI: immune checkpoint inhibitor, ms: millisecond, mV: millivolt, Ref: reference, ULN: upper limit of normal, VEGFi: Vascular Endothelial Growth Factor Inhibitor, Immunomodulator: non-steroidal immunomodulators only

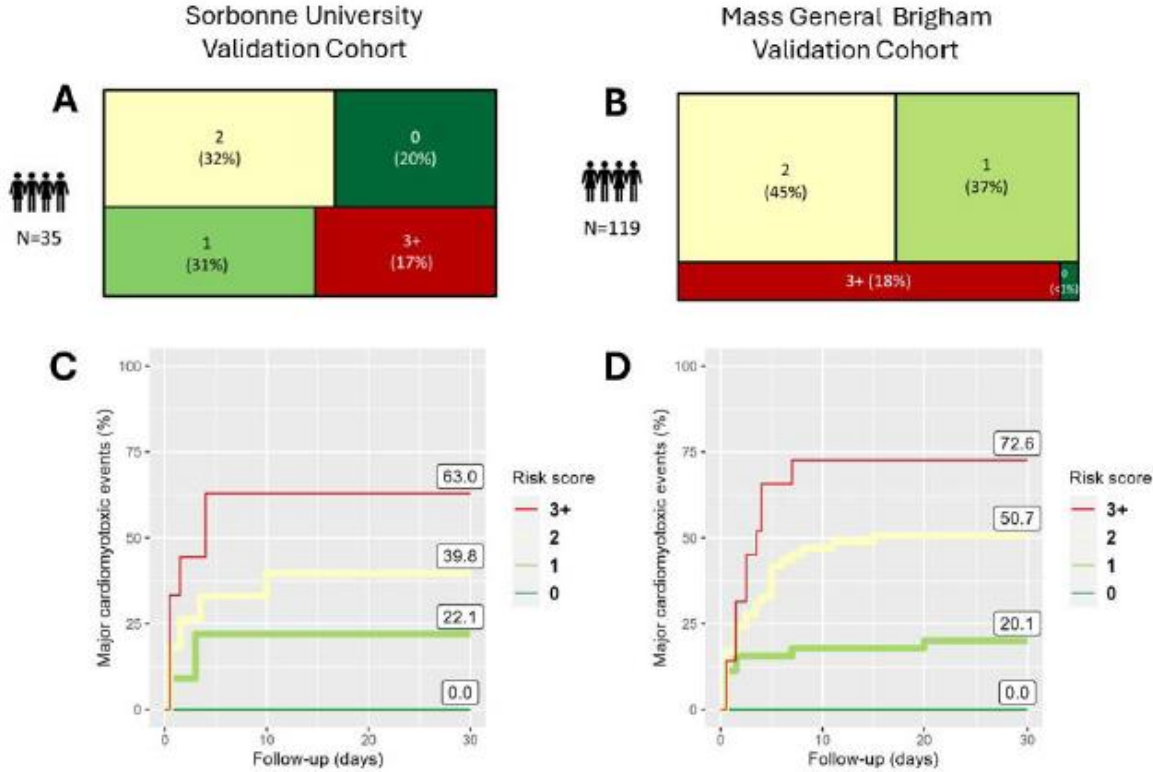
Figure S5: Harrel's 1 c-index of risk score for association with major cardio-myotoxic events. Graphical and tabular display of c-index when applied on a daily basis to Discovery Cohort(A), Sorbonne University Validation Cohort (B), Mass General Brigham Validation Cohort (C)



Abbreviations:

CI: confidence interval

Figure S6: Validation cohorts risk score distribution and cardio-myotoxic event rate. Risk score distribution for Sorbonne University (A) and for Mass General Brigham (B) validation cohorts. Cumulative incidence of major cardio-myotoxic events according to risk score level in the Sorbonne University (C) and in the Mass General Brigham Hospitals (D) validation cohorts



Supplemental Figures

Table S1: Collaborators by institution (n=757 cases for discovery cohort, n=127 institutions, n=17countries; and n=149 cases for replication cohorts, n=2 institutions, n=2 countries)

Center	Country	City	Admin	N, discovery cohort	N, validation cohort	Collaborators
Sorbonne University	France	Paris		101	35	Joe Elie Salem, Stephane Ederhy, Sonali Rao, Yves Allenbach, Thomas Simiowski
Mass General Brigham	United States	Boston	Massachusetts	1	119	Anju Nohria, Osnat Itzhaki Ben Zadok
University of Texas MD Anderson Cancer Center	United States	Houston	Texas	93	0	Nicolas Palaskas, Anita Deswal
Heidelberg University Hospital	Germany	Heidelberg		36	0	Lorenz Lehmann
Aix-Marseille University, University Mediterranean Center of Cardio-Oncology	France	Marseille		31	0	Jennifer Cautela, Franck Thury
Hospices Civils de Lyon	France	Lyon		30	0	Pierre-Yves Courand, Anissa Bouali
University of Michigan	United States	Ann Arbor	Michigan	30	0	Saim S. Hayek
Stanford University	United States	Stanford	California	19	0	Han Zhu
University of Texas Southwestern Medical Center	United States	Dallas	Texas	16	0	Vlad G. Zaha
University of Washington	United States	Seattle	Washington	16	0	Richard K. Cheng
Normandie Univ. UNICAEN, INSERM U1086 ANTICIPE, Caen-Normandy University Hospital.	France	Caen		14	0	Joachim Alexandre
CHU Montpellier	France	Montpellier		14	0	François Roubile
Yale School of Medicine	United States	New Haven	Connecticut	14	0	Lauren A. Baldassarre
University of California San Francisco	United States	San Francisco	California	13	0	Javid Moslehi, Alan H. Baik
Tel Aviv Sourasky Medical Center, School of Medicine, Tel Aviv University	Israel	Tel Aviv-Yafo		12	0	Michal Laufer-Perl
Beth Israel Deaconess Medical Center	United States	Boston	Massachusetts	11	0	Aarti Asnani
Maine Medical Center	United States	Portland	Maine	10	0	Sanjeev Francis
University of Virginia	United States	Charlottesville	Virginia	10	0	Elizabeth M. Gaughan
Vanderbilt University Medical Center	United States	Nashville	Tennessee	10	0	Douglas Johnson, Andrew M Hughes
APHU Hospital Lariboisiere	France	Paris		9	0	Guillaume Bailly
Dartmouth Hitchcock Medical Center	United States	Lebanon	New Hampshire	9	0	Danette L Flint
IUHM Mita Hospital	Japan	Tokyo		9	0	Yuichi Tamura
Medical University of Graz, BioTechMed Graz, St. Johann in Tirol General Hospital	Austria	Graz, St. Johann in Tirol		9	0	Peter Rainer, Lisa Moser
APHU Hospital Bichat	France	Paris		8	0	Dimitri Arangelage
CHU Rangueil Toulouse	France	Toulouse		8	0	Eve Cariou
Rabin Medical Center	Israel	Petah Tiqwa		8	0	Osnat Itzhaki Ben Zadok
University of California San Diego Health	United States	San Diego	California	8	0	Anna Narezkina, John Power
University of Utah	United States	Salt Lake	Utah	7	0	Roberta Florido

Center	Country	City	Admin	N, discovery cohort	N, validation cohort	Collaborators
		City				
University of Texas at Austin Ascension Seton	United States	Austin	Texas	7	0	Yan Liu
Barts Health NHS Trust	United Kingdom	London		6	0	Shanthini M Cruz
Maisonneuve-Rosemont Hospital	France	Bordeaux		6	0	Nahema Issa, Maxime Faure
CHU Nantes	France	Nantes		6	0	Nicolas Pflou
McMaster University	Canada	Hamilton	Ontario	6	0	Darryl Leong, Rodio Baro Vila
Peter MacCallum Cancer Centre	Australia	Melbourne		6	0	Shahneen Sandhu
Disease Unit for Myocarditis and Arrhythmogenic Cardiomyopathies, IROCS San Raffaele Scientific Institute	Italy	Milan		6	0	Giovanni Peretto
Washington University	United States	St. Louis	Missouri	6	0	Isk Turker, Jesus Jimenez
Hôpital Européen Georges Pompidou, Université Paris Cité	France	Paris		5	0	Assiè Estami
APHP Hôpital Henri Mondor	France	Créteil		5	0	Charlotte Ferrière
Bellvitge University Hospital – Catalan Institute of Oncology, IDIBELL, CIBERCV	Spain	Barcelona		5	0	Pedro Moliner
Centre Hospitalier Universitaire Vaudois	Switzerland	Lausanne		5	0	Michel Obeld
Chi Mei Medical Center	Taiwan	Tainan		5	0	Wei Ting Chang
Northwestern University	United States	Chicago	Illinois	5	0	Nausheen Akhter
University of Wisconsin School of Medicine and Public Health	United States	Madison	Wisconsin	5	0	Stephen M. Ewer
Medstar Washington Hospital Center	United States	Washington	District of Columbia	4	0	Seyed Ebrahim Kassalan
University Hospital Erlangen	Germany	Erlangen		4	0	Lucie Heinzerling
University of Pittsburgh Medical Center	United States	Pittsburgh	Pennsylvania	4	0	Joshua E. Levenson, Benay Ozbay
CHU Rennes	France	Rennes		3	0	Elise Paven, Bena Gall
Guangdong Academy of Medical Sciences	China	Guangzhou		3	0	
Hospital Universitario La Paz	Spain	Madrid		3	0	Teresa Lopez Fernandez, Lucia Cobarro
Rambam Medical Center	Israel	Haifa		3	0	Manhal Habib
Rosewell Park Cancer Center	United States	Buffalo	New York	3	0	
University of Tsukuba	Japan	Kitaibaraki		3	0	Kazuko Tajiri
Center for Cancer Research National Cancer Institute National Institutes of Health	United States	Bethesda	Maryland	2	0	
CHU Nice	France	Nice		2	0	Fanny Rocher
CHU Tours, University of Tours	France	Tours		2	0	Theodora Bejan-Angoulvant
Cleveland Clinic Foundation	United States	Cleveland	Ohio	2	0	
Emory University	United States	Atlanta	Georgia	2	0	Mehmet Asim Bilen, Susmita Parashar
Houston Methodist Hospital	United States	Houston	Texas	2	0	
Ohio State University Wexner Medical Center	United States	Columbus	Ohio	2	0	Avirup Guha
The First Affiliated Hospital of Welfang Medical University	China	Welfang		2	0	Wenjing Song

Center	Country	City	Admin	N. discovery cohort	N. validation cohort	Collaborators
University Hospital Basel	Switzerland	Basel		2	0	David Koenig, Kirsten Mertz
University of Alabama Birmingham	United States	Birmingham	Alabama	2	0	Carie Lenneman
University of California at Davis	United States	Davis	California	2	0	
Vidant Medical Center/East Carolina University	United States	Greenville	North Carolina	2	0	
Alfred Health, Monash University	Australia	Melbourne		1	0	Andrew Haydon
Alama Iqbal Medical College	Pakistan	Lahore		1	0	
Anjo Kosei Hospital	Japan	Anjomiachi		1	0	
Baylor College of Medicine	United States	Houston	Texas	1	0	
Bern University Hospital	Switzerland	Bern		1	0	
Cedars-Sinai Medical Center Network	United States	Los Angeles	California	1	0	Anja Karlstedt
Centre Léon Bérard	France	Lyon		1	0	Chloe Lesluk
Charité Campus Mitte (CMM)	Germany	Berlin		1	0	
CHU Brest	France	Brest		1	0	
CHU Clermont Ferrand	France	Clermont-Ferrand		1	0	Romain Tresorier
CHU Lille	France	Lille		1	0	
Clinica Universidad de Navarra	Spain	Pamplona		1	0	
Cliniques universitaires Saint-Luc	Belgium	Bruxelles		1	0	
Cooper University Hospital	United States	Camden	New Jersey	1	0	
Dana-Farber Cancer Institute	United States	Boston	Massachusetts	1	0	
Eisenhower Medical Center	United States	Rancho Mirage	California	1	0	Yazeed Samara
ELK Thorax Center	Germany	Berlin		1	0	Christian Grohe
General Hospital of Chinese People's Liberation Army	China	Beijing		1	0	
Geneva University Hospitals and Medical Faculty	Switzerland	Geneva		1	0	Pierre Yves Dietrich
Hartford Hospital	United States	Hartford	Connecticut	1	0	
HeartCare Centers of Illinois	United States	Chicago	Illinois	1	0	Sean Tierney
Hotel Dieu de France University Hospital	Lebanon	Beirut		1	0	Elie Rassy
ICO Nantes	France	Nantes		1	0	Elvire Mervoyer
Institut Bergonié Centre de Lutte contre le Cancer	France	Bordeaux		1	0	
Japan Community Health Organization Kyushu Hospital	Japan	Fukuoka		1	0	
Keio University	Japan	Tokyo		1	0	Shigeki Suzuki
Kumamoto University	Japan	Kumamoto		1	0	Satoshi Fukushima
Lahey Hospital and Medical Center	United States	Burlington	Massachusetts	1	0	
Markey Cancer Center, University of Kentucky	United States	Lexington	Kentucky	1	0	
Marshall University	United States	Huntington	West Virginia	1	0	
Mayo Clinic	United States	Rochester	Minnesota	1	0	
Georgia Cancer Center, Augusta University	United States	Augusta	Georgia	1	0	Avirup Guha

Center	Country	City	Admin	N, discovery cohort	N, validation cohort	Collaborators
Memorial Sloan Kettering Well Cornell Medical College	United States	New York	New York	1	0	
Mitsui Memorial Hospital	Japan	Tokyo		1	0	
Montreal Heart Institute	Canada	Montreal	Quebec	1	0	Maxime Robert-Halabi
Mount Vernon Cancer Centre	United Kingdom	London		1	0	
Nagoya University Graduate School of Medicine	Japan	Nagoya		1	0	Ryota Morimoto
National Cancer Center Hospital East	Japan	Kashiwa		1	0	Kazuko Tajiri
New York Institute of Technology College of Osteopathic Medicine	United States	New York	New York	1	0	
New York-Presbyterian Brooklyn Methodist Hospital	United States	New York	New York	1	0	
Northwell Health	United States	New York	New York	1	0	Robert Cope and Halperin
Providence St. Joseph Health	United States	Portland	Oregon	1	0	Michael Layoun
Qianfoshan Hospital	China	Jinan		1	0	Jun Wang
Royal North Shore Hospital	Australia	Sydney		1	0	Suran Fernando
Saiseikai Narashino Hospital	Japan	Narashino		1	0	
San Giacomo Hospital	Italy	Monopoli		1	0	Eugenia Rota
Sendai Kousei Hospital	Japan	Sendai		1	0	Yumi Katsume
Shinshu University	Japan	Matsumoto		1	0	Yukiko Kinwa
St. Luke's International Hospital	Japan	Tokyo		1	0	
Sunnybrook Odette Cancer Centre	Canada	Toronto		1	0	Ellen Warner
Teikyo University School of Medicine	Japan	Tokyo		1	0	Nobuhiko Seki
Tokyo Saiseikai Central Hospital	Japan	Tokyo		1	0	
Tokyo Women's Medical University	Japan	Tokyo		1	0	
University Hospital LMU	Germany	Munich		1	0	Lucie Heinzerling, Theresa Ruf
University Hospital Mainz	Germany	Mainz		1	0	
University of Chicago	United States	Chicago	Illinois	1	0	
University of Florida	United States	Gainesville	Florida	1	0	Jess DeLaune
University of Massachusetts, Berkshire Medical Centre	United States	Pittsfield	Massachusetts	1	0	
University of North Carolina Medical Center Chapel Hill	United States	Chapel Hill	North Carolina	1	0	
University of southern California	United States	Los Angeles	California	1	0	
University of Toronto	Canada	Toronto		1	0	Nazanin Aghel
VCU Medical center	United States	Richmond	Virginia	1	0	
Veterans Affairs Puget Sound Health Care System-Seattle	United States	Seattle	Washington	1	0	