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Electrocardiographic Manifestations of Immune Checkpoint Inhibitor Myocarditis

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Key Points

(90/100 words)

Question: What are the electrocardiographic manifestations of immune checkpoint inhibitor (ICI)-associated myocarditis? How do they compare to acute cellular rejection (ACR), which is resembling pathophysiologically to ICI-myocarditis? Which electrocardiographic features are associated with adverse outcomes?

Findings: ICI-myocarditis results in more frequent ventricular arrhythmias and high-degree atrioventricular blocks compared to ACR. Prolonged QRS intervals, decreased voltage, conduction disorders, and pathological Q-waves are predictors of adverse outcomes in ICI-associated myocarditis.

Meaning: ICI-associated myocarditis is a highly arrhythmogenic cardiomyopathy. Ventricular arrhythmias, conduction disorders, low-voltage, and pathological Q-waves are associated with a poor prognosis.

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Abstract (334/350 words)

Importance: Immune-checkpoint inhibitor (ICI)-myocarditis often presents with arrhythmias, but electrocardiographic (ECG) findings have not been well described. ICI-myocarditis and acute cellular rejection (ACR) following cardiac transplantation share similarities on histopathology; however, whether they differ in arrhythmogenicity is unclear.

Objectives: To describe ECG findings in ICI-myocarditis, compare them to ACR, and evaluate their prognostic significance.

Design: Cases of ICI-myocarditis were retrospectively identified through a multicenter network. Grade 2R or 3R ACR was retrospectively identified within one center. Two blinded cardiologists interpreted ECGs.

Setting: 49 medical centers spanning 11 countries.

Participants: 147 adults with ICI-myocarditis, 50 adults with ACR.

Exposure: Myocarditis after ICI exposure per European Society of Cardiology criteria for clinically suspected myocarditis, grade 2R or 3R ACR per the International Society for Heart and Lung Transplantation working formulation for biopsy diagnosis of rejection.

Outcomes: All-cause mortality, myocarditis-related mortality; and composite endpoint (defined as myocarditis-related mortality and life-threatening ventricular arrhythmia).

Results: Of 147 patients, the median age was 67 years (58-77) with 92 (62.6%) men. At 30 days, ICI-myocarditis had an all-cause mortality of 39/146(26.7%), myocarditis-related mortality of 24/146(16.4%), and composite endpoint of 37/146(25.3%). All-cause mortality was more common in patients who developed complete heart block (12/25[48%] vs 27/121[22.3%], hazard ratio (HR)=2.62, 95% confidence interval [1.33-5.18],p=0.01) or life-threatening ventricular

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arrhythmias (12/22[55%] vs 27/124[21.8%], HR=3.10 [1.57-6.12],p=0.001) within 30 days after presentation. Compared to ACR, patients with ICI-myocarditis were more likely to experience life-threatening ventricular arrhythmias (22/147 [16.3%] vs 1/50 [2%];p=0.01) or third-degree heart block (25/147 [17.0%] vs 0/50 [0%];p=0.002). In ICI-myocarditis, overall mortality, myocarditis-related mortality, and composite outcome adjusted for age and sex were associated with pathological Q-waves on presenting ECG (hazard ratio by subdistribution model [HR(sh)]=5.98[2.8-12.79],p<.001; 3.40[1.38-8.33],p=0.008; 2.20[0.95-5.12],p=0.07; respectively) but inversely associated with Sokolow-Lyon Index (HR(sh)/mV=0.57[0.34-0.94],p=0.03; HR(sh)=0.54[0.30-0.97],p=0.04; 0.50[0.30-0.85],p=0.01; respectively). The composite outcome was also associated with conduction disorders on presenting ECG (HR(sh)=3.27[1.29-8.34],p=0.01).

Conclusions: ICI-myocarditis has more life-threatening arrhythmias than ACR and manifests as decreased voltage, conduction disorders, and repolarization abnormalities . Ventricular tachycardias, complete heart block, low-voltage, and pathological Q-waves were associated with adverse outcomes.

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Introduction

Immune checkpoint inhibitors (ICI) have transformed oncology care with nearly 50% of cancer patients eligible for ICI treatment.[1] ICI unleash cytotoxic T-cells to achieve anti-tumor effects but can also cause T-cell and macrophage mediated myocarditis.[2–4] A subset of ICI recipients (0.3% to 1.1%) experience myocarditis, a rare immune related adverse event (IrAE) that can cause cardiogenic shock and fatal arrhythmias.[5,6] The diagnosis of ICI-myocarditis remains challenging.[2,7] Cardiac magnetic resonance imaging (cMRI) and endomyocardial biopsy (EMB) are often difficult to obtain due to patients' critical condition. Furthermore, sensitivity of cMRI is estimated at 48% with EMB also resulting in false negatives.[8] A multimodal approach incorporating biomarker, echocardiographic, and electrocardiographic (ECG) findings may represent a high yield strategy in diagnosing ICI-related myocarditis.[9] However, ECG findings in ICI-myocarditis have yet to be systematically described and their prognostic significance has not yet been studied.

We set out to describe presenting ECG and telemetry events in patients with ICI-myocarditis given that arrhythmogenic events are routinely and easily identified in presenting patients. We compared these findings to ECG from a cohort of heart transplant recipients diagnosed with acute cellular rejection (ACR). We hypothesized that ICI-myocarditis would mimic the low-voltage and QRS prolongation seen in ACR.[4,10,11] This hypothesis was grounded in the many pathologic similarities between ACR and ICI-myocarditis, including lymphocytic infiltration, a similarity that has motivated the use of similar immunosuppressive treatment strategies for both conditions, including corticosteroids and anti-T cell directed therapies.[2–4,12–17] Additionally, we hypothesized that presenting ECG features in ICI-myocarditis would predict death and life-threatening ventricular arrhythmias.

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Methods

ICI-Myocarditis Selection

A retrospective multicenter registry spanning 49 institutions across 11 countries was used to collect 147 cases of ICI-myocarditis (Supplemental Table 1) as defined by European Society of Cardiology criteria for clinically suspected myocarditis with recent ICI exposure.[18] External collaborating institutions were identified through cardio-oncology departments, via a website created to collect cases of ICI-myocarditis (www.cardioonc.org), and by contacting authors of published case reports (Supplementary Data Methods 1). Clinical data was collected and shared by participating collaborators via a HIPPA-compliant REDCap web-based platform (IRB: 181337; *NCT04294771*).[19,20] All 147 cases were analyzed for presence of arrhythmias throughout hospitalization as reported by treating physicians. ECG on admission was independently examined for 125 cases where ECG was obtained within 3 days of admission (Supplemental Figure 1). When multiple presenting ECG were available, ECG closest to presentation and without complete heart block or supraventricular arrhythmias were preferentially selected. Baseline ECG was defined as the most recent ECG obtained before ICI exposure and was available for independent examination in 52 cases.

ACR selection

Heart transplants at Vanderbilt University Medical Center complicated by grade 2R or 3R acute cellular rejection were selected in reverse chronological order and spanned 2013-2019.[21] Cases of concomitant humoral rejection were excluded. ECG obtained less than 10 days after heart transplantation or more than 3 days from diagnostic EMB were excluded. Donor and recipient characteristics were collected via chart review and the Organ Procurement and Transplantation Network database.

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ECG Interpretation

Two blinded cardiologists (BO, JA) systematically quantified standard ECG intervals (PR, QRS, QTc, Sokoloff-Lyon Index) and evaluated for relevant qualitative features. ECG features were aggregated on basis of pathophysiological relatedness (Supplemental Table 2). Inter- and intra-observer variability was excellent (intra-class correlation>0.8) for PR, QRS, QTc and Sokoloff measurements (Supplemental Data Methods 2).

Statistical Analysis

Paired t-test and McNemar's test were used to compare features of presenting ECG to baseline ECG. Non-parametric Wilcoxon and Chi-squared test was used to compare ECG features in ICI-myocarditis to ACR. The primary outcome was myocarditis-related mortality in thirty days. The secondary outcomes were 1) a composite of either myocarditis-related death or life-threatening arrhythmia in thirty days (defined as sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes, pulseless electrical activity, or asystole) and 2) all-cause mortality in thirty days.

The primary outcome analysis used features on the presenting ECG as the independent variable. Since our methodology preferentially selects for ECG that do not exclusively capture heart block, life-threatening ventricular arrhythmias, or supraventricular arrhythmias, a focused secondary analysis used the aggregate incidence of these arrhythmias throughout the entire hospitalization as the independent variable to test association with outcomes of interest. In both analyses, Cox proportional-hazards model determined association with all-cause mortality over the 30-day surveillance period. Competing risk analysis (Subdistribution hazards model, i.e., Fine-Gray model) was used to account for mortality due to causes other than myocarditis for the outcomes of myocarditis-related mortality or composite outcome. These models were separately

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158 adjusted for age and sex in a multivariable analysis. Hazard Ratio (HR), 95% confidence

159 interval, and cumulative incidence curves were presented.

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Results

Demographics

The 147 patients with ICI-myocarditis had a median (IQR) age of 67 years (58-77) and 92/147 (62.6%) were male (Table 1). Median days from first ICI dose to myocarditis presentation was 38 days (21-83). In 146 patients with 30-day surveillance, 39/146 (26.7%) died within 30 days of presentation of which 24/39 (62%) of deaths were attributable to myocarditis. Other leading causes of death included to cancer progression - 6/39 (15%), sepsis - 6/39 (15%), and non-cardiac IrAE 7/39 (18%), of which 6/7 (86%) were attributable to non-cardiac myotoxicities (e.g., myositis). Pacemakers and/or defibrillators were placed in 22/146 (15.1%) patients within 30 days of presentation.

In total, 135/147 (91.8%) patients experienced abnormal ECG during hospitalization. Throughout hospitalization (median: 11 days, IQR:7-24), 101/147 (68.7%) patients experienced conduction disorders, which included second-degree heart block (11/147 (7.5%)) and complete heart block (25/147 (17.0%)). Of note, supraventricular arrhythmias had a cumulative incidence of 35/147 (23.8%). A total of 22/147 (15.0%) patients experienced life-threatening ventricular arrhythmia, including 16/147 (10.9%) sustained ventricular tachycardia, 4/147 (2.7%) ventricular fibrillation, 2/147 (1.4%) torsade de pointes, 4/147 (2.7%) pulseless electrical activity, and 4/147 (2.7%) asystole. A total of 11/147 (7.5%) patients developed both complete heart block and a life-threatening ventricular arrhythmia.

Comparison to Baseline ECG

Baseline ECG obtained before ICI exposure was available for comparison in 52 cases. Paired analysis comparing presenting ECG to baseline ECG showed ICI-myocarditis presents with elevated heart rate (93.9 vs 80.4 bpm;p=0.009) and prolongation of QRS (95.3 vs 93.2

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ms;p=0.02) and QT interval corrected for heart rate using Fridericia's formula (441.8 vs 421.0 ms;p=0.03) (Table 2). There was a significant decrease in cardiac depolarization voltage assessed by the quantitative Sokolow-Lyonn Index (1.39 vs 1.69 mV;p=0.006). The incidence of left bundle branch block (LBBB) (10/52 [19%] vs 3/52 [6%];p=0.046) and sinus tachycardia (25/52 [48%] vs 15/52 [29%];p=0.02) were increased from baseline. In aggregate, conduction disorders (35/52 [67%] vs 23/52 [44%];p=0.01) and repolarization abnormalities (27/52 [52%] vs 13/52 [25%],p=0.008) were significantly increased. Of note, ECG suggestive of pericarditis were infrequent without significant increase from baseline (4/52 [8%] vs 1/52 [2%],p=0.25).

Outcome Analysis by Cumulative Incidence of Arrhythmia

Patients with ICI-myocarditis were more likely to experience all-cause mortality within 30 days if they developed complete heart block (12/25 [48%] vs 27/122 [22.1%]; HR=2.62, 95% confidence interval=[1.33-5.18],p=0.01) or life-threatening ventricular arrhythmias (12/22 [55%] vs 27/125 [21.6%]; HR=3.10 [1.57-6.12],p=0.001) at any point during hospitalization (cumulative incidence curves in Figure 1).

Additionally, myocarditis-related mortality within 30 days was more common in patients who developed complete heart block (8/25 [32%] vs 16/122 [13.1%]; hazard ratio by subdistribution model[HR(sh)=2.73 [1.18-6.32],p=0.019) or life-threatening ventricular arrhythmias (10/22 [45.5%] vs 14/125 [11.2%]; HR(sh)=4.98 [2.24-11.1],p<0.001) (cumulative incidence curves in Figure 1).

Composite outcome of myocarditis-related mortality or life-threatening ventricular arrhythmia within 30 days was also more common in patients who experienced complete heart block (13/25 [52%] vs 24/122 [19.7%]; HR(sh)=3.55 [1.80-6.99],p<0.001) (figure not shown).

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Supraventricular arrhythmia at any point during hospitalization was not associated with either all-cause mortality (13/35 [37%] vs 26/112 [23.2%]; HR=1.67 [0.86-3.25],p=0.13), myocarditis-related mortality (8/35 [22.9%] vs 16/112 [14.3%]; HR(sh)=1.61 [0.71-3.7],p=0.26), or composite outcome within 30 days (13/35 [37.1%] vs 24/112 [21.4%]; HR(sh)=1.72 [0.91-3.26],p=0.10) (cumulative incidence curves in Supplemental Figure 2).

Outcome Analysis by Presenting ECG Features

A total of 125 ICI-myocarditis patients met criteria to be included in the analysis of predictive value of presenting ECG features and 22 were excluded due to initial ECG obtained more than 3 days from admission or initial ECG with paced rhythm or exclusively capturing ventricular tachycardia (flow chart of analyzed ECG in Supplemental Figure 1, characteristics of the population in Supplemental Table 3). Using survival analyses, thirty-day myocarditis-related mortality was significantly associated with pathological Q-waves (7/19 [37%] vs 13/106 [12.3%]; HR(sh)=3.67 [1.46-9.22],p=0.006) and low QRS voltage (3/6 [50%] vs 17/119 [14.3%]; HR(sh)= 4.50 [1.34-15.12],p=0.02) and showed a trend towards inverse association with Sokolow-Lyon Index (HR(sh)/mV=0.55 [0.28-1.06],p=0.08) (cumulative incidence curves in Figure 2, model results in Supplemental Table 4, cumulative incidence curves by Sokolow-Lyon Index in Supplemental Figure 3).

Using survival analyses, composite outcome of myocarditis-related mortality or life-threatening ventricular arrhythmia was inversely associated with Sokolow-Lyon Index (HR(sh)/mV=0.51 [0.30-0.87],p=0.01) and positively associated with RBBB (14/43 [33%] vs 14/82 [17%]; HR(sh)=2.16 [1.05-4.47],p=0.04) and conduction disorders generally (23/79 [29%] vs 5/46 [11%]; HR(sh)=3.05 [1.20-7.76],p=0.02) (cumulative incidence curves in Supplemental Figure 4, model results in Supplemental Table 4, cumulative incidence curvesby Sokolow-Lyon

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Index in Supplemental Figure 3). Composite outcome of myocarditis-related mortality or life-threatening ventricular arrhythmia showed a trend towards association with pathological Q-waves (7/19 [37%] vs 21/106 [19.8%]; HR(sh)=2.10 [0.90-4.89],p=0.09) and low QRS voltage (3/6 [50%] vs 25/119 [21.0%]; HR(sh)= 2.57 [0.90-7.28],p=0.08).

Similarly, all-cause mortality was associated with pathological Q-waves (12/19 [63%] vs 18/106 [17.0%]; HR=5.80 [2.78-12.12],p<0.001) and inversely associated with Sokolow-Lyon Index (HR/mV=0.59 [0.35-0.98],p=0.04) (cumulative incidence curves in Figure 2, model results in Supplemental Table 4, cumulative incidence curves by Sokolow-Lyon Index in Supplemental Figure 3).

Multivariable survival analysis was performed by adding covariates of age and sex into cox proportional-hazards model and sub distribution hazards models. This analysis mirrored the results of survival analyses described above (myocarditis-related mortality & composite outcome: Table 2, all-cause mortality: Supplemental Table 5; Figures 1 & 2; Supplemental Figures 2 & 3).

Comparison to ACR

The 50 patients with ACR had median (IQR) age of 51 years (43-62), 64% (32/50) of whom were male (Supplemental Table 6). Median days from transplant to ACR was 145 days (IQR:26-283). 29/50 (58%) were admitted during or as a result of ACR, with median length of stay of 12 days (IQR:5-21). 2R rejection was seen in 46/50 (92%) and 4/50 (8%) had 3R rejection. Throughout hospitalization (if applicable) or at presenting ECG, 34/50 (68%) patients experienced conduction disorders but second or third-degree heart block was not seen in any patients. There was a cumulative incidence of 6/50 (12%) supraventricular arrhythmias and 1/50

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(2%) life-threatening ventricular arrhythmia. None of the patients required a pacemaker and/or defibrillator within 30 days after ACR diagnosis.

Compared to ACR, ECG at the time of ICI-myocarditis had comparable voltage and QRS duration (Table 3). ICI-myocarditis had significantly more LBBB (20/125 [16.0%] vs 0/50 [0%];p=0.003) and left anterior fascicular block (LAFB) (24/125 [19.2%] versus 3/50 (6%];p=0.02) but fewer right bundle branch block (RBBB) (43/125 [34.4%] vs 27/50 [54%];p=0.02), and right atrial abnormality (4/125 [3.2%] vs 10/50 [20%];p<.001). In aggregate, ICI-myocarditis had more premature ventricular contractions (PVCs) (18/125 [14.4%] vs 1/50 [2%];p=0.02) but fewer repolarization abnormalities (53/125 [42.4%] vs 33/50 [66%];p=0.005). ACR was less severe than ICI-myocarditis in terms of 30-day all-cause mortality (0/50 [0%] vs 39/146 [26.7%];p<0.001), in-hospital incidence of left ventricular ejection fraction less than 50% (4/28 [14.3%] vs 66/141 [46.8%];p=0.001), progression to severe life-threatening ventricular arrhythmias at admission or during hospital stay (1/50 [2%] vs 22/147 [16.3%];p=0.01), and pacemaker or defibrillator placement within 30 days of the ACR or ICI-myocarditis event (0/50 [0%] vs 22/146 [11.1%];p=0.004). Additionally, ACR had a lower cumulative incidence of third-degree heart block (0/50 [0%] vs 25/147 [17.0%];p=0.002) compared to ICI-myocarditis.

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Discussion

In this study, we assessed ECG features of ICI-myocarditis using a large international database. We show that ICI-myocarditis manifests as clinically significant electrocardiographic disturbances including high degree heart block and ventricular arrhythmias, which are strongly associated with poor clinical outcomes. Compared to baseline ECG, there are also other ECG manifestations, including repolarization abnormalities, decreased voltage, and increases in heart rate, QRS, and QTc. Low-voltage, conduction disorders, and pathological Q-waves were predictive of myocarditis-related death, life-threatening cardiac arrhythmias, and/or overall mortality.

This is the first study to systematically analyze ECG in ICI-myocarditis from a large number of patients with ICI-associated myocarditis with two cardiologists systematically quantifying and evaluated the ECG while blinded to the clinical features for each patient. Previous cohort studies had reported electrical disturbances as a major clinical feature of ICI-associated myocarditis.[6,8,22] Our finding that 91.8% of patients have abnormal ECG is supported by Mahmoud et al's cohort of 35 patients where 89% of patients had abnormal ECG.[6] In addition, our finding that 42% of patients present with ST-segment or T wave abnormalities was similar to the 37% in Escudier et al.'s 30 patient cohort and 55% in Zhang et. al's 103 patient cohort.[8,23] In addition, Zhang et al found 80% of patients presented in sinus rhythm with a cumulative incidence of complete heart block of 16% compared to 86% and 17% respectively in our cohort.[8]

Although we hypothesized that the electrophysiological manifestations of ICI-myocarditis would resemble those of ACR, given the striking pathological similarities, our results show that ICI-myocarditis is both more arrhythmogenic and more lethal than ACR. Life-

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293 threatening ventricular arrhythmias, PVCs, and conduction disorders affecting the left ventricle
294 including complete heart block were more common in ICI-myocarditis but not a major feature of
295 ACR.

296 Interestingly, our study also represents the largest description of ECG findings in
297 moderate-severe ACR. While previous studies have correlated ACR with atrial arrhythmias,
298 sustained ventricular arrhythmias, PR, QRS, and QT lengthening, these changes were
299 infrequently seen in presenting ECG among our cohort.[22,24] Instead, most ECG changes could be
300 explained by post-surgical changes, including sinus tachycardia, P-wave enlargement, right
301 bundle branch block, and nonspecific ST changes.[24] While low voltage and pathological Q
302 waves were infrequent, they were not significantly different from the ICI-myocarditis cohort,
303 suggesting that both immune infiltrates had similar electromotive effects despite differing impact
304 on electrical conduction.

305 Our prognostic analysis adds to and is supportive of predictive ECG studies in general
306 myocarditis. While several studies of myocarditis due to heterogenous causes have shown
307 pathological Q-waves to be predictive of fulminant myocarditis, they did not find significant
308 association with long-term survival.[25,26] While studies have shown that low-voltage lacks
309 predictive value for death in allograft rejection, it has not previously been studied in
310 myocarditis.[10,27] It is interesting that while Rassi et. al found Chagas heart disease to have a 9%
311 prevalence of low-voltage with a hazard ratio for mortality of 1.87, we found a similar
312 prevalence of 8% in ICI-myocarditis but with much higher hazard ratio for mortality of
313 approximatively 4.5.[28] This may be explained by differences in acuity between these two
314 inflammatory cardiomyopathies as well as the relatively denser inflammatory infiltrates in ICI-
315 myocarditis.[2,29]

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316 Both low-voltage and pathological Q-waves signify a loss of electromotive force and are
317 intuitive markers for the extent of inflammatory infiltrate and cardiomyocyte damage. Unlike
318 low-voltage where there is a global decrease in electrical current, Q-waves represent potentials
319 from the unaffected ventricular wall opposite to an inflammatory focus that has become
320 electrically inert. The finding that these two features are strong predictors of mortality suggests
321 that suppressing the underlying inflammatory infiltrate may be a greater priority than
322 antiarrhythmic drugs or devices.

323 ICI-myocarditis is histologically characterized by dense, patchy infiltrates of
324 lymphocytes and macrophages that affect both the myocardium and the conduction system.[2]
325 Compared with ACR, which is primarily lymphocytic, ICI-myocarditis is characterized by both
326 lymphocyte and macrophage infiltrates with a higher CD68/CD3 (macrophages/lymphocytes)
327 ratio.[3] Denser infiltrates in ICI-myocarditis are associated with increased myocyte necrosis and a
328 different molecular profile with lower macrophage expression of PD-L1 perhaps reflecting an
329 influx of the reparative M2 macrophage subpopulation.[3] Importantly, macrophages have been
330 shown to electrically couple with cardiomyocytes even in the absence of disease, thereby
331 facilitating depolarization and improving AV conduction.[30] It is possible that changes in
332 macrophage phenotype and density in ICI-myocarditis may mediate the high frequency of
333 conduction system blocks and ventricular ectopy seen in our cohort. Mouse models of ICI-
334 myocarditis have replicated arrhythmogenicity and lympho-histiocytic infiltration seen in
335 humans and may offer future insights into the electrical contribution of immune cells in
336 inflammatory cardiomyopathies.[31] Separately, other novel forms of cancer immunotherapy also
337 demonstrate high levels of arrhythmogenicity; ventricular tachycardias and atrial fibrillation are
338 disproportionately reported in CAR-T therapy while 20% of patients receiving IL-2 therapy

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339 developed arrhythmias requiring pharmacological intervention.[32–35] These examples further
340 illustrate how the emerging relationship between the immune system and cardiac conduction will
341 become increasingly important in treatment of patients receiving immunotherapy and as a target
342 for arrhythmia management more broadly.

343 Although this study would not have been possible without a multicenter approach, this
344 introduced variability in data collection and interpretation. To mitigate this effect, clear criteria
345 for adjudication were provided and each submission was subjected to a bi-institutional review
346 process. Self-reporting allowed us to assemble an ICI-myocarditis cohort of this size but likely
347 selected for more clinically severe cases. To account for this in our comparison to ACR, we
348 excluded Grade 1R rejection. Nevertheless, our findings are less generalizable to low-severity
349 cases of ICI-myocarditis. The comparison to baseline ECG was limited by availability of
350 baseline ECG which likely enriched for patients with pre-existing cardiac disease thereby
351 underestimating ECG changes caused by ICI. Our analysis only interprets initial ECG and thus
352 does fully capture the predictive value of ECG changes that develop during hospitalization.
353 Although we were unable to correct for variance in treatment in the outcome analysis, we believe
354 that the composite outcome of life-threatening ventricular arrhythmia or myocarditis-related
355 death helps mitigate this by capturing early events that would have led to death if not for
356 aggressive therapy.

357 ***Conclusions***

358 On ECG, ICI-myocarditis manifests as diffuse alteration of the cardiac conduction system
359 represented by conduction blocks, decrease in QRS voltage, and appearance of cardiomyocyte
360 death with pathological Q-waves. These features predict severe life-threatening ventricular
361 arrhythmias and death. Clinicians should focus on identifying these ECG changes as part of

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multimodal diagnostic workup for ICI-myocarditis. Patients with these features are at higher risk for adverse outcomes and may benefit from more aggressive treatment and monitoring strategies.

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Tables/Figures

Table 1. ICI-myocarditis cases characteristics and outcomes

	Total
	Med (IQR) N; n/N (%)
Age	67 (58-77) N=147
Female	55/147 (37.4%)
Body Mass Index	25.3 (21.4-28.8) N=138
Hyperlipidemia	49/138 (35.5%)
Diabetes	25/138 (18.1%)
Hypertension	77/140 (55.0%)
Prior Tobacco User	69/137 (50.4%)
Pre-existing Stroke	5/138 (3.6%)
Pre-existing Peripheral Vascular Disease	11/137 (8.0%)
Pre-existing Coronary Artery Disease	27/139 (19.4%)
Pre-existing Heart Failure	16/138 (11.6%)
1 or More Traditional Cardiovascular Risk Factors (defined as HLD or DM2 or HTN or Tobacco use)	115/140 (82.1%)
Prior History of Cardiac Disease (defined as CAD or CHF)	34/137 (24.8%)
Prior History of Cardiovascular Disease (PVD, CVA, CAD, CHF or HTN)	89/138 (64.5%)
Index ICI Therapy Category	
- Anti CTLA-4 & PD1/PDL1 Combination Therapy	27/147 (18.4%)
- Anti CTLA-4 Monotherapy	41/147 (27.9%)
- Anti PD1/PDL1 Monotherapy	79/147 (53.7%)
Days from First ICI Dose to Hospital Admission	38 (21-83) N=139
Days from Last ICI Dose to Hospital Admission	15 (9-22) N=139
Number of Doses ICI Received	2 (1-4) N=140
Cancer Type	
- Bladder Cancer	4/147 (2.7%)
- Breast Cancer	1/147 (0.7%)
- Kidney Cancer	16/147 (10.9%)
- Leukemia	2/147 (1.4%)
- Lung Cancer	52/147 (35.4%)
- Non-Hodgkin Lymphoma	1/147 (0.7%)
- Prostate Cancer	2/147 (1.4%)
- Melanoma	40/147 (27.2%)
- Thymic Cancer (Non-Thymoma)	2/147 (1.4%)
- Esophageal Cancer	4/147 (2.7%)

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- Gastric Cancer	2/147 (1.4%)
- Colorectal Cancer	1/147 (0.7%)
- Endometrial Cancer	1/147 (0.7%)
- Hepatocellular Carcinoma	2/147 (1.4%)
- Cholangiocarcinoma	1/147 (0.7%)
- Squamous Cell Carcinoma	4/147 (2.7%)
- Other Cancer	1/147 (0.7%)
- Mesothelioma	3/147 (2.0%)
- Thymoma	8/147 (5.4%)
At Least One Other Concomitant IrAE	102/147 (69.4%)
Concomitant IrAE: Myasthenia Gravis-Like Syndrome	32/147 (21.8%)
Concomitant IrAE: Immune-Related Myositis / Rhabdomyolysis	45/147 (30.6%)
Abnormal ECG[18]	135/147 (91.8%)
Abnormal Troponin	123/132 (93.2%)
Initial Troponin >10x Upper Limit of Normal	81/126 (64.3%)
Reduced LVEF On Initial TTE Admission (LVEF<50%)	59/141 (41.8%)
Reduced LVEF During Hospitalization For ICI-Myocarditis (LVEF<50%)	66/141 (46.8%)
Cardiac Magnetic Resonance Imaging Compatible with Myocarditis	54/75 (72%)
Cardiac Biopsy Proven Myocarditis	29/40 (73%)
Cumulative Incidence of Arrhythmia Throughout Hospital Stay	
Supraventricular Arrhythmia*	35/147 (23.8%)
- Atrial Fibrillation	31/147 (21.1%)
- Atrial Flutter	2/147 (1.4%)
- Multifocal Atrial Tachycardia	2/147 (1.4%)
Conduction Disorder*	101/147 (68.7%)
- Bundle Branch or Fascicular Blocks	90/147 (61.2%)
- First-Degree Heart Block	23/147 (15.6%)
- Second-Degree Heart Block	11/147 (7.5%)
- Third-Degree Heart Block	25/147 (17.0%)
ECG Finding of Pericarditis (PR Depression or Diffuse ST Elevations)	20/147 (13.6%)
Repolarization Abnormalities (ST-Segment Or T-Wave Changes)	72/147 (49.0%)
Premature Ventricular Complexes (Any Type)	41/147 (27.9%)
Ventricular Arrhythmias (Any Type; Sustained or Non-Sustained)	25/147 (17.0%)
Life-Threatening Ventricular Arrhythmias*	22/147 (15.0%)
- Asystole	4/147 (2.7%)
- Pulseless Electrical Activity	4/147 (2.7%)
- Ventricular Fibrillation	4/147 (2.7%)
- Ventricular Tachycardia Unspecified Morphology, Sustained	7/147 (4.8%)
- Ventricular Tachycardia Monomorphic, Sustained	12/147 (8.2%)
- Ventricular Tachycardia Polymorphic, Sustained	1/147 (0.7%)

* this category includes rhythms below and that patients may experience more than one of these rhythms

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- Ventricular Tachycardia Torsade De Pointes, Sustained	2/147 (1.4%)
Third-Degree Heart Block and/or Life-Threatening Ventricular Arrhythmia	36/147 (24.5%)
Third-Degree Heart Block and Life-Threatening Ventricular Arrhythmia	11/147 (7.5%)
Outcome	
Placement of a Pacemaker and/or Defibrillator Within 30 days	22/146 (15.1%)
Pacemaker Without Defibrillator Within 30 days	21/146 (14.4%)
Length of Stay (In Days)	11 (7-24) N=98
In-Hospital Mortality	42/147 (28.6%)
30-Day All-Cause Mortality	39/146 (26.7%)
30-Day Myocarditis-Related Mortality or Life-Threatening Ventricular Arrhythmia	37/146 (25.3%)
Diagnostic Certainty[9]	
- Definite Myocarditis	81/143 (56.6%)
- Probable Myocarditis	27/143 (18.9%)
- Possible Myocarditis	35/143 (24.5%)
Cause of Death[†] (Of 39 Patients With 30d All-Cause Mortality)	
Myocarditis	24/39 (61.5%)
Cancer Progression	6/39 (15.4%)
Immune Related Adverse Event Other Than Cardiotoxicity[†]	7/39 (17.9%)
- Non-Cardiac Myotoxicities Including Myasthenia Gravis-Like Syndrome Associated with Diaphragmatic Failure	6/7 (85.7%)
- Thrombocytopenia, Immune Related	1/7 (14.3%)
Sepsis	6/39 (15.4%)
Thromboembolic Event	2/39 (5.1%)
Hemorrhage	3/39 (7.7%)
Respiratory Failure (Other Than Diaphragmatic Failure)[‡]	3/39 (7.7%)
- Pulmonary Infection	2/3 (66.7%)
- Acute Respiratory Distress Syndrome	2/3 (66.7%)
Ischemic Stroke	1/39 (2.6%)
Unknown	1/39 (2.6%)

Abbreviations: CAD: coronary artery diseases; CHF: congestive heart failure; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; CVA: Cerebrovascular accident; HTN: Hypertension; ICI: Immune checkpoint inhibitor; IrAE: Immune Related Adverse Event; LVEF: Left ventricular ejection fraction; PD1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PVD: Peripheral vascular disease; TTE: Transthoracic echocardiogram

[†] note more than one cause may contribute to death

[‡] note more than one cause may contribute to respiratory failure

508 ***Table 2: Presenting ECG of ICI-myocarditis as compared to baseline and as predictors of myocarditis-related mortality and***

509 ***composite outcome using survival analyses adjusting for age and sex****

	ICI-Myocarditis, Presenting ECG	**ICI-Myocarditis, Baseline ECG**		**Subdistribution Hazards Model For 30d Myocarditis-Related Mortality Adjusting for Age and Sex**	**Subdistribution Hazards Model For 30d Composite Outcome Adjusting for Age and Sex**
	Med (IQR) N; n/N (%)	**Med (IQR) N; n/N (%)**	**p-value (paired T-test)**	**HR(sh) [95% CI], p-value***	**HR(sh) [95% CI], p-value***
Heart Rate (bpm)	93.9 [72.6-114.7] N=52	80.4 [68.1-94.8] N=52	0.009	1.01 [0.99-1.03], p=.52 N=125	1.00 [0.99-1.02], p=.60 N=125
PR Length (ms)	162.8 [136.0-186.0] N=42	154.1 [136.0-187.6] N=46	0.10	1.00 [0.99-1.02], p=.90 N=107	1 [0.99-1.01], p=.62 N=107
QTcF Length (ms)	441.8 [414.9-462.6] N=49	421.0 [399.2-440.4] N=51	0.03	1.00 [0.99-1.01], p=.59 N=122	1.00 [1.00-1.01], p=.42 N=122
QRS Length (ms)	95.3 [85.7-118.2] N=52	93.2 [82.7-102.5] N=52	0.02	1.01 [0.99-1.02], p=.57 N=125	1.01 [1-1.03], p=.03 N=125
Sokolow-Lyon Index (mV)	1.39 [0.85-2.03] N=52	1.69 [1.28-2.26] N=52	0.006	0.54 [0.30-0.97], p=.04 N=124	0.50 [0.30-0.85], p=.01 N=124
			p-value (McNemar's test)		
CONDUCTION DISORDERS†	35/52 (67%)	23/52 (44%)	0.01	1.91 [0.71-5.14], p=.20 N=125	3.27 [1.29-8.34], p=.01 N=125
- Bundle Branch Block, Left Bundle	10/52 (19%)	3/52 (6%)	0.05	0.85 [0.26-2.79], p=.79 N=125	1.49 [0.62-3.61], p=.37 N=125
- Bundle Branch Block, Right Bundle	14/52 (27%)	9/52 (17%)	0.18	1.63 [0.69-3.85], p=.27 N=125	2.22 [1.06-4.67], p=.04 N=125
- Fascicular Block, Left Anterior	10/52 (19%)	5/52 (10%)	0.23	1.58 [0.57-4.41], p=.38 N=125	1.81 [0.82-3.97], p=.14 N=125
- Fascicular Block, Left Posterior	6/52 (12%)	2/52 (4%)	0.22	1.40 [0.47-4.14], p=.54 N=125	1.56 [0.52-4.62], p=.43 N=125

* Only arrhythmia subgroups with at least n>2 in ICI-myocarditis presenting ECG are shown

† When multiple eligible ECG were available, ECG without complete heart block or supraventricular arrhythmias were preferentially selected for this analysis focusing on PR, QRS and QTc measurements. Please see Table 1 for cumulative incidence of arrhythmias in ICI-myocarditis.

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- Heart Block, First Degree	9/52 (17%)	7/52 (13%)	0.72	1.78 [0.57-5.58], p=.32 N=125	2.14 [0.83-5.53], p=.12 N=125
ECG Findings of Pericarditis	4/52 (8%)	1/52 (2%)	0.25	0.58 [0.14-2.40], p=.46 N=125	0.98 [0.34-2.82], p=.97 N=125
- ST Segment Elevation, Diffuse	3/52 (6%)	1/52 (2%)	0.62	0.63 [0.15-2.61], p=.52 N=125	1.05 [0.36-3.05], p=.93 N=125
PREMATURE VENTRICULAR COMPLEX (ALL TYPES)	9/52 (17%)	3/52 (6%)	0.08	1.36 [0.43-4.32], p=.61 N=125	1.95 [0.74-5.10], p=.18 N=125
- Premature Ventricular Complex	9/52 (17%)	3/52 (6%)	0.08	0.96 [0.27-3.38], p=.95 N=125	1.51 [0.56-4.07], p=.42 N=125
SINUS MECHANISM	42/52 (81%)	46/52 (88%)	0.29	0.58 [0.21-1.59], p=.29 N=125	0.70 [0.29-1.70], p=.43 N=125
- Normal Sinus Rhythm	17/52 (33%)	31/52 (60%)	0.002	0.43 [0.16-1.16], p=.09 N=125	0.61 [0.28-1.32], p=.21 N=125
- Sinus Tachycardia	25/52 (48%)	15/52 (29%)	0.02	1.48 [0.6-3.65], p=.39 N=125	1.28 [0.61-2.68], p=.52 N=125
REPOLARIZATION ABNORMALITIES	27/52 (52%)	13/52 (25%)	0.008	1.57 [0.64-3.89], p=.33 N=125	1.48 [0.68-3.24], p=.33 N=125
- ST Segment Depression, Diffuse	5/52 (10%)	1/52 (2%)	0.22	0.66 [0.09-4.73], p=.68 N=125	0.47 [0.07-3.27], p=.44 N=125
- ST Segment Depression, Regional	4/52 (8%)	0/52 (0%)	NA	1.04 [0.13-8.56], p=.97 N=125	1.48 [0.35-6.32], p=.59 N=125
- T Wave Inversions	21/52 (40%)	12/52 (23%)	0.07	1.98 [0.81-4.82], p=.13 N=125	1.42 [0.63-3.24], p=.40 N=125
SUPRAVENTRICULAR ARRHYTHMIA†	7/52 (13%)	6/52 (12%)	1.00	2.84 [0.99-8.16], p=.052 N=125	2.39 [1.01-5.65], p=.047 N=125
- Atrial Fibrillation†	6/52 (12%)	5/52 (10%)	1.00	2.19 [0.67-7.24], p=.20 N=125	2.11 [0.77-5.76], p=.14 N=125
UNCATEGORIZED					
Premature Atrial Complex	5/52 (10%)	3/52 (6%)	0.68	2.19 [0.57-8.45], p=.26 N=125	1.63 [0.49-5.43], p=.42 N=125
Left Ventricular Hypertrophy	12/52 (23%)	16/52 (31%)	0.34	0.71 [0.21-2.43], p=.58 N=125	0.51 [0.16-1.63], p=.25 N=125
Low QRS Voltage	4/52 (8%)	1/52 (2%)	0.37	6.05 [2.10-17.39], p<.001 N=125	2.70 [0.97-7.49], p=.06 N=125
P Wave Abnormality Suggestive of Left Atrial Enlargement	11/52 (21%)	9/52 (17%)	0.75	1.40 [0.53-3.71], p=.49 N=125	1.09 [0.46-2.59], p=.85 N=125
Q Waves, Pathological	8/52 (15%)	4/52 (8%)	0.22	3.40 [1.38-8.33], p=.008 N=125	2.20 [0.95-5.12], p=.07 N=125

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510 ***Table 3: Comparison on ECG findings in ICI-myocarditis to acute cellular rejection at***

511 ***presentation***

	ICI-Myocarditis, Presenting ECG N=125	**Acute Cellular Rejection 2R/3R Presenting ECG N=50**	
			p-value (Wilcoxon test)
Heart Rate (bpm)	87.6 [71.3-104.6] N=125	88.8 [80.4-110.2] N=50	0.20
PR Interval Length (ms)	161.3 [145.7-180.6] N=107	153.2 [136.5-166.1] N=48	**0.01**
QTcF Length (ms)	432.5 [405.4-462.1] N=122	434.1 [393.5-460.1] N=49	0.59
QRS Length (ms)	95.0 [85.3-122.3] N=125	92.8 [85.5-103.2] N=49	0.15
Sokolow-Lyon Index	1.240 [0.700-1.889] N=124	1.421 [0.889-1.845] N=50	0.40
			p-value (Chi-square test)
CONDUCTION DISORDERS	79/125 (63%) N=125	34/50 (68%) N=50	0.55
- Bundle Branch Block, Left Bundle	20/125 (16%) N=125	0/50 (0%) N=50	**0.003**
- Bundle Branch Block, Nonspecific	2/125 (2%) N=125	2/50 (4%) N=50	0.34
- Bundle Branch Block, Right Bundle	43/125 (34%) N=125	27/50 (54%) N=50	**0.02**
- Escape Rhythm, Ventricular	1/125 (1%) N=125	0/50 (0%) N=50	0.53
- Fascicular Block, Left Anterior	24/125 (19%) N=125	3/50 (6%) N=50	**0.03**
- Fascicular Block, Left Posterior	13/125 (10%) N=125	4/50 (8%) N=50	0.63
- Heart Block, First Degree	18/125 (14%) N=125	5/50 (10%) N=50	0.44
- Heart Block, Third Degree*	5/125 (4%) N=125	0/50 (0%) N=50	0.15

* When multiple eligible ECG were available, ECG without complete heart block or supraventricular arrhythmias were preferentially selected for this analysis focusing on PR, QRS and QTc measurements. Please see Table 1 for cumulative incidence of arrhythmias in ICI-myocarditis and Supplemental-Table-3 for cumulative incidence of arrhythmias in ACR.

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ECG FINDINGS OF PERICARDITIS	17/125 (14%) N=125	2/50 (4%) N=50	0.07
- PR-Segment Depression	1/125 (1%) N=125	0/50 (0%) N=50	0.53
- ST Segment Elevation, Diffuse	16/125 (13%) N=125	2/50 (4%) N=50	0.08
PREMATURE VENTRICULAR COMPLEX (ALL TYPES)	18/125 (14%) N=125	1/50 (2%) N=50	**0.02**
- Premature Ventricular Complex	17/125 (14%) N=125	1/50 (2%) N=50	**0.02**
- Premature Ventricular Complex Bigeminy	2/125 (2%) N=125	0/50 (0%) N=50	0.37
SINUS MECHANISM	107/125 (85.6%) N=125	47/50 (94%) N=50	0.08
- Sinus Tachycardia	51/125 (40.8%) N=125	21/50 (42%) N=50	0.81
REPOLARIZAITON ABNORMALITIES	53/125 (42%) N=125	33/50 (66%) N=50	**0.005**
- ST Segment Elevation, Regional	8/125 (6%) N=125	0/50 (0%) N=50	0.07
- ST Segment Depression, Diffuse	9/125 (7%) N=125	2/50 (4%) N=50	0.43
- ST Segment Depression, Regional	7/125 (6%) N=125	3/50 (6%) N=50	0.92
- T Wave Inversions	41/125 (33%) N=125	29/50 (58%) N=50	**0.002**
- T Wave Notching	0/125 (0%) N=125	1/50 (2%) N=50	0.11
SUPRAVENTRICULAR ARRHYTHMIA Error! Bookmark not defined.	11/125 (9%) N=125	2/50 (4%) N=50	0.27
- Atrial FibrillationError! Bookmark not defined.	10/125 (8%) N=125	1/50 (2%) N=50	0.14
- Atrial Flutter**Error! Bookmark not defined.**	1/125 (1%) N=125	1/50 (2%) N=50	0.50
UNCATEGORIZED			
Premature Atrial Complex	8/125 (6%) N=125	0/50 (0%) N=50	0.07
Premature Junctional Complex	1/125 (1%) N=125	0/50 (0%) N=50	0.53
Left Ventricular Hypertrophy	21/125 (17%) N=125	10/50 (20%) N=50	0.62
Low QRS Voltage	6/125 (5%) N=125	2/50 (4%) N=50	0.82
P Wave Abnormality Suggestive of Left Atrial Enlargement	29/125 (23%) N=125	14/50 (28%) N=50	0.51
P Wave Abnormality Suggestive of Right Atrial Enlargement	4/125 (3%) N=125	10/50 (20%) N=50	**<0.001**
Q-waves, Pathological	19/125 (15%) N=125	4/50 (8%) N=50	0.20
Accelerated Junctional Rhythm	1/125 (1%) N=125	0/50 (0%) N=50	0.53

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514 ***Figure 1: Outcomes by cumulative incidence of arrhythmia***

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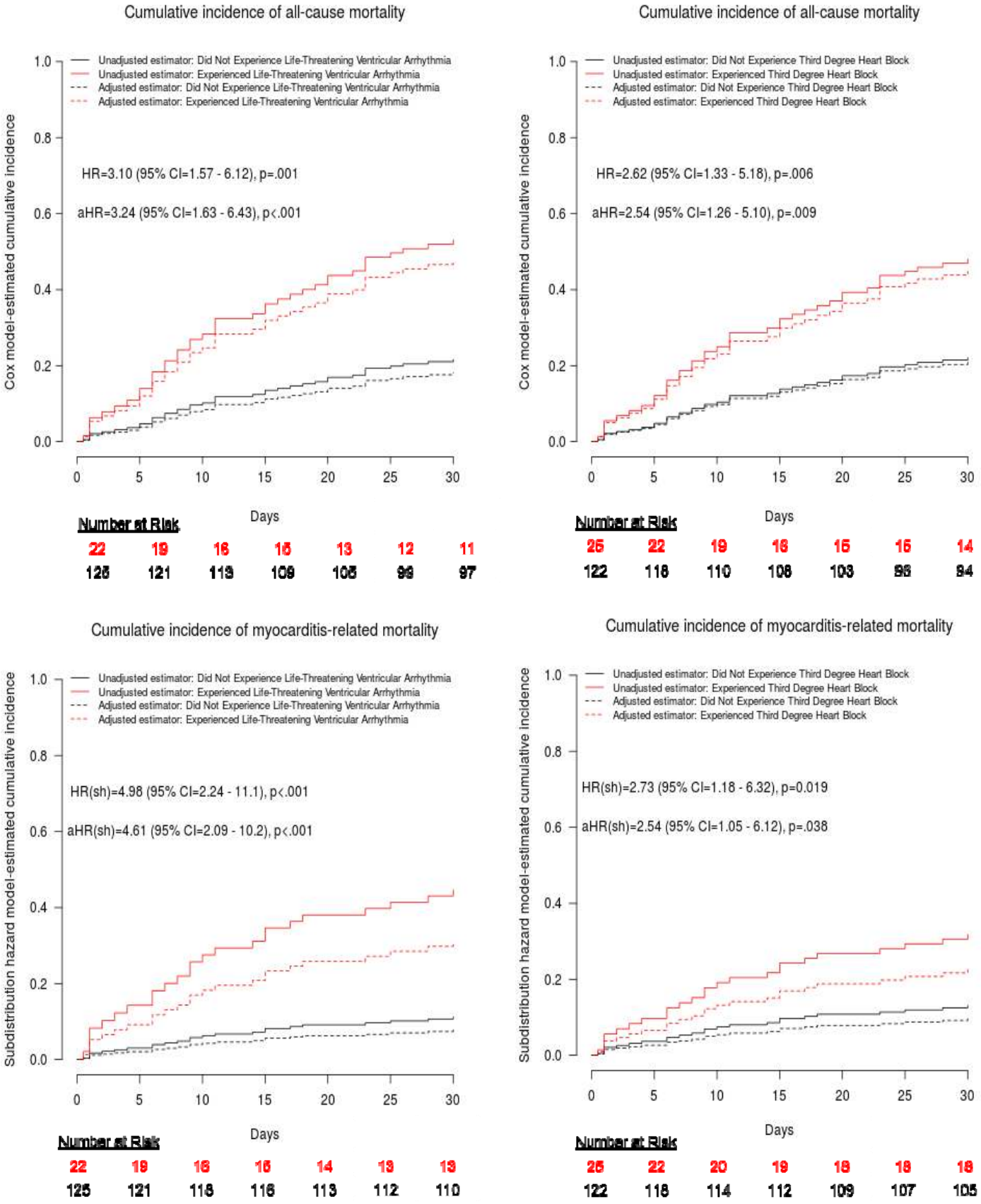

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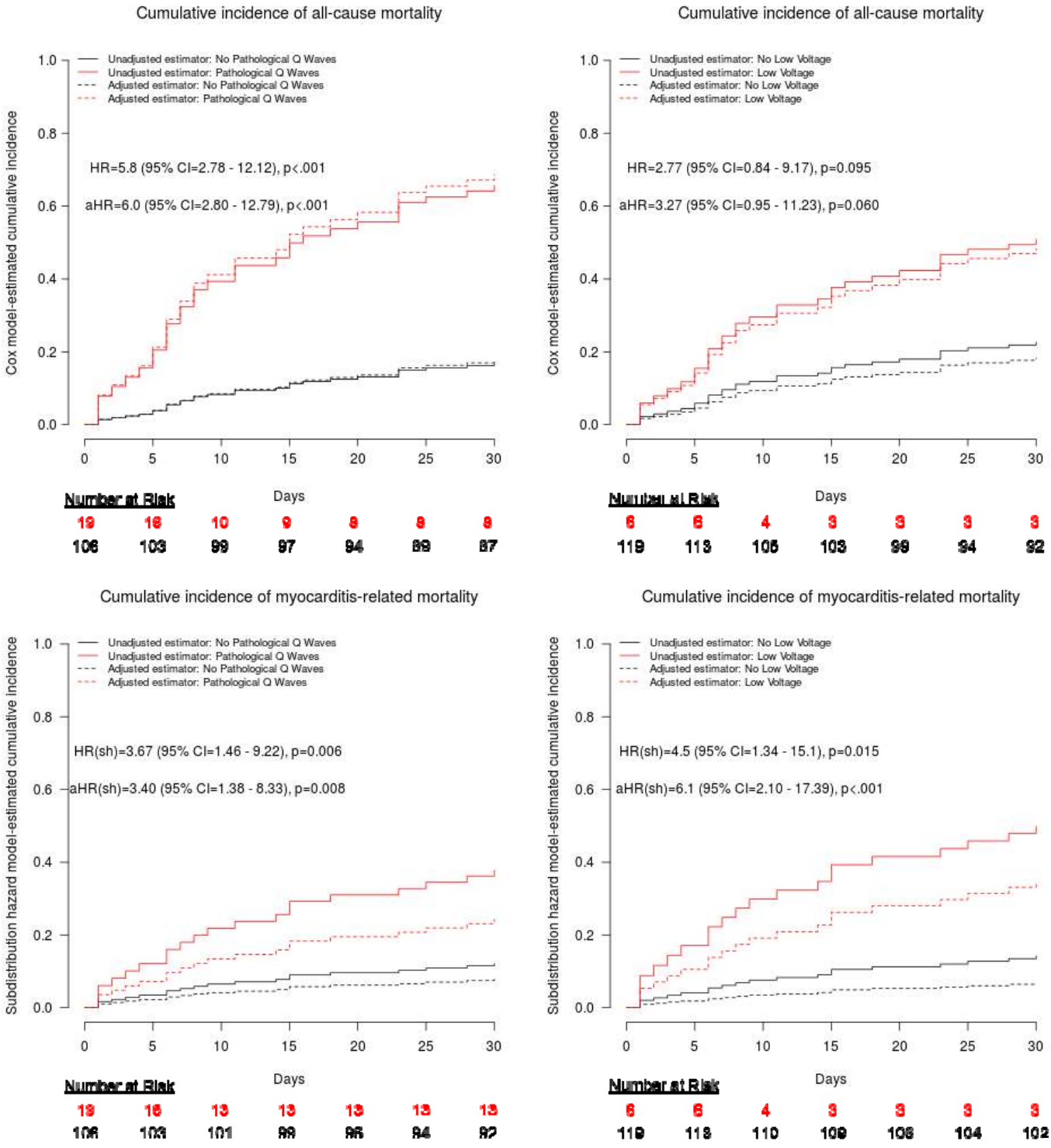
516 ***Figure 2: Outcomes by presenting ECG findings***



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519 ***Supplemental Data.***

520 ***Supplemental Table 1. List of participating institutions***

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* data were collected from published cases in these institutions with no manual confirmation from for data completeness from authors

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521 ***Supplemental Table 2: Glossary of qualitative ECG findings by category***

CONDUCTION DISORDERS - Bundle Branch Block, Left (defined as QRS ≥120ms + broad notched or slurred R wave in I, aVL, V5 & V6)[36] - Nonspecific or Unspecified Intraventricular Conduction Disturbance - Bundle Branch Block, Right (defined as QRS ≥120ms; RSR' pattern in V1-V2; and slurred S wave in I, V6)[36] - Escape Rhythm, Junctional - Escape Rhythm, Ventricular - Fascicular Block, Left Anterior (defined as QRS <120ms, qR in aVL, R-peak time≥45 ms, frontal plane axis between −45° and −90°)[36] - Fascicular Block, Left Posterior (defined as QRS <120ms, qR in III & aVF, R-peak time≥45 ms, frontal plane axis between 90° and 180°)[36] - Heart Block, First Degree (i.e. PR > 200ms) - Heart Block, Second Degree Type I - Heart Block, Second Degree Type II - Heart Block, Third Degree
REPOLARIZATION ABNORMALITIES - ST-Segment Depression, Diffuse (defined as ≥0.05 mV below the baseline)[37] - ST-Segment Depression, Regional (defined as ≥0.05 mV below the baseline)[37] - ST-Segment Elevation, Regional (defined as ≥0.1 mV unless in leads V2 to V3 where defined as ≥0.2 mV in men ≥40 years, ≥2.5 mV in men < 40 years, and ≥0.15 mV in women) - T Wave Inversions - T Wave Notching in ≥ 3 leads (defined as bifid T-wave with a notch duration between the 2 peaks ≥40 ms and an amplitude ≥0.05 mV) - Tall T waves (defined as >1 mV in precordial leads or >0.5 mV in the limb leads)
SINUS MECHANISM - Sinus Bradycardia (i.e. HR < 60 bpm) - Normal Sinus Rhythm - Sinus Tachycardia (i.e. HR > 100 bpm) - Sinus Arrhythmia
ECG FEATURES SUGGESTIVE OF PERICARDITIS - PR-Segment Depression (defined as ≥0.05 mV PR depression from TP segment) - ST-Segment Elevation, Diffuse (defined as ≥1 mV unless in leads V2 to V3 where defined as ≥2 mV in men ≥40 years, ≥2.5 mV in men < 40 years, and ≥1.5 mV in women)
SUPRAVENTRICULAR ARRHYTHMIAS - Atrial Fibrillation - Atrial Flutter - AV (atrioventricular) Nodal Reentrant Tachycardia - Multifocal Atrial Tachycardia - Junctional Tachycardia
VENTRICULAR ARRHYTHMIA (ALL TYPES) - Non-Sustained Ventricular Tachycardia (defined as 3 or more premature ventricular contractions for < 30 seconds at a rate of >100 beats per minute without hemodynamic collapse) + all LIFE-THREATENING VENTRICULAR ARRHYTHMIAS (below)

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LIFE-THREATENING VENTRICULAR ARRHYTHMIA - Sustained (i.e. duration > 30 seconds or requiring intervention due to hemodynamic compromise) Monomorphic Ventricular Tachycardia - Sustained Polymorphic Ventricular Tachycardia - Ventricular Fibrillation - Sustained Torsade de Pointes
UNCATEGORIZED FEATURES - Left Ventricular Hypertrophy (defined as sum of S wave in V1 + R wave in V5 or V6 ≥35 mV or R wave in aVL ≥11 mV) - Low QRS Voltage (defined as QRS voltage < 5 mV in the limb leads and/or < 10mV in precordial leads) - P Wave Abnormality Suggestive Of Left Atrial Enlargement [defined as P-wave duration (120 ms or more) OR widely notched P wave (40 ms or more)][38] - P Wave Abnormality Suggestive Of Right Atrial Enlargement [defined as P wave in lead II (greater than 0.25 mV) OR P wave in V1 or V2(0.15 mV or more) [38] - Premature Atrial Complex - Premature Junctional Complex - Q Waves, Pathological [defined as Q-wave ≥0.03 s and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF or V4–V6 in any 2 leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF).a R wave >0.04 s in V1–V2 and R/S >1 with a concordant positive T wave in absence of conduction defect.] [37]

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Supplemental Table 3: Cumulative incidence of arrhythmia throughout hospital stay for 125 ICI-myocarditis patients in ECG features quantitative outcome analysis

(Please refer to Supplemental Table 2 for full details on diagnostic criteria and categorization of qualitative ECG features)

	n/N (%)
SINUS MECHANISM	107/125 (85.6%)
- Normal Sinus Rhythm	56/125 (44.8%)
- Sinus Bradycardia	2/125 (1.6%)
- Sinus Tachycardia	55/125 (44.0%)
- Sinus Arrhythmia	1/125 (0.8%)
CONDUCTION DISORDERS	87/125 (69.6%)
- Bundle Branch Block, Nonspecific	8/125 (6.4%)
- Bundle Branch Block, Left Bundle	23/125 (18.4%)
- Bundle Branch Block, Right Bundle	45/125 (36.0%)
- Escape Rhythm, Ventricular	4/125 (3.2%)
- Escape Rhythm, Junctional	4/125 (3.2%)
- Fascicular Block, Left Anterior	25/125 (20.0%)
- Fascicular Block, Left Posterior	14/125 (11.2%)
- Heart Block, First Degree	19/125 (15.2%)
- Heart Block, Second Degree Type I	4/125 (3.2%)
- Heart Block, Second Degree Type II	5/125 (4.0%)
- Heart Block, Third Degree	19/125 (15.2%)
ECG FINDINGS OF PERICARDITIS	18/125 (14.4%)
- PR-Segment Depression	1/125 (0.8%)
- ST Segment Elevation, Diffuse	17/125 (13.6%)
REPOLARIZATION ABNORMALITIES	62/125 (49.6%)
- ST segment elevation, regional	13/125 (10.4%)
- ST Segment Depression, Diffuse	11/125 (8.8%)
- ST Segment Depression, Regional	8/125 (6.4%)
- Tall T Waves	1/125 (0.8%)
- T Wave Inversions	45/125 (36.0%)
- T Wave Notching	5/125 (4.0%)
VENTRICULAR EXCITABILITY (PVC or Ventricular Arrhythmia)	42/125 (33.6%)
PREMATURE VENTRICULAR COMPLEX (ALL TYPES)	33/125 (26.4%)
- Premature Ventricular Complex	31/125 (24.8%)
- Premature Ventricular Complex Bigeminy	5/125 (4.0%)
- Premature Ventricular Complex Trigeminy	1/125 (0.8%)
VENTRICULAR ARRHYTMIAS (all types)	18/125 (14.4%)
- Ventricular Tachycardia, Non-Sustained	9/125 (7.2%)
- Ventricular Tachycardia, Sustained	9/125 (7.2%)
LIFE-THREATENING VENTRICULAR ARRHYTHMIA	15/125 (12.0%)
- Asystole	4/125 (3.2%)
- Pulseless Electrical Activity	4/125 (3.2%)

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- Ventricular Fibrillation	4/125 (3.2%)
- Ventricular Tachycardia Unspecified Morphology, Sustained	5/125 (4.0%)
- Ventricular Tachycardia Monomorphic, Sustained	5/125 (4.0%)
- Ventricular Tachycardia Polymorphic, Sustained	1/125 (0.8%)
- Ventricular Tachycardia Torsade de Pointes, Sustained	2/125 (1.6%)
SUPRA-VENTRICULAR ARRHYTHMIAS	30/125 (24.0%)
- Atrial Fibrillation	26/125 (20.8%)
- Atrial Flutter	2/125 (1.6%)
- Multifocal Atrial Tachycardia	2/125 (1.6%)
- AV Nodal Reentrant Tachycardia	2/125 (1.6%)
- Junctional Tachycardia	0/125 (0.0%)
UNCATEGORIZED	
Accelerated Idioventricular Rhythm	3/125 (2.4%)
Accelerated Junctional Rhythm	1/125 (0.8%)
Left Ventricular Hypertrophy	22/125 (17.6%)
Low QRS Voltage	12/125 (9.6%)
Q-Waves, Pathological	22/125 (17.6%)
P Wave Abnormality Suggestive of Left Atrial Enlargement	29/125 (23.2%)
P Wave Abnormality Suggestive of Right Atrial Enlargement	4/125 (3.2%)
Premature Atrial Complex	14/125 (11.2%)
Premature Junctional Complex	2/125 (1.6%)
Sinus Arrest / Sinus Pause	2/125 (1.6%)
Placement of a Pacemaker and/or Defibrillator Within 30 days	19/124 (15.3%)
In-Hospital Mortality	33/125 (26.4%)
30-Day All-Cause Mortality	30/124 (24.2%)
30-Day Myocarditis-Related Mortality or Life-Threatening Ventricular Arrhythmia	28/124 (22.6%)
Cause of Death (of 30 patients with 30d all-cause mortality)	
Myocarditis	20/30 (66.7%)
Cancer Progression	6/30 (20%)
Immune Related Adverse Event Other Than Cardiotoxicity*	6/30 (20%)
- Non-Cardiac Myotoxicities Including Myasthenia Gravis-Like Syndrome Associated with Diaphragmatic Failure	5/6 (83%)
- Thrombocytopenia, Immune Related	1/6 (17%)
Sepsis	4/30 (13%)
Thromboembolic Event	2/30 (7%)
Hemorrhage	1/30 (3%)
Respiratory Failure (Other Than Diaphragmatic Failure)†	2/30 (7%)
- Pulmonary Infection	1/2 (50%)
- Acute Respiratory Distress Syndrome	1/2 (50%)
Ischemic Stroke	1/30 (3%)
Unknown	1/30 (3%)

* note more than one cause may contribute to death

† note more than one cause may contribute to respiratory failure

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528 ***Supplemental Table 4: Presenting ECG of ICI-myocarditis as predictors of all-cause mortality,***
529 ***myocarditis-related mortality, and composite outcome using unadjusted survival analyses***
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	Subdistribution Hazards Model For 30d Myocarditis-Related Mortality	**Subdistribution Hazards Model For 30d Composite Outcome**	**Cox Proportional Hazards Model For 30d All-Cause Mortality**
	unadjusted HR(sh) (95% CI) p-value	**unadjusted HR(sh) (95% CI) p-value**	**unadjusted HR (95% CI) p value**
Heart Rate (bpm)	1.01 [0.99-1.03], p=.35 N=125	1.01 [0.99-1.02], p=.40 N=125	1.00 [0.99-1.02], p=.70 N=125
PR Length (ms)	1.00 [0.98-1.02], p=.97 N=107	1.00 [0.99-1.01], p=.76 N=107	1.00 [0.99-1.01], p=.91 N=107
QTcF Length (ms)	1.00 [0.99-1.01], p=.66 N=122	1.00 [0.99-1.01], p=.52 N=122	1.01 [1.00-1.01], p=.22 N=122
QRS Length (ms)	1.01 [0.99-1.02], p=.51 N=125	1.01 [1.00-1.02], p=.11 N=125	1.00 [0.99-1.02], p=.51 N=125
Sokolow-Lyon Index (mV)	0.55 [0.28-1.06], p=.08 N=124	0.51 [0.30-0.87], p=.01 N=124	0.59 [0.35-0.98], p=.04 N=124
CONDUCTION DISORDERS* **DISORDERS***	1.84 [0.68-5.00], p=.23 N=125	3.05 [1.20-7.76], p=.02 N=125	1.68 [0.75-3.76], p=.21 N=125
Bundle Branch Block, Left Bundle	0.9 [0.27-2.99], p=.87 N=125	1.47 [0.62-3.52], p=.38 N=125	1.06 [0.40-2.76], p=.91 N=125
Bundle Branch Block, Right Bundle	1.67 [0.7-3.99], p=.25 N=125	2.16 [1.05-4.47], p=.04 N=125	1.54 [0.75-3.17], p=.24 N=125
Fascicular Block, Left Anterior	1.47 [0.54-4.04], p=.45 N=125	1.79 [0.81-3.96], p=.15 N=125	0.84 [0.32-2.20], p=.73 N=125
Fascicular Block, Left Posterior	1.48 [0.47-4.69], p=.5 N=125	1.60 [0.55-4.69], p=.39 N=125	1.25 [0.44-3.58], p=.68 N=125
Heart Block, First Degree	1.58 [0.53-4.74], p=.41 N=125	1.87 [0.75-4.68], p=.18 N=125	0.94 [0.33-2.68], p=.90 N=125
Ecg Findings Of Pericarditis	0.68 [0.16-2.84], p=.59 N=125	1.08 [0.38-3.07], p=.89 N=125	0.67 [0.20-2.22], p=.52 N=125
ST Segment Elevation, Diffuse	0.73 [0.17-3.06], p=.67 N=125	1.16 [0.41-3.32], p=.78 N=125	0.73 [0.22-2.40], p=.60 N=125
PREMATURE VENTRICULAR COMPLEX (ALL TYPES)	1.56 [0.53-4.56], p=.42 N=125	1.75 [0.73-4.22], p=.21 N=125	1.21 [0.46-3.16], p=.70 N=125
Premature Ventricular Complex	1.13 [0.34-3.74], p=.84 N=125	1.41 [0.56-3.55], p=.46 N=125	0.95 [0.33-2.72], p=.93 N=125
SINUS MECHANISM	0.55 [0.21-1.48], p=.24 N=125	0.68 [0.28-1.62], p=.38 N=125	0.77 [0.31-1.87], p=.56 N=125
Normal Sinus Rhythm	0.39 [0.14-1.05], p=.06 N=125	0.56 [0.26-1.21], p=.14 N=125	0.58 [0.27-1.23], p=.15 N=125
Sinus Tachycardia	1.62 [0.68-3.84], p=.28 N=125	1.39 [0.67-2.88], p=.38 N=125	1.46 [0.71-3.00], p=.30 N=125
REPOLARIZATION ABNORMALITIES	1.38 [0.58-3.29], p=.47 N=125	1.39 [0.67-2.88], p=.37 N=125	1.44 [0.70-2.94], p=.32 N=125
ST Segment Depression, Diffuse	0.68 [0.09-4.95], p=.70 N=125	0.45 [0.06-3.25], p=.43 N=125	1.64 [0.50-5.41], p=.42 N=125
ST Segment Depression, Regional	0.94 [0.11-7.73], p=.95 N=125	1.37 [0.33-5.68], p=.67 N=125	0.59 [0.08-4.33], p=.61 N=125
T Wave Inversions	1.74 [0.73-4.15], p=.21 N=125	1.34 [0.64-2.80], p=.44 N=125	1.43 [0.69-2.97], p=.34 N=125
SUPRAVENTRICULAR ARRHYTHMIA†	2.86 [1.00-8.2], p=.05 N=125	2.40 [1.00-5.75], p=.05 N=125	2.24 [0.86-5.85], p=.10 N=125
Atrial Fibrillation†	2.25 [0.66-7.64], p=.19 N=125	2.06 [0.76-5.54], p=.15 N=125	1.93 [0.67-5.54], p=.22 N=125
UNCATEGORIZED			
Premature Atrial Complex	2.84 [0.91-8.85], p=.07 N=125	1.76 [0.61-5.09], p=.29 N=125	1.74 [0.53-5.75], p=.36 N=125
Left Ventricular Hypertrophy	0.87 [0.26-2.95], p=.82 N=125	0.55 [0.17-1.77], p=.32 N=125	0.52 [0.16-1.71], p=.28 N=125
Low QRS Voltage	4.50 [1.34-15.12], p=.02 N=125	2.57 [0.90-7.28], p=.08 N=125	2.77 [0.84-9.17], p=.10 N=125
P Wave Abnormality Suggestive of Left Atrial Enlargement	1.36 [0.54-3.40], p=.51 N=125	1.14 [0.49-2.67], p=.76 N=125	0.94 [0.41-2.20], p=.89 N=125
P Wave Abnormality Suggestive of Right Atrial Enlargement	N/A	N/A	0.01 [0-66336310], p=.67 N=125
Q Waves, Pathological	3.67 [1.46-9.22], p=.006 N=125	2.10 [0.90-4.89], p=.09 N=125	5.80 [2.78-12.12], p<.00 N=125

* When multiple eligible ECG were available, ECG without complete heart block or supraventricular arrhythmias were preferentially selected for this analysis focusing on PR, QRS and QTc measurements. Please see Table 1 for cumulative incidence of arrhythmias in ICI-myocarditis and Supplemental-Table-3 for cumulative incidence of arrhythmias in ACR.

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531 ***Supplemental Table 5: Presenting ECG of ICI-myocarditis as predictors of all-cause mortality***

532 ***using survival analyses adjusted for age and sex***

	Cox Proportional Hazards Model For 30d All-Cause Mortality: HR [95% CI], P-Value*
Heart Rate (bpm)	1.01 [0.99-1.02], p=.40 N=125
PR Length (ms)	1.00 [0.99-1.01], p=.55 N=107
QTcF Length (ms)	1.00 [1.00-1.01], p=.36 N=122
QRS Length (ms)	1.00 [0.99-1.01], p=.90 N=125
Sokolow-Lyon Index (mV)	0.57 [0.34-0.94], p=.03 N=124
CONDUCTION DISORDERS†	1.56 [0.69-3.53], p=.29 N=125
- Bundle Branch Block, Left Bundle	1.00 [0.38-2.62], p=.99 N=125
- Bundle Branch Block, Right Bundle	1.48 [0.71-3.06], p=.29 N=125
- Fascicular Block, Left Anterior	0.85 [0.32-2.25], p=.75 N=125
- Fascicular Block, Left Posterior	1.34 [0.47-3.85], p=.59 N=125
- Heart Block, First Degree	0.83 [0.28-2.40], p=.72 N=125
ECG Findings Of Pericarditis	0.75 [0.22-2.51], p=.64 N=125
- ST Segment Elevation, Diffuse	0.83 [0.25-2.81], p=.76 N=125
PREMATURE VENTRICULAR COMPLEX (ALL TYPES)	1.01 [0.37-2.75], p=.99 N=125
- Premature Ventricular Complex	0.77 [0.26-2.30], p=.64 N=125
SINUS MECHANISM	0.77 [0.31-1.89], p=.56 N=125
- Normal Sinus Rhythm	0.50 [0.23-1.09], p=.08 N=125
- Sinus Tachycardia	1.67 [0.80-3.49], p=.17 N=125
REPOLARIZATION ABNORMALITIES	1.52 [0.74-3.12], p=.26 N=125
ST Segment Depression, Diffuse	1.60 [0.48-5.30], p=.44 N=125
ST Segment Depression, Regional	0.53 [0.07-3.90], p=.53 N=125
T Wave Inversions	1.49 [0.71-3.12], p=.29 N=125
SUPRAVENTRICULAR ARRHYTHMIA†	2.21 [0.84-5.79], p=.11 N=125
- Atrial Fibrillation†	1.83 [0.63-5.27], p=.27 N=125
UNCATEGORIZED	
Premature Atrial Complex	1.59 [0.47-5.38], p=.46 N=125
Left Ventricular Hypertrophy	0.49 [0.15-1.61], p=.24 N=125
Low QRS Voltage	3.27 [0.95-11.23], p=.06 N=125
P Wave Abnormality Suggestive of Left Atrial Enlargement	1.10 [0.46-2.63], p=.83 N=125
P Wave Abnormality Suggestive of Right Atrial Enlargement	0.01 [0-77149830], p=.66 N=125
Q Waves, Pathological	5.98 [2.8-12.79], p<.001 N=125

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* Please see Table 1 for cumulative incidence of arrhythmias in ICI-myocarditis and Supplemental-Table-3 for cumulative incidence of arrhythmias in ACR.

† When multiple eligible ECG were available, ECG without complete heart block or supraventricular arrhythmias were preferentially selected for this analysis focusing on PR, QRS and QTc measurements. Please see Table 1 for cumulative incidence of arrhythmias in ICI-myocarditis and Supplemental-Table-3 for cumulative incidence of arrhythmias in ACR.

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535 ***Supplemental Table 6: Baseline characteristics of acute cellular rejection cohort***

	Med (IQR) N; n/N (%)
Recipient Age, Years	51 (43-62) N=50
Female Recipient	18/50 (36%)
Reason for Transplant	
- Dilated Cardiomyopathy	4/50 (8%)
- Ischemic Cardiomyopathy	18/50 (36%)
- Amyloidosis	1/50 (2%)
- Restrictive Cardiomyopathy	1/50 (2%)
- Congenital Heart Disease	4/50 (8%)
- Non-Ischemic Cardiomyopathy, Not Otherwise Specified	17/50 (34%)
- Hypertrophic Cardiomyopathy	2/50 (4%)
- Other	3/50 (6%)
Donor Age	29.0 (22.0-37.0) N=50
Female Donor	13/50 (26%)
Known Cardiac Allograft Vasculopathy	11/50 (22%)
Induction Therapy	
- Basiliximab (Simulect)	26/50 (52%)
- Thymoglobulin (ATG)	3/50 (6%)
- None	20/50 (40%)
- Other	1/50 (2%)
Background/Maintenance Immunosuppressive Regimen	
- Prednisone + Tacrolimus + Mycophenolate	42/50 (84%)
- Prednisone + Cyclosporine + Mycophenolate	3/50 (6%)
- Other	5/50 (10%)
Days from Transplant To Rejection	145 (26-283) N=50
Acute Cellular Rejection Grading Scheme[21]	
- 2R, Moderate	46/50 (92%)
- 3R, Severe	4/50 (8%)
Days from Transplant To ECG	145 (28-283) N=50
Days from Biopsy To ECG	0 (0-1)
30-Day All-Cause Mortality	0/50 (0%)
Placement of A Pacemaker and/or Defibrillator for ACR Related Arrhythmias Within 30 Days Of Diagnosis	0/50 (0%)
Pacemaker Without Defibrillator for ACR Related Arrhythmias Within 30 Days Of Diagnosis	0/50 (0%)
Admitted During or As A Result Of ACR	29/50 (58.0%)
Length of Stay (Days)[‡]	12 (5-21) N=29
Reduced LVEF At Admission Or During Hospital Stay For ACR (Excluding Pre-Transplant LVEF)*	4/28 (14.3%)
In-Hospital Mortality*	0/29 (0%)
Arrhythmias at Any Point During Hospitalization (If Applicable) Or At Presenting ECG (Please Refer To Supplemental Table 2 For Criteria / Classification)	
Supraventricular Arrhythmia[§]	6/50 (12%)
- Atrial Fibrillation	3/50 (6%)

[‡] This refers to the subset of admitted patients

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- Atrial Flutter - Multifocal Atrial Tachycardia	2/50 (4%) 1/50 (2%)
Conduction Disorder[§] - Bundle Branch or Fascicular Blocks - First-Degree Heart Block - Second-Degree Heart Block - Third-Degree Heart Block	34/50 (68%) 33/50 (66%) 6/50 (12%) 0/50 (0%) 0/50 (0%)
ECG Finding of Pericarditis (PR Depression Or Diffuse ST Elevations)	2/50 (4%)
Repolarization Abnormalities (ST-Segment Or T-Wave Changes)	33/50 (66%)
Premature Ventricular Complexes (Any Type)	6/50 (12%)
Ventricular Arrhythmias (Any Type; Sustained or Non-Sustained)	5/50 (10%)
Life-Threatening Ventricular Arrhythmias[§] - Asystole - Pulseless Electrical Activity - Ventricular Fibrillation - Ventricular Tachycardia Unspecified Morphology, Sustained - Ventricular Tachycardia Monomorphic, Sustained - Ventricular Tachycardia Polymorphic, Sustained - Ventricular Tachycardia Torsade De Pointes, Sustained	1/50 (2%) 0/50 (0%) 0/50 (0%) 0/50 (0%) 0/50 (0%) 1/50 (2%) 0/50 (0%) 0/50 (0%)
Third-Degree Heart Block and/or Life-Threatening Ventricular Arrhythmia	1/50 (2%)

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[§] this category includes rhythms below, note that patients may experience more than one of these rhythms

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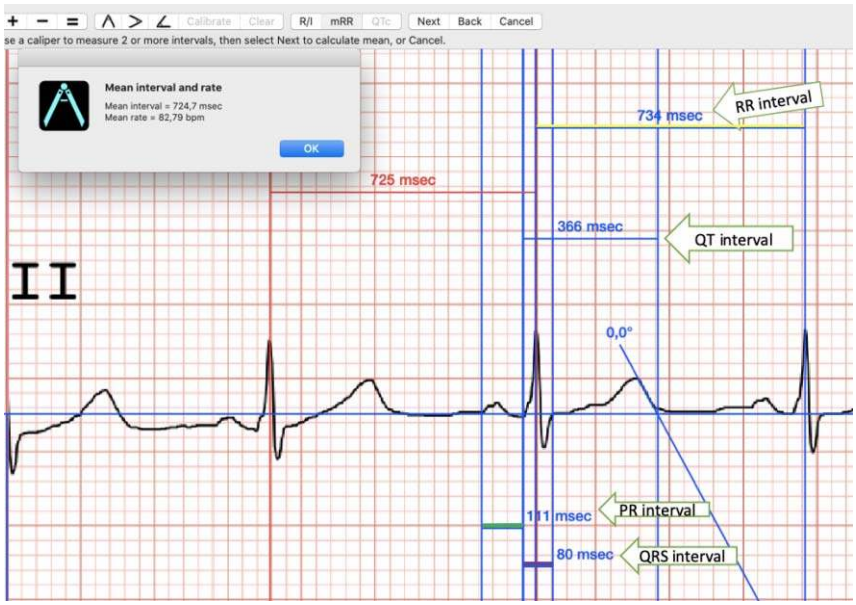
Supplemental Data Methods 1: Systematic review search terms

Pubmed, Scopus, and Google Scholar were queried for case reports published between 1/1/2008 and 5/21/2019 with the search terms myocarditis, cardiotoxicity or cardiac toxicity in addition to (AND) at least one of the following: immune checkpoint inhibitor, pembrolizumab, ipilimumab, nivolumab, avelumab, atezolizumab, durvalumab, tremelimumab, anti-CTLA-4, anti-PD-L1, anti-PD-1, CTLA-4 inhibitor, PD-L1 inhibitor, OR PD-1 inhibitor.

Supplemental Data Methods 2: ECG interval measurement

The QT interval was measured using the tangent method from the beginning of the QRS complex to the end of the T-wave. Lead II was preferentially used, but when unsuitable, V5 and V6 were used. The average of three consecutive PQRST complexes was used for each interval's measurements. PVCs were excluded. In the rare cases in which three consecutive complexes were not available, two complexes were used. The heart rate corrected QT interval (QTc) was calculated using Bazett's (QTcB=QT interval/) and Fredericia's formula (QTcF=QT interval/(RR interval)$^{1/3}$.

Figure: ECG measurement with EP Calipers application (note that values used were an average of measurements across three consecutive PQRST complexes)



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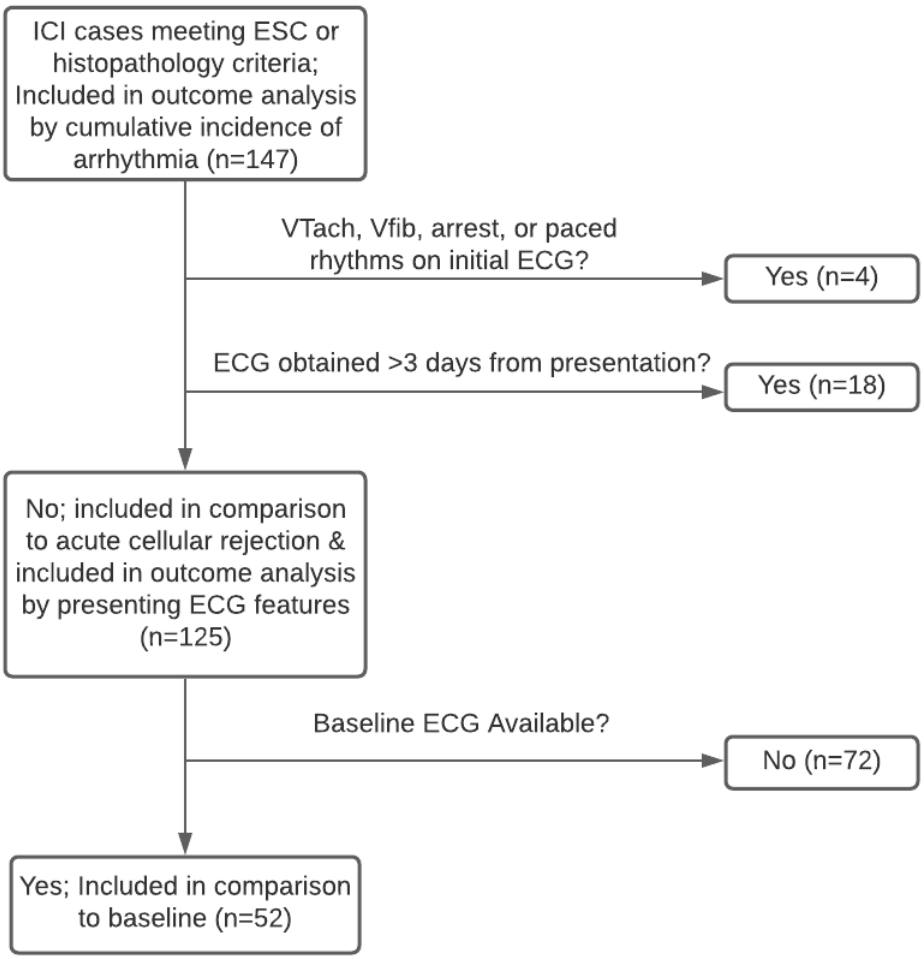
570 ***Supplemental Figure 1: Flowchart***



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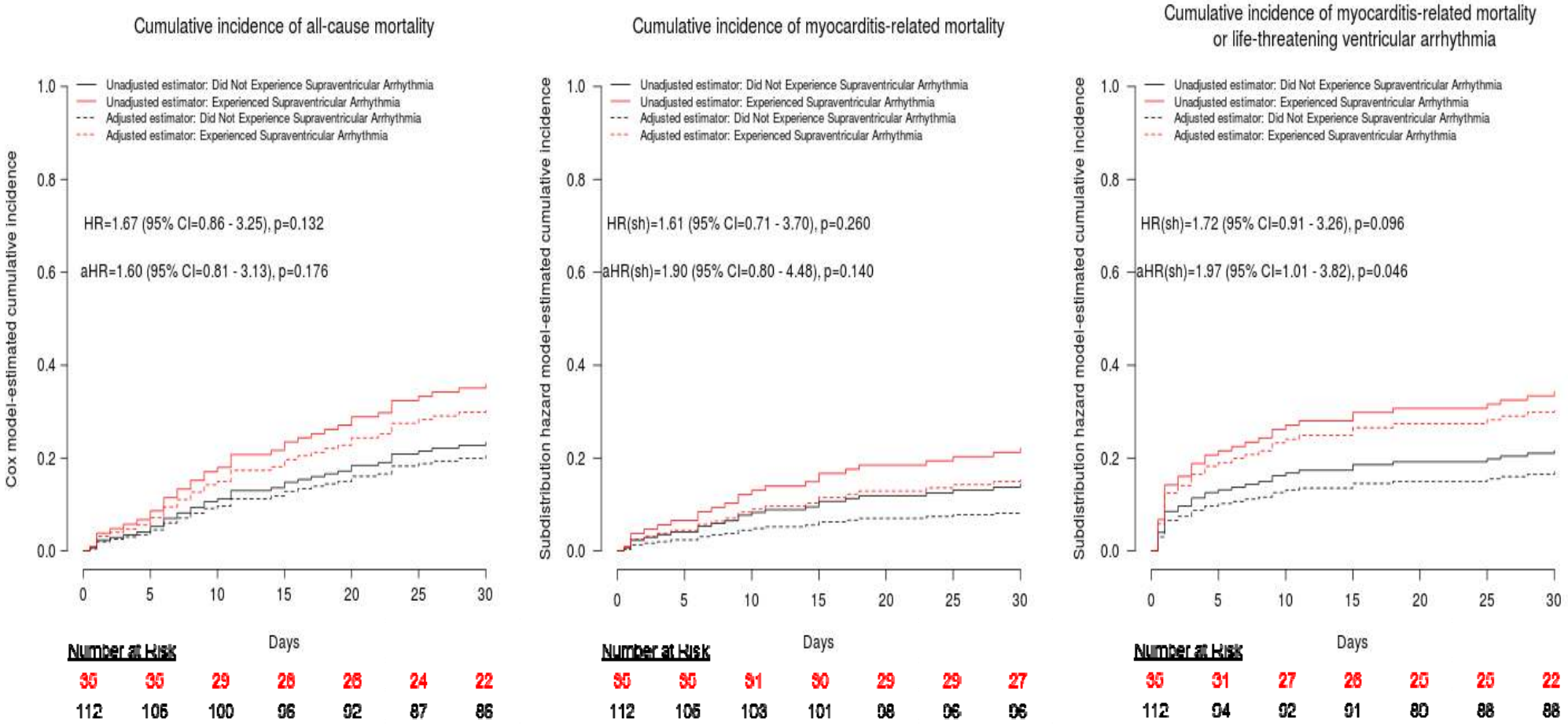
574 ***Supplemental Figure 2: Outcomes by cumulative incidence of supraventricular arrhythmia***



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575 ***Supplemental Figure 3: Model-estimated Cumulative Incidence of Event at 30-day by Sokolow-Lyon Index***

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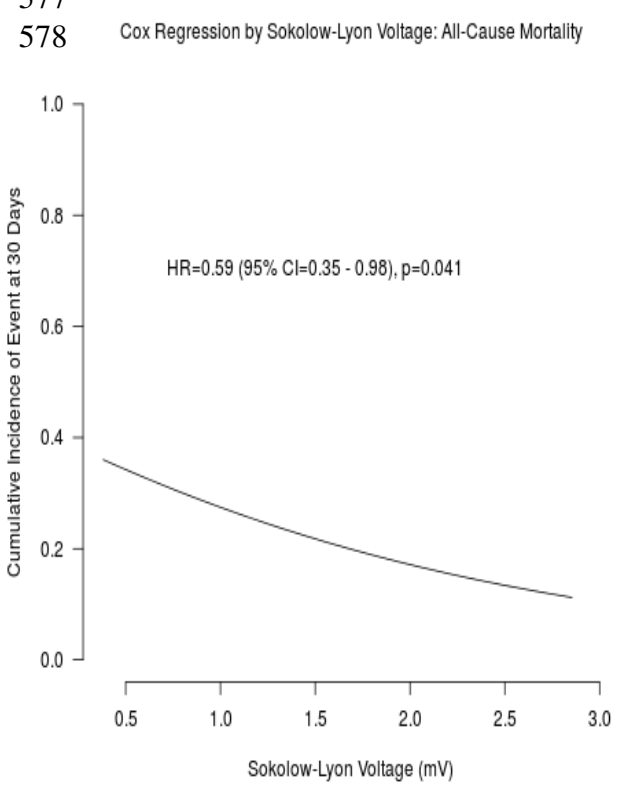

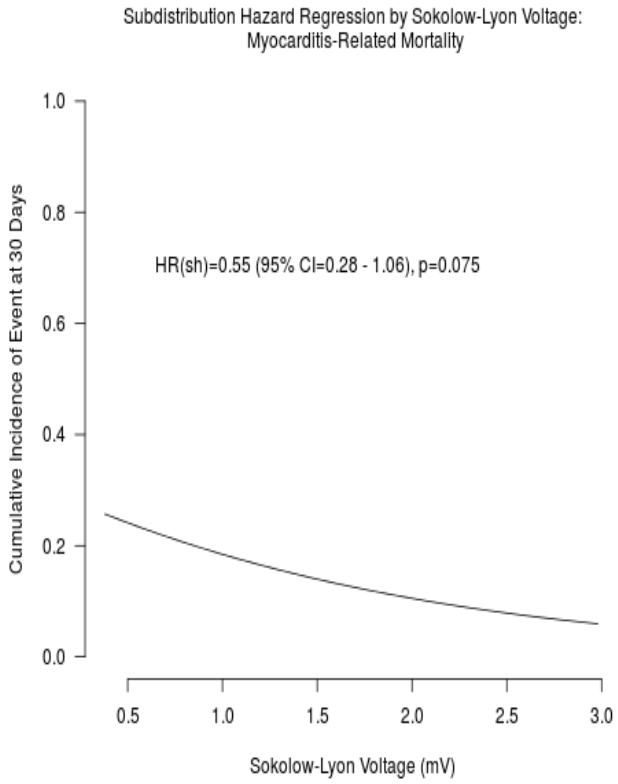

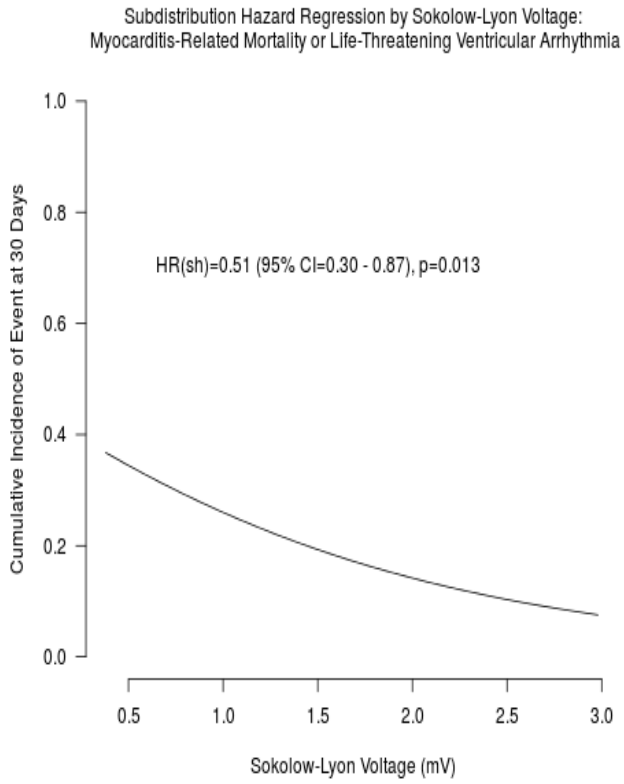

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579 ***Supplemental Figure 4: Cumulative incidence function by presenting ECG findings (composite outcome)***

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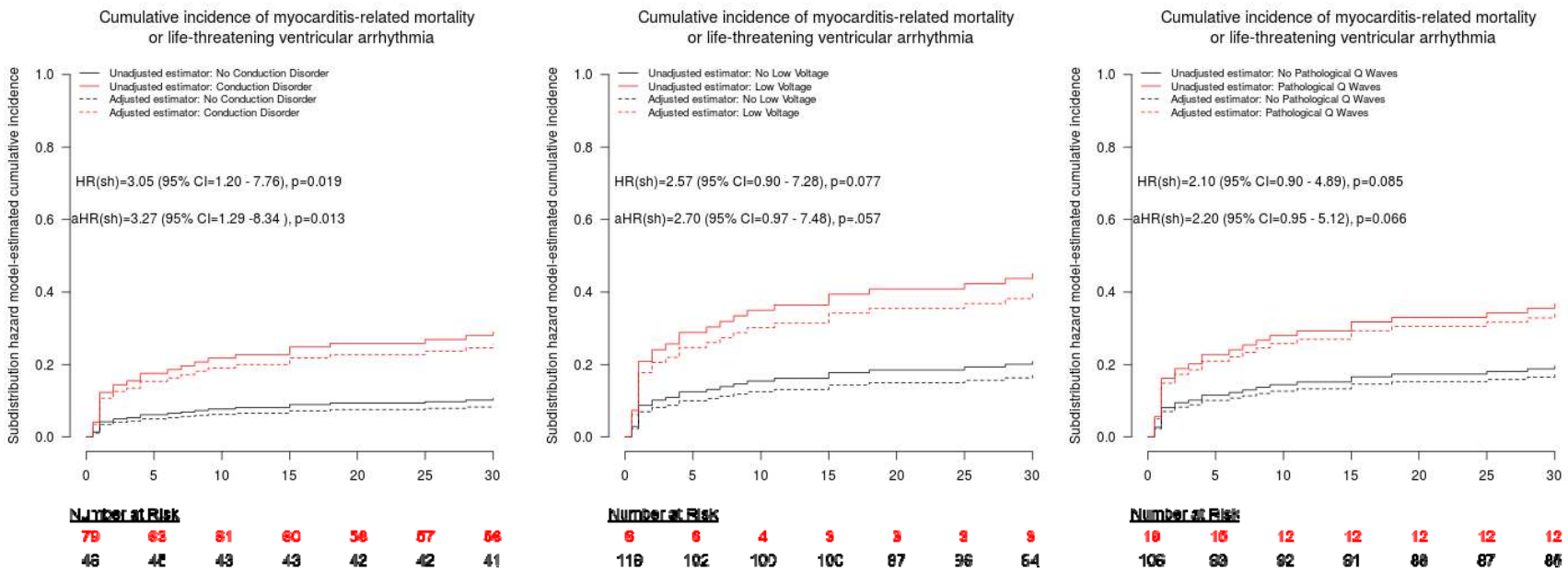

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