Electrocardiographic features of immune checkpoint inhibitor associated myocarditis

Daniel A Zlotoff ,[1] Malek Z O Hassan,[2] Amna Zafar,[2] Raza M Alvi,[2]
Magid Awadalla,[2] Syed S Mahmood,[3] Lili Zhang,[4] Carol L Chen,[5]
Stephane Ederhy,[6] Ana Barac,[7] Dahlia Banerji,[2] Maeve Jones-O'Connor,[1]
Sean P Murphy,[1] Merna Armanious,[8] Brian J Forrestal,[7] Michael C Kirchberger,[9]
Otavio R Coelho-Filho,[10] Muhammad A Rizvi,[11] Gagan Sahni,[12] Anant Mandawat,[13]
Carlo G Tocchetti,[14] Sarah Hartmann,[2] Hannah K Gilman,[2]
Eduardo Zatarain-Nicolás,[15] Michael Mahmoudi,[16] Dipti Gupta,[5] Ryan Sullivan,[17]
Sarju Ganatra,[18] Eric H Yang,[19] Lucie M Heinzerling,[20] Franck Thuny ,[21]
Leyre Zubiri,[17] Kerry L Reynolds,[17] Justine V Cohen,[22] Alexander R Lyon,[23]
John Groarke,[24] Paaladinesh Thavendiranathan,[25] Anju Nohria,[24]
Michael G Fradley,[8] Tomas G Neilan[1,2]

Correspondence to
Tomas G Neilan;
tneilan@mgh.harvard.edu

ABSTRACT

Background Myocarditis is a highly morbid complication of immune checkpoint inhibitor (ICI) use that remains inadequately characterized. The QRS duration and the QTc interval are standardized electrocardiographic measures that are prolonged in other cardiac conditions; however, there are no data on their utility in ICI myocarditis.
Methods From an international registry, ECG parameters were compared between 140 myocarditis cases and 179 controls across multiple time points (pre-ICI, on ICI prior to myocarditis, and at the time of myocarditis). The association between ECG values and major adverse cardiac events (MACE) was also tested.
Results Both the QRS duration and QTc interval were similar between cases and controls prior to myocarditis. When compared with controls on an ICI (93±19 ms) or to baseline prior to myocarditis (97±19 ms), the QRS duration prolonged with myocarditis (110±22 ms, p<0.001 and p=0.009, respectively). In contrast, the QTc interval at the time of myocarditis (435±39 ms) was not increased compared with pre-myocarditis baseline (422±27 ms, p=0.42). A prolonged QRS duration conferred an increased risk of subsequent MACE (HR 3.28, 95% CI 1.98 to 5.62, p<0.001). After adjustment, each 10 ms increase in the QRS duration conferred a 1.3-fold increase in the odds of MACE (95% CI 1.07 to 1.61, p=0.011). Conversely, there was no association between the QTc interval and MACE among men (HR 1.33, 95% CI 0.70 to 2.53, p=0.38) or women (HR 1.48, 95% CI 0.61 to 3.58, p=0.39).
Conclusions The QRS duration is increased in ICI myocarditis and is associated with increased MACE risk. Use of this widely available ECG parameter may aid in ICI myocarditis diagnosis and risk-stratification.

BACKGROUND

Since the introduction of ipilimumab in 2011, immune checkpoint inhibitors (ICIs) have improved oncological care, offering new therapeutic options for a variety of cancers.[1] Through activation of the immune system, ICIs can enhance antitumor activity but may also lead to immune-related adverse events (irAEs).[2 3] Myocarditis is an uncommon irAE.[4 5] The incidence of ICI-associated myocarditis is unclear, with estimates ranging from 0.09% to 1.1%.[3 6–10] There are several potential cardiac adverse effects associated with ICIs but the focus on myocarditis is due to the morbidity and mortality associated with that diagnosis.[11 12] Specifically, data from multiple groups report a mortality ranging from 17% to 50%.[3 6 7 13] In comparison, the mortality of non-ICI myocarditis is far less than 5%.[14 15] Therefore, there is a significant need for improved diagnostic and risk-stratification methods in ICI myocarditis, as well as newly recognized cardiac toxicities related to other forms of immune therapy for cancer.[16 17]

The QRS duration and the QTc interval are standardized measures routinely available from a 12-lead ECG. The QRS duration corresponds to ventricular depolarization, while the QTc interval predominantly represents ventricular repolarization. Monitoring of the QRS duration is employed in the care of patients who are at risk of developing arrhythmias and heart failure.[18 19] Measurement of the QTc interval is also routinely used in both oncology trials and routine oncology care.[20] However, there are no data on the utility of measurement of

the QRS duration and the QTc interval among patients with ICI myocarditis. Therefore, the goal of this study was to evaluate whether the QRS duration and QTc interval increase with ICI myocarditis and whether these parameters associate with the development of subsequent adverse cardiac events.

METHODS
Patients
Data on myocarditis cases (n=140) were obtained from a 23-center international registry specifically designed for collating cases of ICI myocarditis.[5 7 21] Cases were included between November 2013 and April 2019. Controls (n=179) were selected patients from a Massachusetts General Hospital registry of patients treated with an ICI during the same time interval for whom ECG data were available. Controls were not selected to match on any parameter with the cases.

ECG data
ECGs were obtained at various timepoints relative to ICI initiation and to the development of myocarditis (among cases). The acquisition of an ECG was not protocol-specified and was performed at the discretion of the medical care team. ECGs were recorded using the preferred system at each registry site and the parameters were derived automatically by those systems. Forty randomly selected ECGs (20 from controls and 20 from myocarditis cases) were also manually interpreted by a reader (DAZ) blinded to the case/control identity and the automated measurements. These manually measured values were then compared with those which had been automatically derived. The primary measures of interest included the PR interval, QRS duration, and the QTc interval. The PR interval represents the time delay between atrial depolarization and ventricular depolarization and was included in the analysis to assess which measures of intracardiac conduction were affected in ICI myocarditis. QT interval correction for heart rate was calculated using the Fridericia formula[22] as this is more accurate than the commonly used Bazett formula and considered the most appropriate strategy by the US Food and Drug Administration.[23 24] Based on standardized criteria, a QRS duration greater than 110 ms was considered prolonged.[25] Similarly, based on standardized criteria, a QTc interval greater than 450 ms in men and 460 ms in women was considered prolonged.[26]

Clinical data
Clinical data of interest obtained retrospectively from electronic medical records included patient demographics, medications, prior medical conditions, lab values, and cardiovascular risk factors. Data relevant to cancer included the cancer type, prior cancer therapies, and specific ICI treatments.

Definitions and outcomes of interest
Myocarditis was diagnosed through one of the following standardized approaches: (1) histopathological features on endomyocardial biopsy or autopsy or (2) a clinically accepted scoring system designed for suspected myocarditis that uses clinical findings, biomarkers, and imaging features.[27] This latter clinical diagnostic algorithm relies on the presence of one or more clinical features (chest pain, heart failure, arrhythmias, or cardiogenic shock) plus one or more diagnostic findings (ECG abnormalities, elevated troponin levels, functional or structural abnormalities on cardiac imaging, or evidence of edema or late gadolinium enhancement on cardiac MRI) occurring in the absence of significant coronary disease or known alternative causes.[27] This standardized scoring system was devised because an endomyocardial biopsy is typically performed in less than 15% of myocarditis cases.[28] The main outcome of interest was major adverse cardiac events (MACE), which was a composite of cardiovascular death,[29] cardiac arrest,[30] cardiogenic shock,[31] and hemodynamically significant complete heart block.[7]

Statistical analysis
Continuous variables were summarized as either the mean±SD or as the median and IQR, as appropriate, and categorical variables were presented as percentages. Comparisons between myocarditis cases and controls were made with Fisher's exact test for categorical variables or with the Wilcoxon rank sum test for continuous variables (age and body mass index (BMI), both of which demonstrated non-Gaussian distribution). Comparisons of ECG parameters by case and ICI exposure status used the Kruskal-Wallis test with Dunn's correction for multiple comparisons. The relationship between measured ECG parameters and left ventricular ejection fraction (EF) or left ventricular end-diastolic volume (LVEDV) was analyzed with simple linear regression and the associations were tested with the Pearson correlation coefficient. HRs for the association of dichotomized ECG parameters with MACE were determined using Cox proportional hazard models with follow-up time used as the time scale. The assumption of proportionality was verified by the method of Therneau and Grambsch.[32] Kaplan-Meier curves and the log-rank test were used to analyze the relationship between QRS duration or QTc interval and MACE-free survival. The χ^2 test was used to compare the frequencies of MACE component endpoints among myocarditis cases and subgroups. Multivariable logistic regression was used to address the relationship between multiple covariates, including ECG parameters at the time of myocarditis, and MACE risk. All statistical tests were two-sided and p<0.05 was considered significant. Statistical analysis was performed using R V.3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS V.26 (IBM Corporation).

RESULTS
Patient characteristics

One hundred and forty patients with ICI myocarditis and 179 controls were included in the analysis. The median time between ICI initiation and myocarditis diagnosis was 58 days, and 91 cases (65.0%) occurred within the first 90 days of ICI therapy. Of the 140 cases, 70 (50.0%) were diagnosed based on clinical criteria, 58 patients (41.4%) were diagnosed by pathology from an endomyocardial biopsy, and 12 patients (8.6%) were diagnosed based on autopsy pathology. The median duration of follow-up for myocarditis cases was 69 days (IQR 19–153). Myocarditis patients had a higher BMI than controls (28±6.1 vs 26±5.8, p=0.002); otherwise, cases and controls had similar rates of cardiovascular risk factors (table 1). The most common cancer in both groups was melanoma. Renal cell cancer was more common among myocarditis cases (8.6% vs 2.2%, p=0.02). The use of atezolizumab was higher among cases (7.1% vs 1.7%, p=0.02). There was a lower frequency of anti-programmed cell death 1 (PD-1) therapy use in the myocarditis group (87.1% vs 96.1%, p=0.005); conversely, there was a greater frequency of anti-programmed death ligand 1 (PD-L1) therapy use in the myocarditis group (11.4% vs 2.2%, p=0.001). The use of ipilimumab/nivolumab combination therapy was also more common in the myocarditis group (25.7% vs 11.2%, p=0.001). The rates of pneumonitis (24.3% vs 12.3%, p=0.007) and neurological adverse events (8.6% vs 2.2%, p=0.02) were higher in the myocarditis group.

ECG characteristics

We compared computer-derived ECG parameters between controls and myocarditis cases at three different time-points: prior to initiation of ICI ("pre-ICI"), after the initiation of ICI but prior to development of myocarditis ("on-ICI"), and at the time of presentation with myocarditis. For validation of this approach, we also manually measured the parameters from 40 random ECGs (20 control and 20 cases) and found these values to be similar to the computer-derived values (online supplemental file 1). The median time intervals between pre-ICI baseline ECG and initiation of ICI were 103 days (IQR 24–215) and 82 days (IQR 35–172), controls and cases, respectively. The median time intervals between initiation of ICI and on-ICI ECG were 165 days (IQR 41–379) and 44 days (IQR 11–152), controls and cases, respectively. The pre-ICI baseline PR interval, QRS duration, and QTc (corrected for heart rate with the Fridericia formula, subsequently designated QTc-F) interval were similar between controls and cases (figure 1A–C). The on-ICI (prior to development of myocarditis for cases) PR interval, QRS duration, and QTc-F did not change from baseline and were similar between cases and controls. Additionally, among cases prior to the development of myocarditis, there was no increase in these parameters between the pre-ICI values and the on-ICI values. With the development of myocarditis, the PR interval did not increase. In contrast, the QRS duration at the time of myocarditis (110±22 ms) did

increase and was greater than the QRS duration of cases pre-ICI (99±20 ms, p=0.001), controls on-ICI (93±19 ms, p<0.001), and cases on-ICI prior to the development of myocarditis (97±19, p=0.009). Cases were stratified by QRS duration using the cut-off of 110 ms, the upper limit of normal in adults.[25] A normal QRS duration of ≤110 ms was observed in 74 cases (52.8%), while 66 (47.1%) had a prolonged QRS duration >110 ms. A similar testing strategy was adopted for the QTc-F interval. The QTc-F interval at time of myocarditis (435±39 ms) was increased when compared with controls on ICI (419±28 ms, p=0.02) but not when compared with values from cases prior to the development of myocarditis (422±27 ms, p=0.42). Of 99 male cases, 29 (29.3%) had a normal QTc-F≤450 ms, while 70 (70.7%) had a prolonged QTc-F>450 ms. Among women with myocarditis, 25 (61.0%) had a normal QTc-F≤460 ms, while 16 (39.0%) had a prolonged QTc-F>460 ms. We also analyzed the QTc interval across time points using the Bazett formula to correct for heart rate (subsequently designated QTc-B). With this approach, the QTc-B interval at the time of myocarditis (460±36 ms) was increased when compared with either on-ICI controls (440±28 ms, p<0.001) or on-ICI cases (440±29 ms, p=0.007) (online supplemental file 2).

Sensitivity of QRS duration for the diagnosis of ICI myocarditis

Given the significantly prolonged QRS duration observed during myocarditis, the sensitivity and specificity of QRS duration towards myocarditis diagnosis was determined. Applying a cut-off of >110 ms achieved a sensitivity of 48.6% and specificity of 87.0% for the diagnosis of myocarditis; the application of a higher cut-off of >130 ms yielded a sensitivity of 16.4% and a specificity of 92.6% (online supplemental table 1). A receiver-operating characteristic curve applying QRS duration towards myocarditis diagnosis had an area under the curve of 0.73 (online supplemental figure 3). Using the change in QRS duration (ΔQRS; equal to the QRS duration at time of myocarditis minus the QRS duration at baseline prior to myocarditis) yielded a sensitivity of 51.7% when applying a diagnostic threshold of >10 ms; this decreased to 31.0% and 21.6% for >20 ms and >30 ms, respectively.

Association of ECG parameters with left ventricular size and function

We analyzed the relationship between the measured ECG parameters and left ventricular EF and LVEDV among myocarditis cases (figure 2A–C). The QRS duration was not related to either echocardiographic EF (r=−0.10, 95% CI −0.27 to 0.07, p=0.25) or MRI-derived EF (r=−0.095, 95% CI −0.29 to 0.11, p=0.35), but was directly related to the LVEDV (r=0.32, 95% CI 0.13 to 0.49, p=0.001). The QTc-F interval was inversely associated with the echocardiographic EF (r=−0.20, 95% CI −0.36 to −0.02, p=0.026) and the MRI-derived EF (r=−0.20, 95% CI −0.039 to −0.01, p=0.044), but was not related to the LVEDV (r=0.16, 95% CI −0.04 to 0.35, p=0.12).

Table 1 Baseline characteristics

Characteristic	Controls, n (%) (n=179)	Myocarditis, n (%) (n=140)	P value
Age at ICI Initiation	64.1±13.9	65.9±14.7	0.02
Sex			
Male	118 (65.9)	99 (70.7)	0.40
Female	61 (34.1)	41 (29.3)	0.40
Body mass index, kg/m^2	25.8±5.8	27.8±6.1	0.002
Cardiovascular risk factors and disease			
Hypertension	109 (60.9)	81 (57.9)	0.65
Diabetes mellitus	29 (16.2)	31 (22.1)	0.20
CKD	29 (16.2)	9 (8.5)*	0.07
COPD	26 (14.5)	19 (17.6)*	0.51
Coronary artery disease	23 (12.8)	20 (14.3)	0.74
Stroke	20 (11.2)	7 (5.0)	0.07
Heart failure	12 (6.7)	8 (5.7)	0.82
Pre-ICI cardiovascular medications			
Statin	45 (25.1)	45 (32.1)	0.17
Aspirin	43 (24.0)	33 (23.6)	1.00
Beta-blocker	56 (31.3)	33 (23.6)	0.13
ACE-I or ARB	34 (19.0)	37 (26.4)	0.14
CCB	31 (17.3)	16 (11.4)	0.15
Primary cancer type			
Melanoma	86 (48.0)	57 (40.7)	0.21
Non-small cell lung cancer	36 (20.1)	24 (17.1)	0.56
Head and neck	13 (7.3)	6 (4.3)	0.34
Small cell lung cancer	7 (3.9)	1 (0.7)	0.08
Renal cell carcinoma	4 (2.2)	12 (8.6)	0.02
Hodgkin's lymphoma	2 (1.1)	2 (1.4)	1.00
Glioblastoma	2 (1.1)	2 (1.4)	1.00
Other	29 (16.2)	36 (25.7)	0.05
ICI type (monotherapy or combination)			
Nivolumab	100 (55.9)	67 (47.9)	0.18
Pembrolizumab	72 (40.2)	55 (39.3)	0.91
Ipilimumab	65 (36.3)	49 (35.0)	0.82
Atezolizumab	3 (1.7)	10 (7.1)	0.02
Durvalumab	1 (0.6)	3 (2.1)	0.32
Tremelimumab	1 (0.6)	4 (2.9)	0.17
Avelumab	0 (0.0)	3 (2.1)	0.08
Any anti-PD-1	172 (96.1)	122 (87.1)	0.005
Any anti-CTLA-4	66 (36.9)	53 (37.9)	0.91
Any anti-PD-L1	4 (2.2)	16 (11.4)	0.001
Type of combined ICI			
Ipilimumab+nivolumab	20 (11.2)	36 (25.7)	0.001
Ipilimumab+pembrolizumab	0 (0.0)	2 (1.4)	0.19
Tremelimumab+avelumab	0 (0.0)	1 (0.7)	0.44
Tremelimumab+durvalumab	0 (0.0)	2 (1.4)	0.19

Continued

Table 1 Continued

Characteristic	Controls, n (%) (n=179)	Myocarditis, n (%) (n=140)	P value
Other adverse events			
None	108 (60.3)	64 (45.7)	0.01
Colitis	24 (13.4)	13 (9.3)	0.29
Pneumonitis	22 (12.3)	34 (24.3)	0.007
Pituitary/adrenal axis disorder	13 (7.3)	7 (5.0)	0.49
Hepatitis	10 (5.6)	16 (11.4)	0.07
Dermatitis	5 (2.8)	10 (7.1)	0.11
Neurological	4 (2.2)	12 (8.6)	0.02
Other	6 (3.4)	7 (5.0)	0.57
Prior cancer therapies			
Anthracycline chemotherapy	3 (1.7)	8 (5.7)	0.07
VEGF inhibitor	7 (3.9)	1 (0.7)	0.08

Values are n (%) or mean±SD (for age and BMI only).

*Certain patients with incomplete data were not included in analysis for some variables in the myocarditis group; percentages were derived from lower denominators in these rows (106 for CKD and 108 for COPD).

ACE-I, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICI, immune checkpoint inhibitor; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; VEGF, vascular endothelial growth factor.

Association of QRS duration with MACE

Overall, 69 of the 140 cases (49%) experienced a MACE. The median time to a MACE was 34 days (IQR 12–103) and 68% of MACE occurred within the first 90 days after diagnosis of myocarditis. A non-sinus rhythm at presentation with myocarditis was associated with an HR for MACE of 1.94 relative to sinus rhythm at presentation (95% CI 1.27 to 3.43, log-rank p=0.01) (online supplemental figure 4). Using an unadjusted Cox proportional hazard model, a QRS duration >110 ms was associated with a HR for MACE of 3.28 relative to a QRS duration ≤110 ms (95% CI 1.98 to 5.62, p<0.001) (figure 3A). Increased QRS duration at the time of myocarditis was associated with increased MACE risk after adjustment for age, sex, and cardiovascular comorbidities (table 2). Specifically, an increase in the QRS duration of 10 ms conferred a 1.30-fold increase in the odds of MACE (95% CI 1.07 to 1.61, p=0.011). We also assessed the prognostic utility of troponin in ICI myocarditis. Troponin data were available for 138 of the 140 patients. Of these 138, 125 (90.6%) had an elevated troponin. Of the 125 patients with elevated troponins, 68 (54.4%) experienced a MACE, while of the 13 patients with normal troponins, only 1 (7.7%) had a MACE (p=0.002). An elevated troponin was common and was not associated with increased MACE risk in the multivariable model (OR 2.54, 95% CI 0.69 to 10.83, p=0.17).

Rates for each of the four MACE components (cardiovascular death, cardiac arrest, cardiogenic shock, and complete heart block) were higher among patients with a QRS duration >110 ms than among those with a QRS duration ≤110 ms (figure 4). The most common MACE component in each was cardiovascular death (16.2% among those with QRS ≤110 ms, and 39.4% among those with QRS >110 ms).

Association of QTc interval with MACE

In contrast, a prolonged QTc-F interval was not associated with increased risk for MACE among men (HR 1.33, 95% CI 0.70 to 2.53, p=0.38) or women (HR 1.48, 95% CI 0.61 to 3.58, p=0.39) (figure 3B,C). We also tested the association using QTc interval values corrected for heart rate using the Bazett formula. With this approach, among men, a QTc-B of >450 ms was associated with an increased risk of MACE (HR 2.81, 95% CI 1.42 to 5.38, p=0.002) (online supplemental file 5A). Among women, a QTc-B duration of >460 ms was also associated with an increased risk of MACE (HR 3.00, 95% CI 1.08 to 8.32, log-rank p=0.03) (online supplemental file 5B).
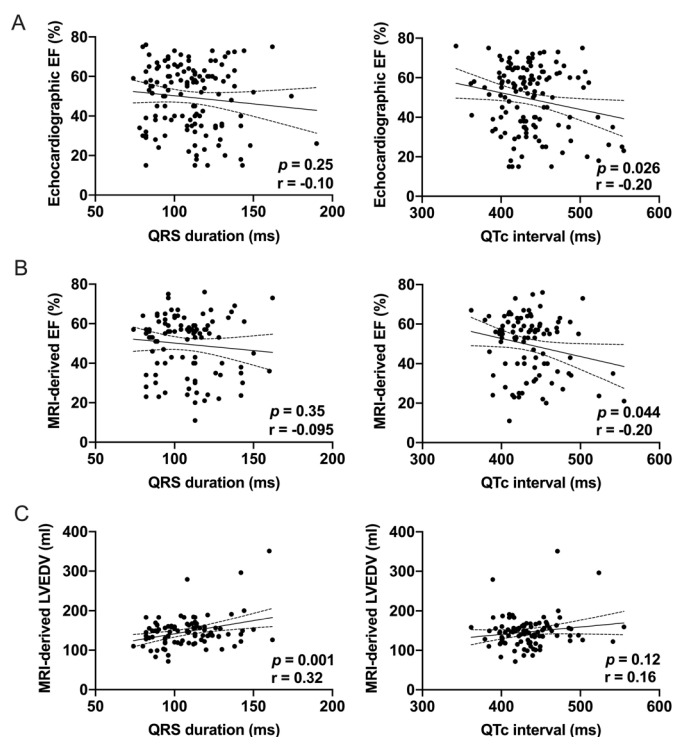
DISCUSSION

In this paper, we present novel findings describing increases in the QRS duration that may aid the diagnosis and risk-stratification of ICI myocarditis. This study has several unique and widely generalizable findings. First, we found that ICI myocarditis is associated with an unchanged PR interval but an increased QRS duration when compared with controls or cases at earlier time-points (both prior to the initiation of ICI therapy and on ICI therapy but prior to the development of myocarditis). The QTc-F interval was prolonged compared with on-ICI controls but not on-ICI cases. Second, the increase in ECG intervals correlated with structural (LVEDV) and functional (EF) changes in the heart. Third, prolongations
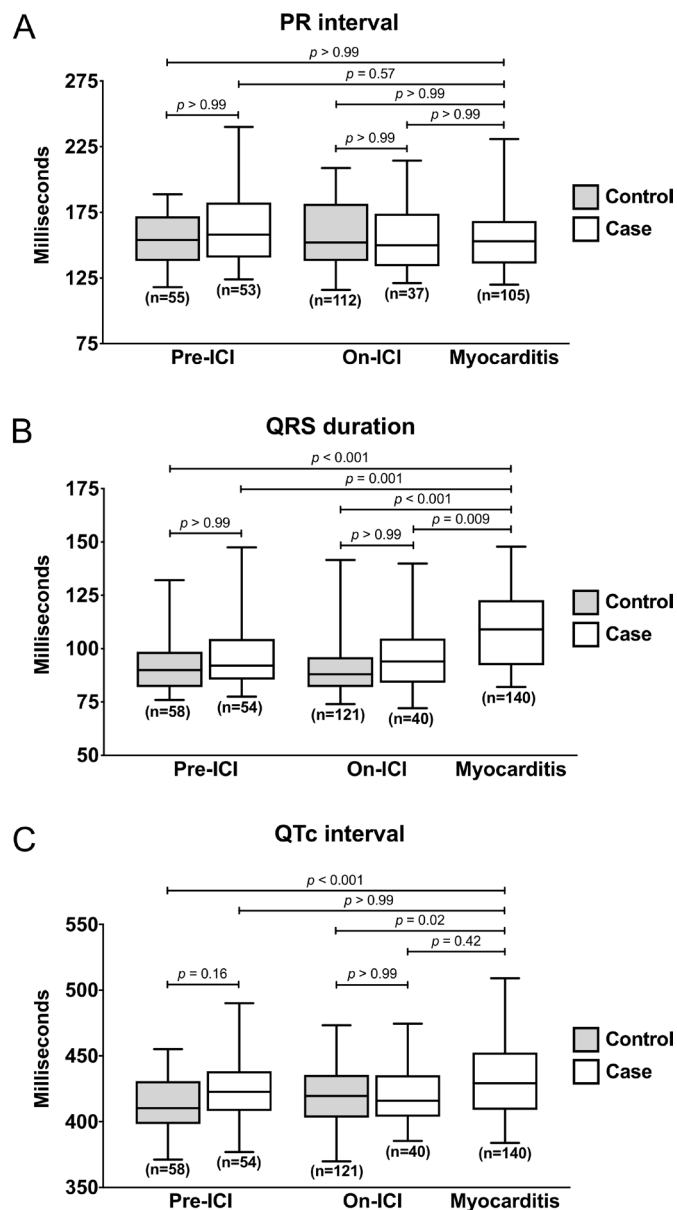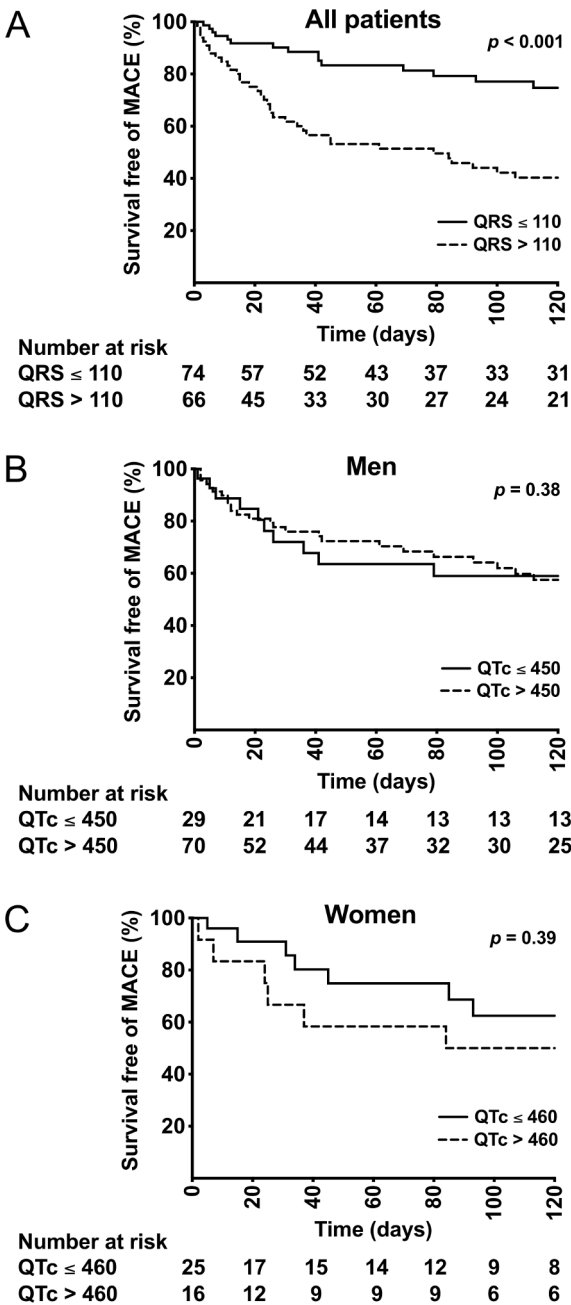
Figure 1 Changes in ECG parameters with ICI myocarditis. (A) PR interval, (B) QRS duration, and (C) QTc-F interval values were derived from ECGs obtained pre-ICI therapy ("baseline or pre-ICI"), after initiating ICI therapy ("on-ICI"), or at the time of myocarditis (for cases only; "myocarditis"). Shown are box-and-whisker plots with the central line indicating the median value, the margins of the box indicating the 25th/75th percentiles, and the whiskers indicating the 5th/95th percentiles. ICI, immune checkpoint inhibitor.

Figure 2 Relationship between ECG parameters, ejection fraction, and left ventricular volumes. (A) Scatter-plots of QRS duration (left) or QTc-F interval (right) versus echocardiographic left ventricular EF. Shown are the linear regression lines with their 95% CI. (B) Scatter-plots of QRS duration (left) or QTc-F interval (right) versus EF. (C) Scatter-plots of QRS duration (left) or QTc-F interval (right) versus LVEDV. EF, ejection fraction; LVEDV, left ventricular end-diastolic volume.

of QRS duration but not QTc-F interval at the time of myocarditis diagnosis were associated with an increased risk of MACE; specifically, a QRS duration >110 ms was associated with a 3.28-fold increased risk of MACE. This association between prolonged QRS duration and MACE persisted after adjustment for several cardiovascular covariates. Fourth, each of the individual components of MACE occurred more frequently in myocarditis patients with a prolonged QRS duration, with cardiovascular death the most common.

Despite its high morbidity, the diagnosis of ICI myocarditis can be challenging.[21 33–36] First, the presentation can be non-specific, both in terms of clinical symptoms and testing abnormalities.[7 13 21 34–36] Second, the utility of standard cardiac testing in the diagnosis and risk-stratification of ICI myocarditis is not yet well established.[21 35 36] Serum troponin levels, typically a hallmark of myocardial injury/myocarditis, may be only modestly elevated, may be elevated for other reasons, or, in rare cases, even normal.[7 13] Collectively, the available non-invasive diagnostic tests (including serum troponin levels, electrocardiography, and echocardiography) all fail to provide high specificity.[4 21 34 35 37] Third, the gold standard diagnostic test, endomyocardial biopsy, confers procedural risk that may be prohibitive for some patients and is not commonly performed.[35 38] Our study now provides novel data that the QRS duration and QTc interval may be used as part of a diagnostic algorithm. However, changes in these ECG parameters can too have limited specificity, highlighting the fact that no test can be interpreted in isolation. Rather, surveillance of these values may be an effective and rapid means of identifying ICI recipients who should receive additional, more specific, cardiovascular testing. Prospective data will be needed to demonstrate the efficacy of this approach.

A All patients

Survival free of MACE (%) vs Time (days)

$p < 0.001$

QRS ≤ 110
QRS > 110

Number at risk

QRS ≤ 110	74	57	52	43	37	33	31
QRS > 110	66	45	33	30	27	24	21

B Men

Survival free of MACE (%) vs Time (days)

$p = 0.38$

QTc ≤ 450
QTc > 450

Number at risk

QTC ≤ 450	29	21	17	14	13	13	13
QTC > 450	70	52	44	37	32	30	25

C Women

Survival free of MACE (%) vs Time (days)

$p = 0.39$

QTc ≤ 460
QTc > 460

Number at risk

QTC ≤ 460	25	17	15	14	12	9	8
QTC > 460	16	12	9	9	9	6	6

Figure 3 Association between QRS duration or QTc-F interval and MACE. (A) Kaplan-Meier curves indicate the occurrence of MACE over 120 days from time of diagnosis for myocarditis patients stratified by QRS duration. Similar analyses were performed for male (B) and female (C) myocarditis patients stratified by QTc-F interval as indicated. P value obtained from the log-rank test. MACE, major adverse cardiac events.

Table 2 Association with major adverse cardiac events (MACE) by multivariable analysis

Variable	OR	95% CI	P value
QRS duration	1.30	1.07 to 1.61	0.011
Age	1.01	0.98 to 1.04	0.61
Male sex	0.55	0.21 to 1.40	0.22
Hypertension	0.62	0.24 to 1.55	0.31
Diabetes mellitus	1.32	0.48 to 3.73	0.59
Coronary artery disease	0.34	0.07 to 1.36	0.14
Ejection fraction <50%	4.20	1.80 to 10.38	0.001
Elevated troponin	2.54	0.69 to 10.83	0.17

QRS duration was determined at the time of myocarditis diagnosis. For the QRS duration row, the OR reflects the MACE risk for an increase of 10 ms from the mean value across the myocarditis cohort. For the age row, the OR reflects the MACE risk for an increase of 1 year. For all other rows, the ORs reflect the MACE risk comparing those with the designated condition compared with those without.
OR, odds ratio.

duration or QTc interval were each associated with poor outcomes, though only a prolonged QRS duration was found to be an independent predictor after adjustment for covariates.[41] However, a more recent study of non-ICI myocarditis patients failed to find an association between QRS duration or QTc interval and adverse outcomes, though the sensitivity to detect an association was limited by a markedly lower adverse event rate.[42] As background, ICI myocarditis has a higher adverse event rate compared with other irAEs or non-ICI lymphocytic myocarditis, and therefore the prognostic associations of prolonged ECG parameters may be more easily identified.[3 14 15]

Cardiac inflammation alters intracardiac conduction patterns and can promote arrhythmogenesis.[43 44] This may occur through several non-mutually exclusive mechanisms: (1) interplay between immune cells and cardiac fibroblasts and/or cardiomyocytes, leading to fibrosis[45]; (2) direct participation of immune cells, namely macrophages, in cardiac conduction[46]; and (3) the effects of

Our study also suggests that the QRS duration may be used to risk-stratify ICI myocarditis patients. Prolongations of these values are associated with poor outcomes in a variety of conditions, including heart failure and acute myocardial infarction.[39 40] The prognostic significance of a prolonged QRS duration or QTc interval in non-ICI myocarditis is not clear. One study of patients with suspected myocarditis reported that a prolonged QRS

Figure 4 Frequency of MACE components. Frequencies of the indicated outcome among all myocarditis patients stratified by QRS duration are shown. Numbers at the end of each bar indicate the fraction of patients in each stratum with the indicated event. MACE, major adverse cardiac events.

autoantibodies and cytokines on cardiomyocyte ion channels.[47] In addition, patients with chronic inflammatory conditions have increased rates of conduction abnormalities, demonstrating that even inflammation outside the heart can affect cardiac conduction.[48 49]

In our analysis, the QT interval was corrected for heart rate using the Fridericia formula as this is more accurate than the commonly used Bazett formula and considered the most appropriate strategy by the US Food and Drug Administration.[22–24 50] The Bazett formula, however, remains frequently used in clinical practice, so we performed the same analysis using the Bazett-corrected QTc interval. With these values, an association between QTc-B interval and MACE was observed for both men and women, suggesting a potential role for the Bazett-corrected QTc interval towards ICI myocarditis risk stratification.

These findings should be interpreted within the overall limitations of the retrospective study design. First, the clinical data collection was not protocolized and was instead derived from medical records at each participating center, which in some cases led to incomplete data. Second, the timing of ECGs relative to ICI therapy initiation was not standardized, thereby leading to variability within each cohort. Third, we identified differences in the use of anti-PD-1 agents, anti-PD-L1 agents, and combination therapy between the control and myocarditis groups which may have confounded our results. Fourth, all controls were derived from a single center.

In summary, we observed prolongation of the QRS duration in the setting of ICI myocarditis. A QRS duration, but not QTc-F interval, greater than normal was associated with increased risk of MACE. These findings illustrate the potential diagnostic and prognostic value of easily obtained ECG parameters in ICI myocarditis.

Author affiliations
[1]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
[2]Cardiovascular Imaging Research Center (CIRC), Division of Cardiology and Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, USA
[3]Cardio-Oncology Program, Cardiology Division, NewYork-Presbyterian Hospital, Weill Cornell Medicine, New York, New York, USA
[4]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA
[5]Cardiology Division, Memorial Sloan Kettering Cancer Center, Weill Cornell Medicine, New York, New York, USA
[6]Cardio-Oncology Program, Division of Cardiology, Hopitaux Universitaires Est Parisien, Paris, France
[7]Cardio-Oncology Program, MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, Washington, DC, USA
[8]Cardio-Oncology Program, Division of Cardiovascular Medicine, H. Lee Moffitt Cancer Center & Research Institute and University of South Florida, Tampa, Florida, USA
[9]Department of Dermatology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany
[10]Discipline of Cardiology, Department of Medicine, Faculty of Medical Science, State University of Campinas, Campinas, Brazil
[11]Division of Oncology and Hematology, Department of Medicine, Lehigh Valley Hospital, Allentown, Pennsylvania, USA
[12]Cardiology Division, Mount Sinai Medical Center, New York, New York, USA
[13]Cardio-Oncology Program, Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia, USA
[14]Department of Translational Medical Sciences, Interdepartmental Center of Clinical and Translational Research (CIRCET), Interdepartmental Hypertension Research Center (CIRIAPA), Università degli Studi di Napoli Federico II, Naples, Italy
[15]Cardiology Department, Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red CardioVascular (CIBER-CV), Madrid, Spain
[16]Faculty of Medicine, University of Southampton, Southampton, UK
[17]Massachusetts General Hospital Cancer Center, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
[18]Cardio-Oncology Program, Division of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA
[19]UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, California, USA
[20]Department of Dermatology and Allergy, LMU Klinikum, Munich, Germany
[21]Mediterranean University Center of Cardio-Oncology, Aix-Marseille University, North Hospital, Marseille, France
[22]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[23]Cardio-Oncology Service, Royal Brompton Hospital and Imperial College London, London, UK
[24]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA
[25]Ted Rogers Program in Cardiotoxicity Prevention, Peter Munk Cardiac Center, Division of Cardiology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada

Twitter Amna Zafar @AZafar_MD, Dahlia Banerji @DahliaBanerjiMD, Eduardo Zatarain-Nicolás @EduZatarain, Franck Thuny @franckthuny and Tomas G Neilan @ TomasNeilan

ORCID iDs
Daniel A Zlotoff http://orcid.org/0000-0001-9007-7295
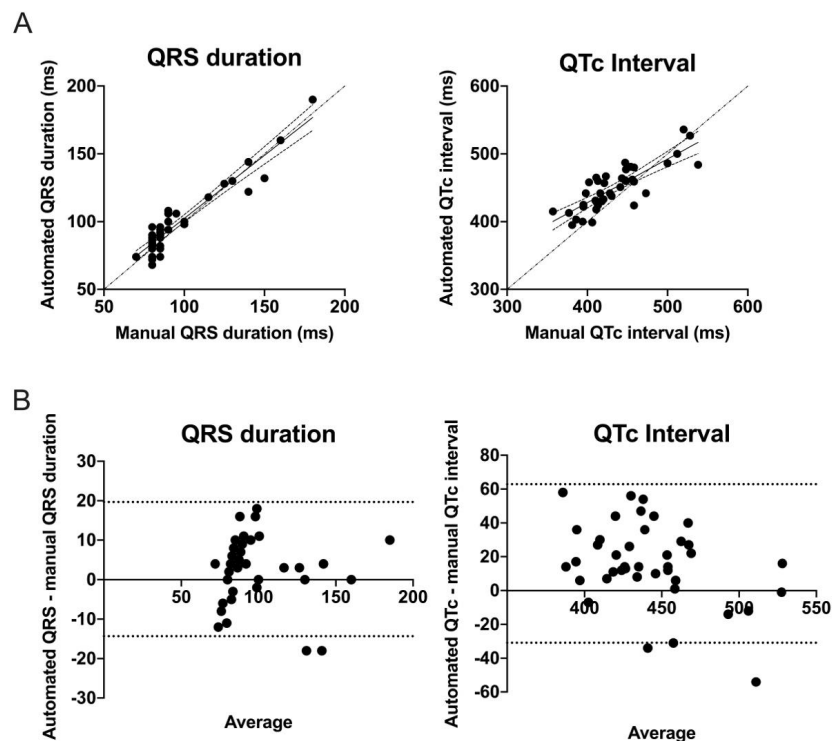Franck Thuny http://orcid.org/0000-0002-8727-7154

REFERENCES

1 Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell* 2015;27:450–61.
2 Postow MA, Sidlow R, Hellmann MD. Immune-Related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018;378:158–68.
3 Wang DY, Salem J-E, Cohen JV, *et al*. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol* 2018;4:1721–8.
4 Hu J-R, Florido R, Lipson EJ, *et al*. Cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res* 2019;115:854–68.
5 Awadalla M, Golden DLA, Mahmood SS, *et al*. Influenza vaccination and myocarditis among patients receiving immune checkpoint inhibitors. *J Immunother Cancer* 2019;7:53.
6 Salem J-E, Manouchehri A, Moey M, *et al*. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018;19:1579–89.
7 Mahmood SS, Fradley MG, Cohen JV, *et al*. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;71:1755–64.
8 Zhang L, Jones-O'Connor M, Awadalla M, *et al*. Cardiotoxicity of immune checkpoint inhibitors. *Curr Treat Options Cardiovasc Med* 2019;21:32.
9 Ganatra S, Neilan TG. Immune checkpoint inhibitor-associated myocarditis. *Oncologist* 2018;23:879–86.
10 Johnson DB, Balko JM, Compton ML, *et al*. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375:1749–55.
11 Drobni ZD, Alvi RM, Taron J, *et al*. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. *Circulation* 2020;142:2299–311.
12 Ederhy S, Cautela J, Ancedy Y, *et al*. Takotsubo-Like Syndrome in Cancer Patients Treated With Immune Checkpoint Inhibitors. *JACC Cardiovasc Imaging* 2018;11:1187–90.
13 Escudier M, Cautela J, Malissen N, *et al*. Clinical features, management, and outcomes of immune checkpoint Inhibitor-Related cardiotoxicity. *Circulation* 2017;136:2085–7.
14 Grün S, Schumm J, Greulich S, *et al*. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol* 2012;59:1604–15.
15 Gräni C, Eichhorn C, Bière L, *et al*. Prognostic Value of Cardiac Magnetic Resonance Tissue Characterization in Risk Stratifying Patients With Suspected Myocarditis. *J Am Coll Cardiol* 2017;70:1964–76.
16 Neilan TG, Rothenberg ML, Amiri-Kordestani L, *et al*. Myocarditis associated with immune checkpoint inhibitors: an expert consensus on data gaps and a call to action. *Oncologist* 2018;23:874–8.
17 Alvi RM, Frigault MJ, Fradley MG, *et al*. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol* 2019;74:3099–108.
18 Heymans S, Eriksson U, Lehtonen J, *et al*. The Quest for New Approaches in Myocarditis and Inflammatory Cardiomyopathy. *J Am Coll Cardiol* 2016;68:2348–64.
19 Sagar S, Liu PP, Cooper LT. Myocarditis. *Lancet* 2012;379:738–47.
20 Porta-Sánchez A, Gilbert C, Spears D, *et al*. Incidence, diagnosis, and management of QT prolongation induced by cancer therapies: a systematic review. *J Am Heart Assoc* 2017;6. doi:10.1161/JAHA.117.007724. [Epub ahead of print: 07 Dec 2017].

21 Awadalla M, Mahmood SS, Groarke JD, *et al*. Global longitudinal strain and cardiac events in patients with immune checkpoint Inhibitor-Related myocarditis. *J Am Coll Cardiol* 2020;75:467–78.
22 Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. 1920. *Ann Noninvasive Electrocardiol* 2003;8:343–51.
23 Muluneh B, Richardson DR, Hicks C, *et al*. Trials and tribulations of corrected QT interval monitoring in oncology: rationale for a Practice-Changing standardized approach. *J Clin Oncol* 2019;37:2719–21.
24 US Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for Non-Antiarrhythmic drugs — questions and answers (R3), 2017. Available: https://www.fda.gov/media/71379/download
25 Surawicz B, Childers R, Deal BJ, *et al*. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part III: intraventricular conduction disturbances: a scientific statement from the American heart association electrocardiography and arrhythmias Committee, Council on clinical cardiology; the American College of cardiology Foundation; and the heart rhythm Society. endorsed by the International Society for computerized Electrocardiology. *J Am Coll Cardiol* 2009;53:976–81.
26 Rautaharju PM, Surawicz B, Gettes LS, *et al*. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American heart association electrocardiography and arrhythmias Committee, Council on clinical cardiology; the American College of cardiology Foundation; and the heart rhythm Society. endorsed by the International Society for computerized Electrocardiology. *J Am Coll Cardiol* 2009;53:982–91.
27 Caforio ALP, Pankuweit S, Arbustini E, *et al*. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of cardiology Working group on myocardial and pericardial diseases. *Eur Heart J* 2013;34:2636–48. 48a-48d.
28 Ammirati E, Cipriani M, Moro C, *et al*. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: multicenter Lombardy registry. *Circulation* 2018;138:1088–99.
29 Hicks KA, Tcheng JE, Bozkurt B, *et al*. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American heart association Task force on clinical data standards (writing Committee to develop cardiovascular endpoints data standards). *J Am Coll Cardiol* 2015;66:403–69.
30 Neilan TG, Farhad H, Mayrhofer T, *et al*. Late gadolinium enhancement among survivors of sudden cardiac arrest. *JACC Cardiovasc Imaging* 2015;8:414–23.
31 Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation* 2008;117:686–97.
32 Therneau TM, Grambsch PM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;81:515–26.
33 Trachtenberg B, Hussain F, Mukherjee A. Immune checkpoint Inhibitor-Related cardiotoxicity. *Methodist Debakey Cardiovasc J* 2018;14:e1–4.
34 Zhang L, Zlotoff DA, Awadalla M, *et al*. Major adverse cardiovascular events and the timing and dose of corticosteroids in immune checkpoint inhibitor-associated myocarditis. *Circulation* 2020;141:2031–4.
35 Zhang L, Awadalla M, Mahmood SS, *et al*. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. *Eur Heart J* 2020;41:1733–43.
36 Norwood TG, Westbrook BC, Johnson DB, *et al*. Smoldering myocarditis following immune checkpoint blockade. *J Immunother Cancer* 2017;5:91.
37 Sarocchi M, Grossi F, Arboscello E, *et al*. Serial troponin for early detection of nivolumab cardiotoxicity in advanced non-small cell lung cancer patients. *Oncologist* 2018;23:936–42.
38 Shah M, Tayar JH, Abdel-Wahab N, *et al*. Myositis as an adverse event of immune checkpoint blockade for cancer therapy. *Semin Arthritis Rheum* 2019;48:736–40.
39 Lund LH, Jurga J, Edner M, *et al*. Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction. *Eur Heart J* 2013;34:529–39.
40 Yerra L, Anavekar N, Skali H, *et al*. Association of QRS duration and outcomes after myocardial infarction: the VALIANT trial. *Heart Rhythm* 2006;3:313–6.

41 Ukena C, Mahfoud F, Kindermann I, *et al*. Prognostic electrocardiographic parameters in patients with suspected myocarditis. *Eur J Heart Fail* 2011;13:398–405.

42 Chen S, Hoss S, Zeniou V, *et al*. Electrocardiographic predictors of morbidity and mortality in patients with acute myocarditis: the importance of QRS-T angle. *J Card Fail* 2018;24:3–8.

43 Swirski FK, Nahrendorf M. Cardioimmunology: the immune system in cardiac homeostasis and disease. *Nat Rev Immunol* 2018;18:733–44.

44 Lazzerini PE, Laghi-Pasini F, Boutjdir M, *et al*. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. *Nat Rev Immunol* 2019;19:63–4.

45 Suthahar N, Meijers WC, Silljé HHW, *et al*. From inflammation to Fibrosis-Molecular and cellular mechanisms of myocardial tissue remodelling and perspectives on differential treatment opportunities. *Curr Heart Fail Rep* 2017;14:235–50.

46 Hulsmans M, Clauss S, Xiao L, *et al*. Macrophages facilitate electrical conduction in the heart. *Cell* 2017;169:510–22. e20.

47 Lazzerini PE, Capecchi PL, Laghi-Pasini F, *et al*. Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. *Nat Rev Cardiol* 2017;14:521–35.

48 Seferović PM, Ristić AD, Maksimović R, *et al*. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. *Rheumatology* 2006;45 Suppl 4:iv39–42.

49 Prasad M, Hermann J, Gabriel SE, *et al*. Cardiorheumatology: cardiac involvement in systemic rheumatic disease. *Nat Rev Cardiol* 2015;12:168–76.

50 Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353–70.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)
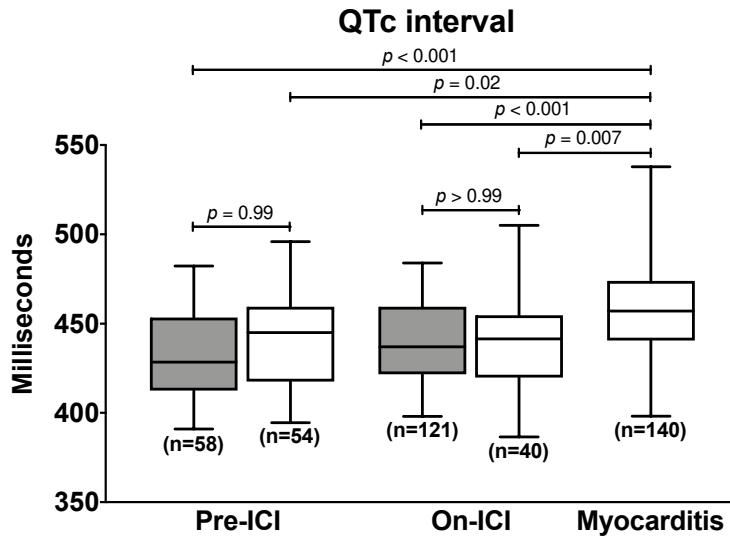
J Immunother Cancer

SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Relationship between automated and manual ECG measurements.

40 ECGs (20 from controls and 20 from cases at time of myocarditis) were randomly selected and a blinded reader manually measured the QRS duration and QTc interval. (A) Scatter-plots of manual vs automated QRS duration (left) and QTc interval measurements (right). Each dot represents a single ECG. The line of linear regression (solid line) and its 95% CI is shown (dashed line), along with the line of identity (alternating dashes/dots line). The slope of the linear regression line for the QRS data was 0.93 (95% CI 0.82 to 1.04), and for QTc data was 0.64 (95% CI 0.50 to 0.79). (B) Bland-Altman plots depicting the same data. The dotted lines represent the 95% limits of agreement. QRS measurements showed a bias of +2.7 ms towards the automated values (95% limits of agreement -14.3 to 19.7); the QTc measurements showed a bias of +16 ms towards the automated values (95% limits of agreement -30.9 to 62.9).

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

J Immunother Cancer

Supplemental Figure 2. QTc interval changes (corrected by Bazett) with ICI myocarditis.

QTc interval values were derived from ECGs obtained pre-ICI therapy ("Pre-ICI"), after initiating ICI therapy ("On-ICI"), or at the time of myocarditis (for cases only; "Myocarditis"). Shown are box-and-whisker plots with the central line indicating the median value, the margins of the box indicating the 25th/75th percentiles, and the whiskers indicating the 5th/95th percentiles.

	QRS duration (ms)			ΔQRS (ms)		
	>110	>120	>130	>10	>20	>30
Sensitivity (%)	48.6	27.9	16.4	51.7	31.0	21.6
Specificity (%)	87.0	90.1	92.6	n/a	n/a	n/a

Supplemental Table 1. Sensitivities and specificities of QRS duration towards the diagnosis of myocarditis. QRS duration was measured at time of diagnosis of myocarditis. ΔQRS is equal to the QRS duration at time of myocarditis minus the QRS duration at baseline prior to myocarditis.
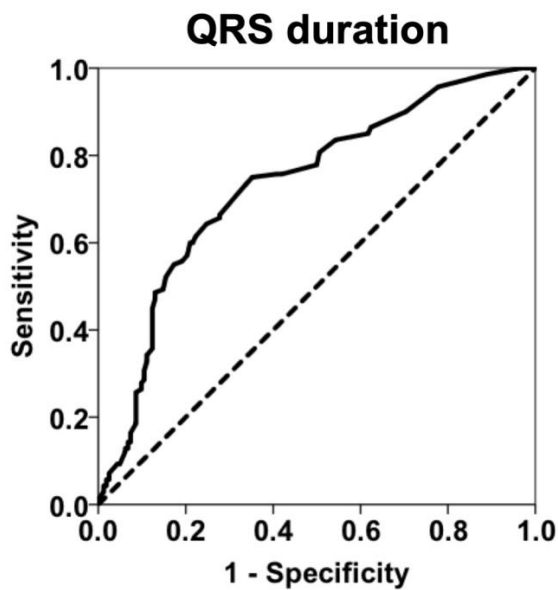
Supplemental Figure 3. Receiver operating characteristic (ROC) curve. (A) ROC curve for QRS duration towards the diagnosis of ICI myocarditis for all patients in the myocarditis cohort. Area under the curve is 0.73.
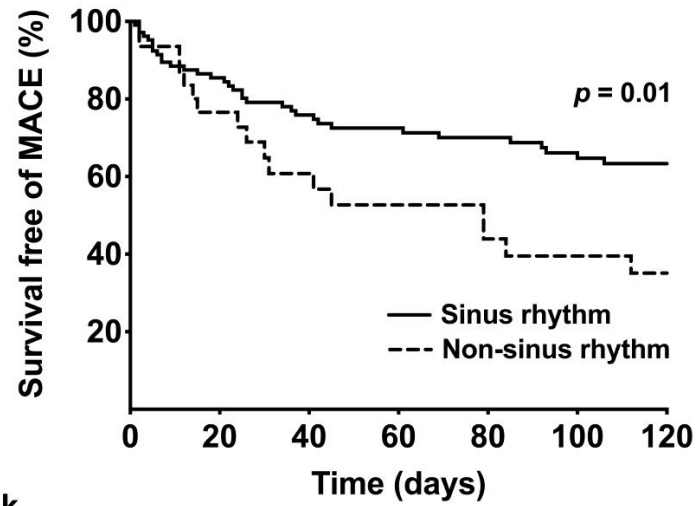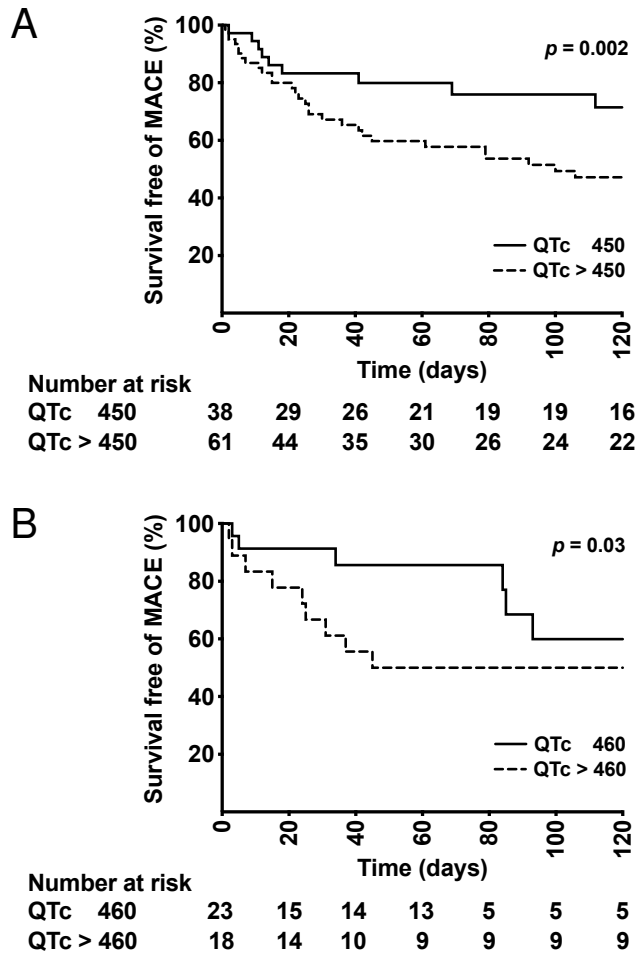
Supplemental Figure 4. Association between rhythm at presentation and MACE risk.

Kaplan-Meier curves indicate the occurrence of MACE over 120 days from time of diagnosis for myocarditis patients stratified by type of rhythm at presentation.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

J Immunother Cancer

Supplemental Figure 5. Association between QTc interval (corrected by Bazett) and MACE risk. Kaplan-Meier curves indicate the occurrence of MACE over 120 days from time of diagnosis for male (A) and female (B) myocarditis cases stratified by QTc interval at presentation.