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CLINICAL RESEARCH

Association of early electrical changes with cardiovascular outcomes in immune checkpoint inhibitor myocarditis☆

Apport de l'ECG dans la prédiction des événements cardiovasculaires associés aux myocardites induites par les inhibiteurs de point de contrôle immunitaire

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Abbreviations: ACR, Acute Cellular Rejection; aHR, Adjusted Hazard Ratio; aHR(sh), Adjusted Hazard Ratio by subdistribution hazards model; CI, Confidence Interval; ICI, Immune Checkpoint Inhibitor; ICI-myocarditis, immune Checkpoint Inhibitor-associated Myocarditis; IQR, Interquartile Range; PVC, Premature Ventricular Complex; QTc, corrected QT interval.

☆ Tweet: ECG changes predict cardiovascular outcomes in ICI myocarditis.

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KEYWORDS
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Summary
Background. — Immune-checkpoint inhibitor-associated myocarditis (ICI-myocarditis) often presents with arrhythmias, but the prognostic value of early electrocardiogram findings is unclear. Although ICI-myocarditis and acute cellular rejection (ACR) following cardiac transplantation use similar treatment strategies, differences in arrhythmia burden are unknown.
Objective. — To evaluate the association of electrocardiogram findings in ICI-myocarditis with myocarditis-related mortality and life-threatening arrhythmia.
Methods. — A total of 125 cases of ICI-myocarditis were identified retrospectively across 49 hospitals worldwide; 50 cases of grade 2R or 3R ACR were included as comparators. Two cardiologists blinded to clinical data interpreted electrocardiograms. Associations between electrocardiogram features, myocarditis-related mortality and the composite of myocarditis-related mortality and life-threatening arrhythmias were examined. Adjusted hazard ratios (aHRs) were calculated.
Results. — The cohort had 78 (62.4%) men; median (interquartile range) age was 67 (58—76) years. At 30 days, myocarditis-related mortality was 20/124 (16.1%), and 28/124 (22.6%) met the composite endpoint. Patients who developed complete heart block (aHR by subdistribution hazards model [aHR(sh)] 3.29, 95% confidence interval [CI] 1.24—8.68; $P = 0.02$) or life-threatening cardiac arrhythmias (aHR(sh) 6.82, 95% CI: 2.87—16.21; $P < 0.001$) had a higher risk of myocarditis-related mortality. Pathological Q waves (aHR(sh) 3.40, 95% CI: 1.38—8.33; $P = 0.008$), low QRS voltage (aHR(sh) 6.05, 95% CI: 2.10—17.39; $P < 0.001$) and Sokolow-Lyon index (aHR(sh)/mV 0.54, 95% CI: 0.30—0.97; $P = 0.04$) on admission electrocardiogram were also associated with increased risk of myocarditis-related mortality. These associations were mirrored in the composite outcome analysis. Compared with ACR, ICI-myocarditis had a higher incidence of life-threatening cardiac arrhythmias (15/125 [12.0%] vs 1/50 [2%]; $P = 0.04$) and third-degree heart block (19/125 [15.2%] vs 0/50 [0%]; $P = 0.004$).
Conclusions. — Electrocardiograms in ICI-myocarditis with ventricular tachycardias, heart block, low-voltage and pathological Q waves were associated with myocarditis-related mortality and life-threating arrhythmia. Arrhythmia burden in ICI-myocarditis exceeds that of ACR after heart transplant.

MOTS CLÉS
Myocardite ;
Cardio-oncologie ;
Immunothérapie ;
Électrophysiologie

Résumé
Contexte. — Les myocardites induites par les inhibiteurs de point de contrôle immunitaire (ICI) sont souvent compliquées d'arythmies cardiaques. Néanmoins, la valeur prédictive des anomalies ECG dans ce contexte reste à définir. Les myocardites-ICI et les rejets aiguës cellulaires (ACR) au décours de la transplantation cardiaque ont des physiopathologies et des traitements similaires, mais leurs différences en termes de pro-arythmogenicité cardiaque est inconnue.
Objectifs. — Évaluer l'apport de l'ECG dans la prédiction de la mortalité associée aux myocardites-ICI et du risque de survenue d'arythmies cardiaques potentiellement mortelles.
Méthodes. — Un total de 125 cas de myocardites-ICI ont été identifiés rétrospectivement dans 49 hôpitaux internationaux. Un total de 50 cas d'ACR de grade 2R ou 3R ont été inclus comme comparateurs. Deux cardiologues en aveugle des données cliniques ont interprété les ECG. Les associations entre les caractéristiques de l'ECG, la mortalité liée à la myocardite et le

composite de la mortalité liée à la myocardite et d'arythmies potentiellement mortelles ont été examinées.
Résultats. — La cohorte était composée de 78 (62,4 %) hommes avec un âge médian de 67 ans (IQR = 58—76). À 30 jours, la mortalité liée à la myocardite était de 20/124 (16,1 %) et l'incidence du critère composite était de 28/124 (22,6 %). Les patients ayant développé un bloc auriculo-ventriculaire complet (aHR(sh) = 3,29(1,24—8,68), $p = 0,02$) ou des arythmies cardiaques potentiellement mortelles (aHR(sh) = 6,82(2,87—16,21), $p < 0,001$) avaient un risque plus élevé de mortalité liée à la myocardite. La présence d'ondes Q pathologiques (aHR(sh)) = 3,40(1,38—8,33), $p = 0,008$) ; le microvoltage (aHR(sh) = 6,05(2,10—17,39), $p < 0,001$) et l'indice de Sokolow-Lyon (aHR(sh)/mV = 0,54(0,30—0,97), $p = 0,04$) à l'ECG d'admission étaient également associé à un risque accru de mortalité liée à la myocardite. Comparativement à l'ACR, la myocardite-ICI avait une incidence plus élevée d'arythmies cardiaques menaçant le pronostic vital (15/125 (12,0 %) contre 1/50 (2 %) ; $p = 0,04$) et de bloc auriculo-ventriculaire du troisième degré (19/125 (15,2 %) vs 0/50 (0 %) ; $p = 0,004$).
Conclusions. — L'identification sur l'ECG des myocardites-ICI de tachycardies ventriculaires, de bloc auriculo-ventriculaires de haut degré, de microvoltage et d'ondes Q pathologiques sont prédictifs de la mortalité liée à la myocardite. L'arythmogenicité des myocardites-ICI est supérieure à celle de l'ACR en post-transplantation cardiaque.

Background

Cancer treatment has been revolutionized by immune checkpoint inhibitors (ICIs), with nearly 50% of patients with cancer eligible for ICIs [1]. ICIs harness the immune system to attack cancer cells, with a rare, but major, side effect of T cell- and macrophage-mediated myocarditis [2—6]; this immune-related adverse event occurs in 0.3% to 1.1% of ICI recipients, and can result in cardiogenic shock and fatal arrhythmias [4,6]. Recently, presenting electrocardiogram changes in immune checkpoint inhibitor-associated myocarditis (ICI-myocarditis), such as low voltage, pathological Q waves and prolonged QRS, have been associated with all-cause mortality [15]. However, given the competing risks for mortality in critically ill cancer patients, the link between these electrical disturbances and cardiac deterioration is not clear.

The primary purpose of this paper is to investigate the association of electrocardiographic findings with myocarditis-related mortality and life-threatening cardiac arrhythmia. As a secondary analysis, this study also compares electrocardiograms in patients with ICI-myocarditis with electrocardiograms in heart transplant recipients diagnosed with acute cellular rejection (ACR). Although fundamental mechanistic differences between the two cohorts prevents this comparison from yielding pathophysiological insights, comparing ICI-myocarditis with ACR highlights differences in the clinical burden of arrhythmia between two conditions that utilize similar corticosteroid and anti-T cell immunosuppression strategies [3,5,9—14].

Methods

ICI-myocarditis selection

A retrospective multicentre registry spanning 49 institutions across 11 countries (Table A.1) was used to collect 125 cases of ICI-myocarditis where presenting electrocardiograms were available. The characteristics of this cohort have been described previously [15]. 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. Clinical data, including incidence of arrhythmias throughout hospitalization, were collected and shared by participating collaborators via a Health Insurance Portability and Accountability Act (HIPPA)-compliant REDCap web-based platform (IRB: 181337; ClinicalTrials.gov Identifier: NCT04294771) [16,17].

Cases were included if they met European Society of Cardiology criteria for clinically suspected myocarditis with recent ICI exposure [18]. Cases were excluded if the electrocardiogram obtained within 3 days of admission was unavailable for independent review or exclusively captured paced or ventricular rhythms. When multiple presenting electrocardiograms were available, the electrocardiogram closest to presentation and without complete heart block or supraventricular arrhythmias was used preferentially, as this allowed for more complete electrocardiogram quantitative interpretation.

ACR selection

Heart transplants at Vanderbilt University Medical Center complicated by grade 2R or 3R ACR were selected in reverse chronological order, and spanned 2013—2019 [19]. Cases of concomitant humoral rejection were excluded. Electrocardiograms obtained < 10 days after heart transplantation or > 3 days from diagnostic endomyocardial biopsy were excluded. Donor and recipient characteristics were collected via chart review and the Organ Procurement and Transplantation Network database.

Electrocardiogram interpretation

Two cardiologists (B. O. and J. A.), blinded to the clinical data, systematically quantified standard electrocardiogram intervals (PR, QRS, corrected QT interval [QTc],

Sokoloff-Lyon index; after excluding premature ventricular complexes [PVCs]), and evaluated relevant qualitative features. Electrocardiogram features were aggregated based on pathophysiological relatedness (Table A.2). Inter- and intraobserver variabilities were excellent (intraclass correlation > 0.8) for PR, QRS, QTc and Sokoloff-Lyon index measurements (Fig. A.1).

Outcomes

The primary outcome was myocarditis-related mortality within 30 days. The secondary outcome was a composite of either myocarditis-related death or life-threatening cardiac arrhythmia (defined as sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes, pulseless electrical activity or asystole) within 30 days.

Statistical analysis

Non-parametric Wilcoxon (for quantitative data) and χ^2 (for qualitative data) tests were used to compare electrocardiogram features in ICI-myocarditis and ACR.

The primary outcome (myocarditis-related mortality within 30 days) analysis used features on the presenting electrocardiogram as the independent variable. As this methodology preferentially selected for electrocardiograms that did not exclusively capture heart block, life-threatening cardiac 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 both outcomes. In both analyses, the Cox proportional-hazards model determined association with all-cause mortality over the 30-day surveillance period. Competing risk analysis (subdistribution hazards model, i.e. the Fine-Gray model) was used to account for mortality resulting from causes other than myocarditis. These models were adjusted for age and sex in a multivariable analysis. Adjusted hazard ratios (aHRs), 95% confidence intervals (CIs) and cumulative incidence curves are presented.

Results

Demographics and electrocardiographic abnormalities

The 125 patients with ICI-myocarditis had a median (interquartile range [IQR]) age of 67 (58—76) years, and 78/125 (62.4%) were male (Table 1). The median (IQR) number of days from first ICI dose to myocarditis presentation was 38 (22—83) days. In 124 patients with 30-day surveillance, 30/124 (24.2%) died within 30 days of presentation; 20 of these 30 deaths (66.7%) were attributable to myocarditis. Other leading causes of death included cancer progression (6/30, 20%), sepsis (4/30, 13%) and non-cardiac immune-related adverse event (6/30, 20.0%; five of which [83.3%] were attributable to non-cardiac myotoxicities [e.g. myositis]). Pacemakers and/or defibrillators were placed in 18/124 (14.5%) patients within 30 days of presentation.

In total, 116/125 (92.8%) patients had an abnormal electrocardiogram during hospitalization. Throughout hospitalization (median 10 days; IQR 6—23 days), 87/125 (69.6%) patients experienced conduction disorders, including second-degree heart block (9/125, 7.2%) and complete heart block (19/125, 15.2%). Of note, 30/125 (24.0%) patients experienced supraventricular arrhythmias during the study period. A total of 15/125 (12.0%) patients experienced life-threatening cardiac arrhythmias, including sustained ventricular tachycardia (9/125, 7.2%), ventricular fibrillation (4/125, 3.2%), torsade de pointes (2/125, 1.6%), pulseless electrical activity (4/125, 3.2%) and asystole (4/125, 3.2%). There was no association between previous cardiovascular disease and the development of life-threatening cardiac arrhythmia (Table 1). A total of 7/125 (5.6%) patients developed both complete heart block and a life-threatening cardiac arrhythmia.

Serial electrocardiograms for one patient with ICI-myocarditis who developed ventricular arrhythmia are presented as an illustrative example (Fig. 1) [20].

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 (9/19 [47%] vs 21/105 [20.0%]; aHR (adjusted on age and sex) 2.91, 95% CI: 1.30—6.47; $P = 0.009$) or life-threatening cardiac arrhythmias (8/15 [53%] vs 13/109 [11.9%]; aHR 3.61, 95% CI: 1.59—8.20; $P = 0.002$) at any point during hospitalization.

Additionally, myocarditis-related mortality within 30 days was more common in patients who developed complete heart block (7/19 [37%] vs 13/105 [12.4%]; aHR (adjusted on age and sex) by subdistribution hazards model [aHR(sh)] 3.29, 95% CI: 1.24—8.68; $P = 0.02$) or life-threatening cardiac arrhythmias (8/15 [53%] vs 12/109 [11.0%]; aHR(sh) 6.82, 95% CI: 2.87—16.21; $P < 0.001$) (cumulative incidence curves are shown in Fig. 2).

Supraventricular arrhythmia during hospitalization was not associated with either myocarditis-related mortality (7/30 [23%] vs 13/94 [14%]; aHR(sh) 1.95, 95% CI: 0.74—5.15; $P = 0.18$) or composite outcome (9/30 [30%] vs 19/94 [20.2%]; aHR(sh) 1.80, 95% CI: 0.81—4.01; $P = 0.15$) within 30 days. The composite outcome of myocarditis-related mortality or life-threatening cardiac arrhythmia within 30 days was also more common in patients who experienced complete heart block (9/19 [47%] vs 19/105 [18.1%]; aHR(sh) 4.43, 95% CI: 1.85—10.59; $P < 0.001$) (Fig. A.2).

Outcome analysis by presenting electrocardiogram features

Using survival analyses, 30-day myocarditis-related mortality was significantly associated with a presenting electrocardiogram that had pathological Q waves (7/19 [37%] vs 13/106 [12.3%]; aHR(sh) 3.40, 95% CI: 1.38—8.33; $P = 0.008$) and low QRS voltage (3/6 [50%] vs 17/119 [14.3%]; aHR(sh) 6.05, 95% CI: 2.10—17.39; $P < .001$), and had an inverse association with Sokolow-Lyon index (aHR(sh)/mV 0.54, 95% CI: 0.30—0.97; $P = 0.04$) (cumulative incidence curves are shown in Fig. 3, model results in Table 2 and cumulative incidence curves by Sokolow-Lyon index in Fig. 4).

Table 1 Immune checkpoint inhibitor-associated myocarditis baseline characteristics and outcomes.

	Total	Did not develop life-threatening cardiac arrhythmia	Developed life-threatening cardiac arrhythmia	*P*
	(*n* = 125)	(*n* = 110)	(*n* = 15)	
Age (years)	67 (58—76)	68.5 (58.0—77.0)	65.0 (59.0—71.0)	0.39
Female sex	47/125 (37.6)	40/110 (36.4)	7/15 (46.7)	0.44
Body mass index	25.4 (21.4—29.1)	25.1 (21.2—28.3)	32.7 (22.6—34.1)	0.045
Hyperlipidaemia	43/119 (36.1)	38/106 (35.8)	5/13 (38.5)	0.85
Diabetes	20/119 (16.8)	19/106 (17.9)	1/13 (7.7)	0.35
Hypertension	64/120 (53.3)	58/107 (54.2)	6/13 (46.2)	0.58
Previous tobacco user	62/119 (52.1)	54/106 (50.9)	8/13 (61.5)	0.47
Pre-existing stroke	4/120 (3.3)	4/107 (3.7)	0/13 (0.0)	0.48
Pre-existing PVD	9/119 (7.6)	9/106 (8.5)	0/13 (0.0)	0.27
Pre-existing CAD	25/120 (20.8)	22/107 (20.6)	3/13 (23.1)	0.83
Pre-existing heart failure	16/120 (13.3)	16/106 (15.1)	0/14 (0.0)	0.12
One or more traditional cardiovascular risk factors[a]	98/120 (81.7)	87/107 (81.3)	11/13 (84.6)	0.77
History of cardiac disease[b]	32/119 (26.9)	29/106 (27.4)	3/13 (23.1)	0.74
History of cardiovascular disease[c]	76/119 (63.9)	68/106 (64.2)	8/13 (61.5)	0.85
Index ICI therapy category				0.35
Anti CTLA-4 & PD1/PDL1 combination	22/125 (17.6)	18/110 (16.4)	4/15 (26.7)	
Anti CTLA-4 monotherapy	34/125 (27.2)	32/110 (29.1)	2/15 (13.3)	
Anti PD1/PDL1 monotherapy	69/125 (55.2)	60/110 (54.5)	9/15 (60.0)	
Days from first ICI dose to hospital admission	38.0 (22.0—83.0)	40.0 (23.5—88.0)	20.0 (15.0—32.0)	0.004
Days from last ICI dose to hospital admission	15.5 (9.0—22.0)	16.0 (9.0—24.0)	12.0 (9.5—17.0)	0.09
Number of ICI doses received	2 (1—4)	2 (1—4)	2 (1—3)	0.17
Cancer type				0.95
Bladder cancer	4/125 (3.2)	3/110 (2.7)	1/15 (6.7)	
Breast cancer	1/125 (0.8)	1/110 (0.9)	0/15 (0.0)	
Kidney cancer	13/125 (10.4)	10/110 (9.1)	3/15 (20.0)	
Leukaemia	2/125 (1.6)	2/110 (1.8)	0/15 (0.0)	
Lung cancer	45/125 (36.0)	41/110 (37.3)	4/15 (26.7)	
Non-Hodgkin lymphoma	1/125 (0.8)	1/110 (0.9)	0/15 (0.0)	
Prostate cancer	2/125 (1.6)	2/110 (1.8)	0/15 (0.0)	
Melanoma	32/125 (25.6)	28/110 (25.5)	4/15 (26.7)	
Thymic cancer (non-thymoma)	1/125 (0.8)	1/110 (0.9)	0/15 (0.0)	
Oesophageal cancer	3/125 (2.4)	2/110 (1.8)	1/15 (6.7)	
Gastric cancer	2/125 (1.6)	2/110 (1.8)	0/15 (0.0)	
Colorectal cancer	1/125 (0.8)	1/110 (0.9)	0/15 (0.0)	
Endometrial cancer	1/125 (0.8)	1/110 (0.9)	0/15 (0.0)	
Hepatocellular carcinoma	2/125 (1.6)	2/110 (1.8)	0/15 (0.0)	
Cholangiocarcinoma	1/125 (0.8)	1/110 (0.9)	0/15 (0.0)	
Squamous cell carcinoma	3/125 (2.4)	2/110 (1.8)	1/15 (6.7)	
Other cancer	7/125 (5.6)	7/110 (6.4)	0/15 (0.0)	
Mesothelioma	1/125 (0.8)	1/110 (0.9)	0/15 (0.0)	
Thymoma	3/125 (2.4)	2/110 (1.8)	1/15 (6.7)	
At least one other concomitant immune-related AE	82/125 (65.6)	69/110 (62.7)	13/15 (86.7)	0.07
Concomitant immune-related AE: myasthenia gravis-like syndrome	27/125 (21.6)	21/110 (19.1)	6/15 (40.0)	0.07
Concomitant immune-related AE: immune-related myositis/rhabdomyolysis	39/125 (31.2)	32/110 (29.1)	7/15 (46.7)	0.17
Abnormal ECG	116/125 (92.8)	101/110 (91.8)	15/15 (100.0)	0.25

Table 1 (*Continued*)

	Total	Did not develop life-threatening cardiac arrhythmia	Developed life-threatening cardiac arrhythmia	*P*
	(*n* = 125)	(*n* = 110)	(*n* = 15)	
Abnormal troponin	107/117 (91.5)	93/102 (91.2)	14/15 (93.3)	0.78
Initial troponin > 10× upper limit of normal	74/112 (66.1)	61/98 (62.2)	13/14 (92.9)	0.02
Reduced LVEF (< 50%) on initial TTE admission	49/121 (40)	42/106 (40)	7/15 (47)	0.60
Reduced LVEF (< 50%) during hospitalization for ICI-myocarditis	54/121 (45)	46/106 (43)	8/15 (53)	0.47
CMR imaging compatible with myocarditis	46/66 (70)	43/62 (69)	3/4 (75)	0.81
Cardiac biopsy-proven myocarditis	26/34 (76)	23/30 (77)	3/4 (75)	0.94
Cumulative incidence of arrhythmia throughout hospital stay				
Supraventricular arrhythmia[d]	30/125 (24.0)	26/110 (23.6)	4/15 (26.7)	0.80
Atrial fibrillation	26/125 (20.8)	22/110 (20.0)	4/15 (26.7)	0.55
Atrial flutter	2/125 (1.6)	2/110 (1.8)	0/15 (0.0)	0.60
Multifocal atrial tachycardia	2/125 (1.6)	2/110 (1.8)	0/15 (0.0)	0.60
Conduction disorder[d]	87/125 (69.6)	72/110 (65.5)	15/15 (100.0)	0.006
Bundle branch or fascicular blocks	78/125 (62.4)	64/110 (58.2)	14/15 (93.3)	0.008
First-degree heart block	19/125 (15.2)	14/110 (12.7)	5/15 (33.3)	0.04
Second-degree heart block	9/125 (7.2)	8/110 (7.3)	1/15 (6.7)	0.93
Third-degree heart block	19/125 (15.2)	12/110(10.9)	7/15 (46.7)	< 0.001
ECG finding of pericarditis (PR depression or diffuse ST elevations)	18/125 (14.4)	15/110 (13.6)	3/15 (20.0)	0.51
Repolarization abnormalities (ST-segment or T wave changes)	62/125 (49.6)	54/110 (49.1)	8/15 (53.3)	0.76
PVC (any type)	33/125 (26.4)	28/110 (25.5)	5/15 (33.3)	0.52
Life-threatening cardiac arrhythmias[d]	15/125 (12.0)	NA	NA	NA
Asystole	4/125 (3.2)	NA	NA	NA
Pulseless electrical activity	4/125 (3.2)	NA	NA	NA
Ventricular fibrillation	4/125 (3.2)	NA	NA	NA
Ventricular tachycardia unspecified morphology, sustained	5/125 (4.0)	NA	NA	NA
Ventricular tachycardia monomorphic, sustained	5/125 (4.0)	NA	NA	NA
Ventricular tachycardia polymorphic, sustained	1/125 (0.8)	NA	NA	NA
Torsade de pointes, sustained	2/125 (1.6)	NA	NA	NA
Third-degree heart block and/or life-threatening cardiac arrhythmia	27/125 (21.6)	NA	NA	NA
Third-degree heart block and life-threatening cardiac arrhythmia	7/125 (5.6)	NA	NA	NA
Outcome				
Placement of a pacemaker and/or defibrillator within 30 days	18/124 (14.5)	11/109 (10.1)	7/15 (46.7)	< 0.001
Length of stay (days)	10.0 (6.0—23.0)	10.0 (6.0—22.0)	26.5 (12.0—45.0)	0.06
In-hospital mortality	33/125 (26.4)	23/110 (20.9)	10/15 (66.7)	< 0.001
30-day all-cause mortality	30/124 (24.2)	22/109 (20.2)	8/15 (53.3)	0.005
Diagnostic certainty (Bonaca et al. criteria) [35]				0.16
Definite myocarditis	71/119 (59.7)	60/105 (57.1)	11/14 (78.6)	
Probable myocarditis	20/119 (16.8)	20/105 (19.0)	0/14 (0.0)	
Possible myocarditis	28/119 (23.5)	25/105 (23.8)	3/14 (21.4)	
Cause of death[e] (among 30 patients with 30-day all-cause mortality)				
Myocarditis	20/30 (66.7)	12/22 (54.5)	8/8 (100.0)	0.02

Table 1 (*Continued*)

	Total	Did not develop life-threatening cardiac arrhythmia	Developed life-threatening cardiac arrhythmia	*P*
	(*n* = 125)	(*n* = 110)	(*n* = 15)	
Cancer progression	6/30 (20.0)	6/22 (27.3)	0/8 (0.0)	0.10
Immune-related AE other than cardiotoxicity	6/30 (20.0)	5/22 (22.7)	1/8 (12.5)	0.54
Non-cardiac myotoxicities[f]	5/6 (83.3)	4/5 (80.0)	1/1 (100.0)	0.62
Thrombocytopenia, immune related	1/6 (16.7)	1/5 (20.0)	0/1 (0.0)	0.62
Sepsis	4/30 (13.3)	3/22 (13.6)	1/8 (12.5)	0.94
Thromboembolic event	2/30 (6.7)	2/22 (9.1)	0/8 (0.0)	0.38
Haemorrhage	1/30 (3.3)	1/22 (4.5)	0/8 (0.0)	0.54
Respiratory failure (other than diaphragmatic failure)	2/30 (6.7)	2/22 (9.1)	0/8 (0.0)	0.38
Pulmonary infection	1/2 (50.0)	NA	NA	NA
Acute respiratory distress syndrome	1/2 (50.0)	NA	NA	NA
Ischaemic stroke	1/30 (3.3)	1/22 (4.5)	0/8 (0.0)	0.54
Unknown	1/30 (3.3)	1/22 (4.5)	0/8 (0.0)	0.54

Data are expressed as median (interquartile range) or number/number (%). AE: adverse event; CAD: coronary artery disease; CHF: congestive heart failure; CMR: cardiac magnetic resonance; CTLA-4: cytotoxic T lymphocyte-associated protein 4; CVA: cerebrovascular accident; ECG: electrocardiogram; ICI: immune checkpoint inhibitor; LVEF: left ventricular ejection fraction; NA: not applicable; PD1: programmed cell death protein 1; PDL1: programmed death ligand 1; PVC: premature ventricular complex; PVD: peripheral vascular disease; TTE: transthoracic echocardiogram.

[a] Defined as hyperlipidaemia, type 2 diabetes, hypertension or tobacco use.

[b] Defined as CAD or CHF.

[c] PVD, CVA, CAD, CHF or hypertension.

[d] This category includes the rhythms below; patients may experience more than one of these rhythms.

[e] Note that more than one cause may contribute to death.

[f] Including myasthenia gravis-like syndrome associated with diaphragmatic failure.

Using survival analyses, the composite outcome of myocarditis-related mortality or life-threatening cardiac arrhythmia was inversely associated with the presenting electrocardiogram's Sokolow-Lyon index (aHR(sh)/mV 0.50, 95% CI: 0.30—0.85; *P* = 0.01), and was positively associated with right bundle branch block (14/43 [33%] vs 14/82 [17%]; aHR(sh) 2.22, 95% CI: 1.06—4.67; *P* = 0.04) and conduction disorders generally (23/79 [29%] vs 5/46 [11%]; aHR(sh) 3.27, 95% CI: 1.29—8.34; *P* = 0.01) (cumulative incidence curves are shown in Fig. 3, model results in Table 2 and cumulative incidence curves by Sokolow-Lyon index in Fig. 4).

The composite outcome of myocarditis-related mortality or life-threatening cardiac arrhythmia showed a trend towards association with pathological Q waves (7/19 [37%] vs 21/106 [19.8%]; aHR(sh) 2.20, 95% CI: 0.95—5.12; *P* = 0.07) and low QRS voltage (3/6 [50%]) vs 25/119 [21.0%]; aHR(sh) 2.70, 95% CI: 0.97—7.48; *P* = 0.06).

Univariate survival analysis for the previous outcome analysis (also including overall mortality), without adjustment on age and sex, using the Cox proportional hazards model and the subdistribution hazards model, can be found in Table 3, Figs. 2 and 3.

Comparison with ACR

The 50 patients with ACR had a median (IQR) age of 51 (43—62) years, and 64% (32/50) were male (Table 4). The median (IQR) number of days from transplant to ACR was 145 (26—283) days. Twenty-nine of 50 (58%) were admitted during or as a result of ACR, with a median (IQR) length of stay of 12 (5—21) days. 2R rejection was seen in 46/50 (92%), and 4/50 (8%) had 3R rejection. Throughout hospitalization (if applicable) or at presenting electrocardiogram, 34/50 (68%) patients experienced conduction disorders, but second- or third-degree heart block was not seen in any patient. There was a cumulative incidence of 6/50 (12%) supraventricular arrhythmias and 1/50 (2%) life-threatening cardiac arrhythmia. None of the patients required a pacemaker and/or defibrillator within the 30 days after ACR diagnosis.

Relative to ACR, the presenting electrocardiogram of ICI-myocarditis had similar voltage and QRS duration (Table 5). Patients with ICI-myocarditis were more likely to have underlying left bundle branch block (20/125 [16.0%] vs 0/50 [0%]; *P* = 0.003) and left anterior fascicular block (24/125 [19.2%]) vs 3/50 [6%]; *P* = 0.03), but were less likely to have right bundle branch block (43/125 [34%] vs 27/50 [54%]; *P* = 0.02) or right atrial abnormality (4/125 [3.2%] vs 10/50 [20%]; *P* < 0.001). In total, the presenting electrocardiogram in ICI-myocarditis had more 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 30/124 [24.2%]; *P* < 0.001), in-hospital incidence of reduced left ventricular ejection fraction < 50% (4/28 [14.3%] vs 54/121 [44.6%]; *P* = 0.003), progression to life-threatening cardiac arrhythmias at admission or during

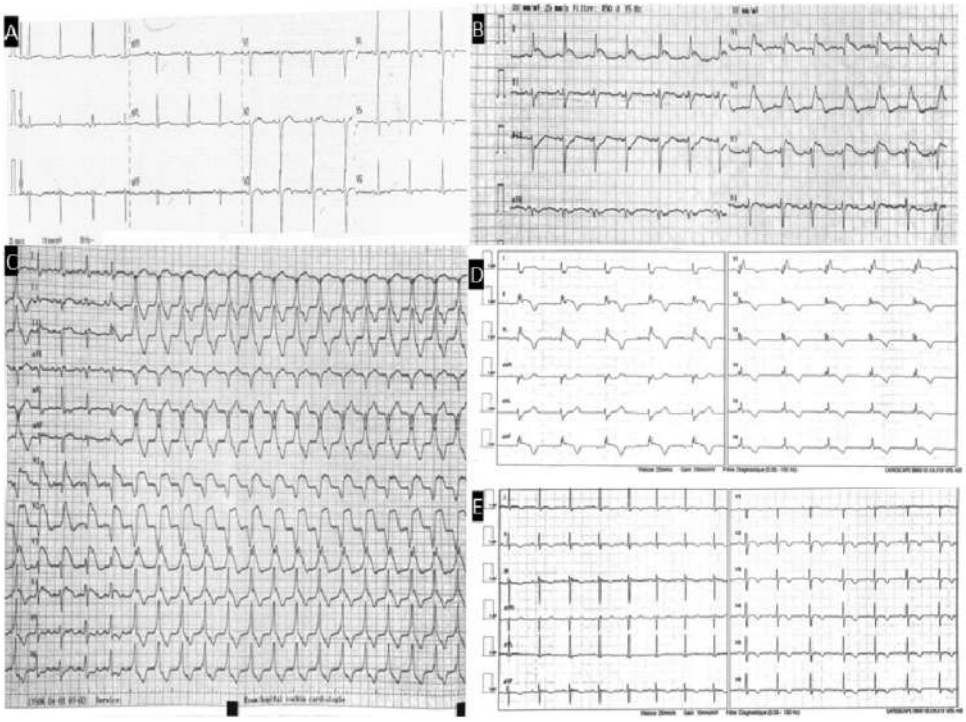

Figure 1. Illustrative case of immune checkpoint inhibitor-associated myocarditis (ICI-myocarditis) with ventricular arrhythmia [20]. Evolution of full electrocardiograms through an example ICI-myocarditis event. A. Baseline before ICI: QRS duration (80 ms) and Sokolow-Lyon voltage criteria (2.2 mV) were normal. B. Day 2 after admission for myocarditis: QRS duration increased (150 ms) and voltage decreased (0.7 mV), with appearance of right bundle branch bock and Q waves in anterior leads. C. Day 7: cardiogenic shock, 24 h before start of immunosuppressant, associated with accelerated ventricular rhythm. D. Day 9: Reversion to regular sinus rhythm after treatment within 48 hours, with progressive improvement of electrocardiogram features (at day 9, QRS duration 120 ms and voltage 0.7 mV). E. Day 17: QRS duration and voltage restored to approximately normal baseline values (82 ms and 1.6 mV, respectively), and Q waves and right bundle branch block disappeared.

hospital stay (1/50 [2%] vs 15/125 [12.0%]; $P = 0.04$) and pacemaker or defibrillator placement within 30 days of the ACR or ICI-myocarditis event (0/50 [0%] vs 18/124 [14.5%]; $P = 0.004$). Additionally, ACR had a lower cumulative incidence of third-degree heart block (0/50 [0.0%] vs 19/125 [15.2%]; $P = 0.004$) compared with ICI-myocarditis.

Discussion

This study assessed electrocardiogram features of ICI-myocarditis using a large international database. The incidence of myocarditis among ICI recipients has been estimated to be ~1%, which is similar to estimates from participating centres in this registry (Table A.3) [6]. This analysis shows that ICI-myocarditis manifests as clinically significant electrocardiographic disturbances, including high-degree heart block and ventricular arrhythmias, both of which are strongly associated with adverse cardiovascular outcomes. Low voltage, conduction disorders and pathological Q waves were predictive of myocarditis-related death and life-threatening cardiac arrhythmias, in addition to overall mortality. Furthermore, we show that compared with a contemporary cohort of cardiac transplant recipients experiencing ACR, ICI-myocarditis presents with more electrocardiographic abnormalities, and more frequently devolves to life-threatening arrhythmias. Life-threatening cardiac arrhythmias, PVCs and conduction disorders affecting the left ventricle, including complete heart block, were more common in ICI-myocarditis, but were not seen frequently in ACR. Although ACR and ICI-myocarditis both follow similar immunosuppression protocols, these findings suggest that arrhythmia management is a higher priority in ICI-myocarditis, and probably requires a different approach.

This analysis is among the largest contemporary studies of electrocardiogram findings in moderate-to-severe ACR. Whereas early studies correlated ACR with atrial arrhythmias, sustained ventricular arrhythmias, PR, QRS and QT lengthening, these changes were seen infrequently on presenting electrocardiograms among this cohort [21,22]. Instead, most abnormalities on the presenting electrocardiogram could be explained by postsurgical changes, including sinus tachycardia, P wave enlargement, right bundle branch block and non-specific ST changes [22].

This prognostic analysis directly links electrocardiographic changes early in the course of ICI-myocarditis with cardiovascular outcomes. A previously published description of this cohort by our group focused exclusively on all-cause mortality, which can be driven by non-cardiac causes in this critically ill population of cancer patients [15]. The findings of this study do not completely match the results of Zlotoff

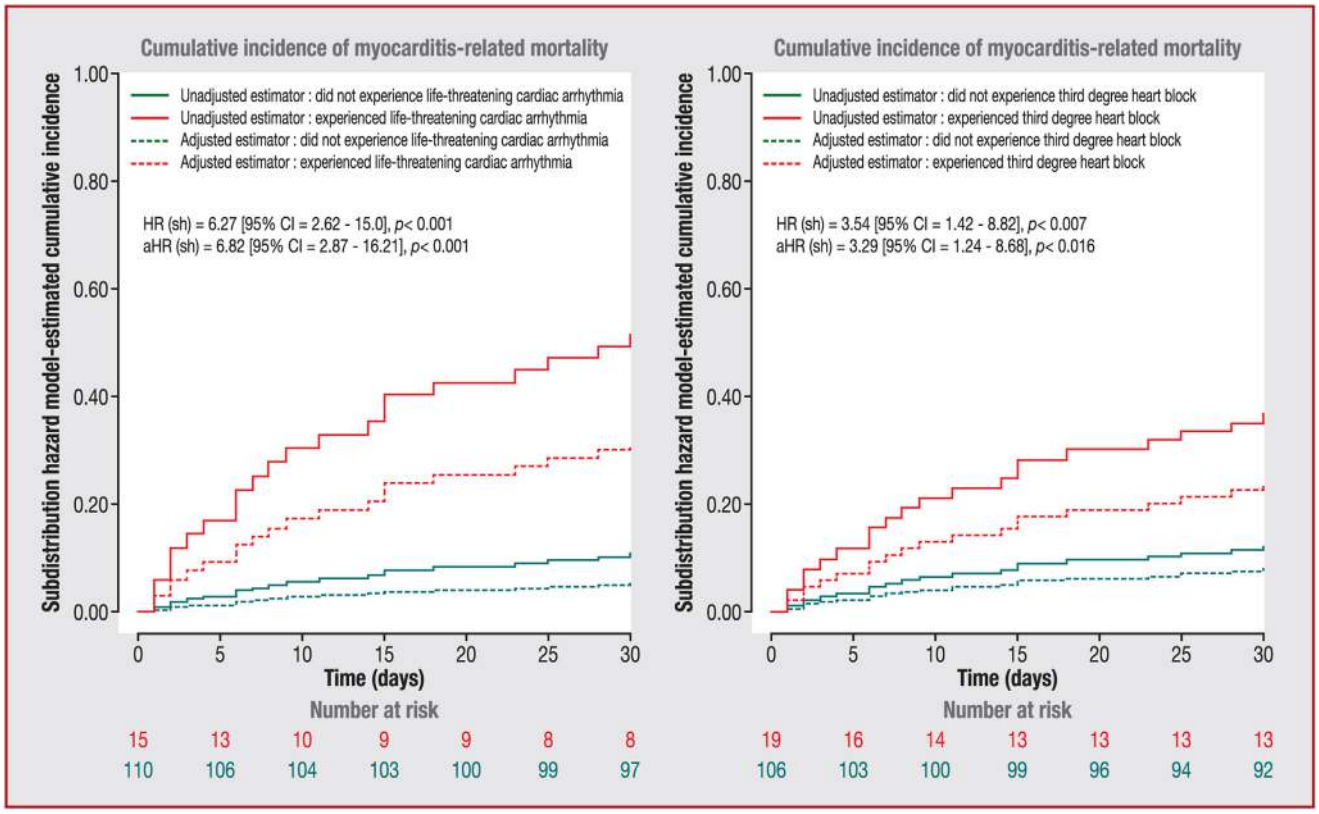

Figure 2. Myocarditis-related mortality by cumulative incidence of arrhythmia. aHR(sh): adjusted hazard ratio by subdistribution hazards model; CI: confidence interval; HR(sh): hazard ratio by subdistribution hazards model.

et al., who studied automated electrocardiogram intervals (without qualitative control for exclusion of PVCs, ventricular paced rhythm, ventricular arrhythmias and complete atrioventricular blocks), and found QRS duration to predict major adverse cardiac events in 140 cases of ICI-myocarditis [7]. Whereas we did initially find QRS to be related to adverse cardiovascular events in a preliminary analysis, this association was lost once paced ventricular complexes, PVCs and electrocardiogram in ventricular arrhythmias and complete atrioventricular blocks were excluded from QRS measurement, suggesting that heart block and ventricular arrhythmia mediate cardiac outcomes instead of QRS prolongation while in sinus rhythm in this population.

This prognostic analysis adds to and is supportive of predictive electrocardiogram studies in general myocarditis. Although several studies of myocarditis resulting from heterogenous causes have shown pathological Q waves to be predictive of fulminant myocarditis, they did not find a significant association with long-term survival [23,24]. Whereas studies have shown that low voltage lacks predictive value for death in allograft rejection, it has not been previously studied in myocarditis [8,25]. However, in a study of Chagas heart disease by Rassi et al., there was a 9% prevalence of low voltage, with an HR for mortality of 1.87 (95% CI: 1.03—3.37). In contrast, results presented in this paper show an 8% prevalence in ICI-myocarditis, and HRs of 3.27 (95% CI: 0.95—11.23) for all-cause mortality and 4.50 (95% CI: 1.34—15.12) for myocarditis-related mortality [26].

Low voltage and pathological Q waves are both manifestations of electrically inert myocardium. That these two features are confirmed as predictors of cardiovascular outcomes in this study suggests that loss of electromotive forces drives cardiac decompensation. In ICI-myocarditis, immune infiltrates lead to cardiomyocyte necrosis and electrical inactivity [27,28]. Therefore, it is reasonable to surmise that terminating these processes through early detection and immunosuppression of ICI-myocarditis may be a critical step in improving outcomes.

ICI-myocarditis is histologically characterized by dense patchy infiltrates of lymphocytes and macrophages that affect both the myocardium and the conduction system [2]. Compared with ACR, which is primarily lymphocytic, ICI-myocarditis is characterized by both lymphocyte and macrophage infiltrates, with a higher CD68/CD3 ratio (macrophages/lymphocytes) [3]. Denser infiltrates in ICI-myocarditis are associated with increased myocyte necrosis and a different molecular profile, with lower macrophage expression of programmed death ligand 1, perhaps reflecting an influx of the reparative M2 macrophage subpopulation [3]. Importantly, macrophages have been shown to electrically couple with cardiomyocytes, even in the absence of disease, thereby facilitating depolarization and improving atrioventricular conduction [29]. It is possible that changes in macrophage phenotype and density in ICI-myocarditis may mediate the high frequency of conduction system blocks and ventricular ectopy seen in this study. Mouse models of

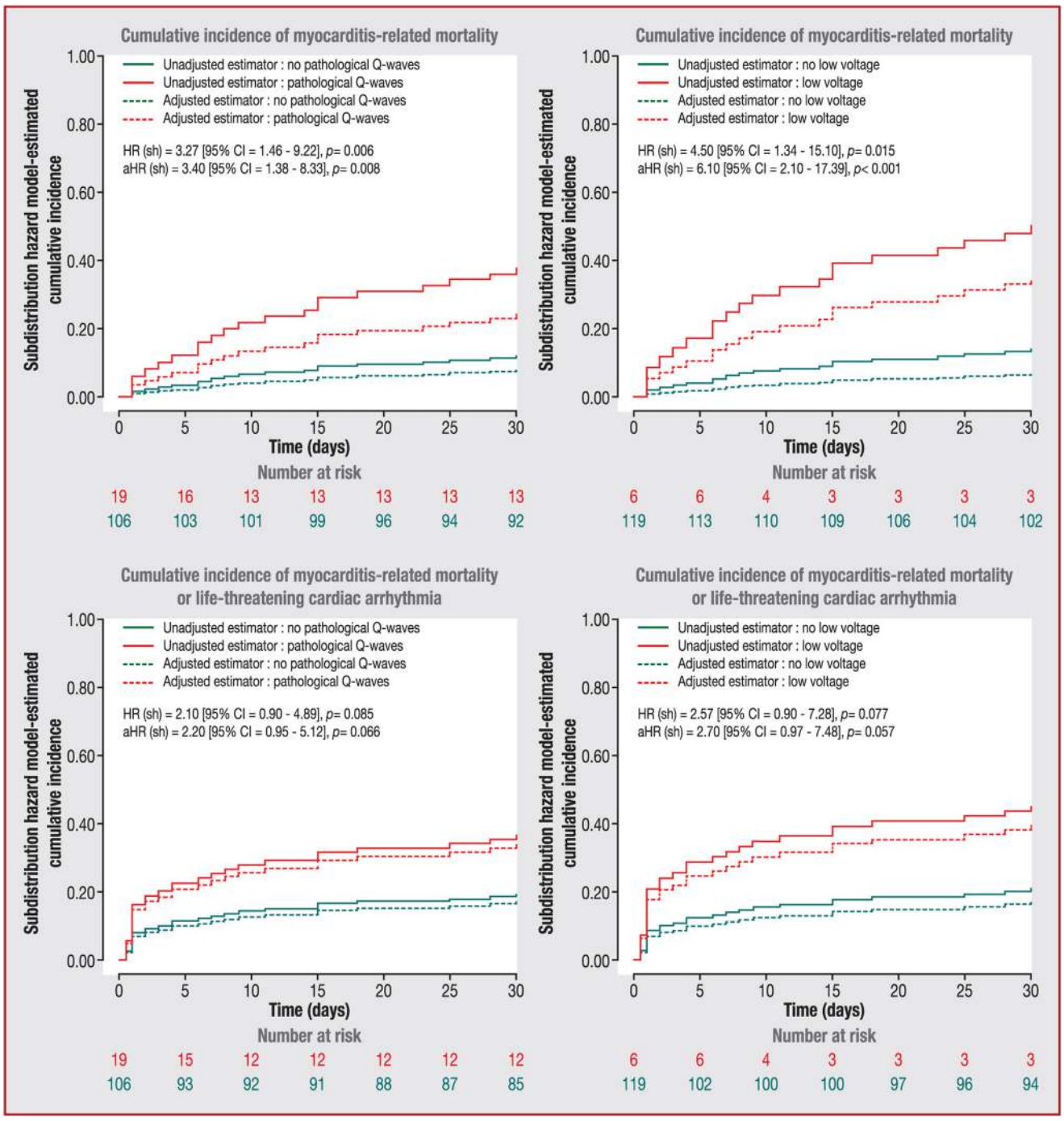

Figure 3. Outcomes by presenting electrocardiogram findings. aHR(sh): adjusted hazard ratio by subdistribution hazards model; CI: confidence interval; HR(sh): hazard ratio by subdistribution hazards model.

ICI-myocarditis have replicated arrhythmogenicity and lymphohistiocytic infiltration seen in humans, and may offer future insights into the electrical contribution of immune cells in inflammatory cardiomyopathies [28]. Separately, other novel forms of cancer immunotherapy also demonstrate high levels of arrhythmogenicity: ventricular tachycardias and atrial fibrillation are disproportionately reported in CAR-T therapy; and 20% of patients receiving interleukin-2 therapy developed arrhythmias requiring pharmacological intervention [30—34]. These examples further illustrate how the emerging relationship between the immune system and cardiac conduction will become increasingly important in the treatment of patients receiving immunotherapy, and as a target for arrhythmia management more broadly.

To standardize inclusion criteria across this multicentre study, clear criteria for adjudication were provided, and each submission was subjected to a bi-institutional review process. Nevertheless, this self-reporting process probably

Table 2 Presenting electrocardiogram of immune checkpoint inhibitor-associated myocarditis as predictor of 30-day all-cause mortality, myocarditis-related mortality and composite outcome, using survival analyses adjusting for age and sex ($n = 125$).

	30-day myocarditis-related mortality		30-day composite outcome		30-day all-cause mortality	
	aHR[a] (95% CI)	P[b]	aHR[a] (95% CI)	P[b]	aHR[c] (95% CI)	P[b]
Heart rate (beats/min)	1.01 (0.99—1.03)	0.52	1.00 (0.99—1.02)	0.60	1.01 (0.99—1.02)	0.40
PR length (ms) ($n = 107$)	1.00 (0.99—1.02)	0.90	1.00 (0.99—1.01)	0.62	1.00 (0.99—1.01)	0.55
QTcF length (ms) ($n = 122$)	1.00 (0.99—1.01)	0.59	1.00 (1.00—1.01)	0.42	1.00 (1.00—1.01)	0.36
QRS length (ms)	1.01 (0.99—1.02)	0.57	1.01 (1—1.03)	0.03	1.00 (0.99—1.01)	0.90
Sokolow-Lyon index (mV) ($n = 124$)	0.54 (0.30—0.97)	0.04	0.50 (0.30—0.85)	0.01	0.57 (0.34—0.94)	0.03
Conduction disorders[d]	1.91 (0.71—5.14)	0.20	3.27 (1.29—8.34)	0.01	1.56 (0.69—3.53)	0.29
Bundle branch block, left bundle	0.85 (0.26—2.79)	0.79	1.49 (0.62—3.61)	0.37	1.00 (0.38—2.62)	0.99
Bundle branch block, right bundle	1.63 (0.69—3.85)	0.27	2.22 (1.06—4.67)	0.04	1.48 (0.71—3.06)	0.29
Fascicular block, left anterior	1.58 (0.57—4.41)	0.38	1.81 (0.82—3.97)	0.14	0.85 (0.32—2.25)	0.75
Fascicular block, left posterior	1.40 (0.47—4.14)	0.53	1.56 (0.52—4.62)	0.43	1.34 (0.47—3.85)	0.59
Heart block, first degree	1.78 (0.57—5.58)	0.32	2.14 (0.83—5.53)	0.12	0.83 (0.28—2.40)	0.72
ECG findings of pericarditis	0.58 (0.14—2.40)	0.46	0.98 (0.34—2.82)	0.97	0.75 (0.22—2.51)	0.64
ST-segment elevation, diffuse	0.63 (0.15—2.61)	0.52	1.05 (0.36—3.05)	0.93	0.83 (0.25—2.81)	0.76
PVC (all types)	1.36 (0.43—4.32)	0.61	1.95 (0.74—5.10)	0.18	1.01 (0.37—2.75)	0.99
PVC	0.96 (0.27—3.38)	0.95	1.51 (0.56—4.07)	0.42	0.77 (0.26—2.30)	0.64
Sinus mechanism	0.58 (0.21—1.59)	0.29	0.70 (0.29—1.70)	0.43	0.77 (0.31—1.89)	0.56
Normal sinus rhythm	0.43 (0.16—1.16)	0.09	0.61 (0.28—1.32)	0.21	0.50 (0.23—1.09)	0.08
Sinus tachycardia	1.48 (0.6—3.65)	0.39	1.28 (0.61—2.68)	0.52	1.67 (0.80—3.49)	0.17
Repolarization abnormalities	1.57 (0.64—3.89)	0.33	1.48 (0.68—3.24)	0.33	1.52 (0.74—3.12)	0.26
ST-segment depression, diffuse	0.66 (0.09—4.73)	0.68	0.47 (0.07—3.27)	0.44	1.60 (0.48—5.30)	0.44
ST-segment depression, regional	1.04 (0.13—8.56)	0.97	1.48 (0.35—6.32)	0.59	0.53 (0.07—3.90)	0.53
T wave inversions	1.98 (0.81—4.82)	0.13	1.42 (0.63—3.24)	0.40	1.49 (0.71—3.12)	0.29
Supraventricular arrhythmia[d]	2.84 (0.99—8.16)	0.052	2.39 (1.01—5.65)	0.047	2.21 (0.84—5.79)	0.11
Atrial fibrillation[d]	2.19 (0.67—7.24)	0.20	2.11 (0.77—5.76)	0.14	1.83 (0.63—5.27)	0.27
Uncategorized						
Premature atrial complex	2.19 (0.57—8.45)	0.26	1.63 (0.49—5.43)	0.42	1.59 (0.47—5.38)	0.46
Left ventricular hypertrophy	0.71 (0.21—2.43)	0.58	0.51 (0.16—1.63)	0.25	0.49 (0.15—1.61)	0.24
Low QRS voltage	6.05 (2.10—17.39)	< 0.001	2.70 (0.97—7.49)	0.06	3.27 (0.95—11.23)	0.06
P wave abnormality suggestive of LA enlargement	1.40 (0.53—3.71)	0.49	1.09 (0.46—2.59)	0.85	1.10 (0.46—2.63)	0.83
Q waves, pathological	3.40 (1.38—8.33)	0.008	2.20 (0.95—5.12)	0.07	5.98 (2.8—12.79)	< 0.001

aHR: adjusted hazard ratio; CI: confidence interval; ECG: electrocardiogram; LA: left atrial; PVC: premature ventricular complex; QTcF: heart rate corrected QT interval using Fridericia's formula.

[a] Subdistribution hazards model.

[b] The P-values displayed have not been corrected for multiple testings, and require caution when analysing them.

[c] Cox proportional hazards model.

[d] When multiple eligible ECGs were available, ECGs without complete heart block or supraventricular arrhythmias were preferentially selected for this analysis, focusing on PR, QRS and QTc measurements. See Table 1 for cumulative incidence of arrhythmias in immune checkpoint inhibitor-associated myocarditis.

selected for severe cases of ICI-myocarditis, making these results less generalizable to low-severity cases. Further, the prognostic analysis only interpreted the initial electrocardiogram, and does not fully capture the predictive value of electrocardiogram changes that develop during hospitalization. Although variance in treatment could not be corrected for in the outcome analysis, the composite outcome of life-threatening cardiac arrhythmia or myocarditis-related death helps to mitigate this effect by capturing early events that would have led to death if not for aggressive therapy. Finally, although ACR and ICI-myocarditis had different rates of hospital and intensive care unit admissions, we believe that the descriptive comparison of arrhythmia burden still provides a useful framework for clinicians.

Table 3 Presenting electrocardiogram of immune checkpoint inhibitor-associated myocarditis as predictor of all-cause mortality, myocarditis-related mortality and composite outcome, using unadjusted survival analyses ($n = 125$).

	30-day myocarditis-related mortality		30-day composite outcome		30-day all-cause mortality	
	aHR[a] (95% CI)	P[b]	aHR[a] (95% CI)	P[b]	aHR[c] (95% CI)	P[b]
Heart rate (beats/min)	1.01 (0.99–1.03)	0.35	1.01 (0.99–1.02)	0.40	1.00 (0.99–1.02)	0.70
PR length (ms) ($n = 107$)	1.00 (0.98–1.02)	0.97	1.00 (0.99–1.01)	0.76	1.00 (0.99–1.01)	0.91
QTcF length (ms) ($n = 122$)	1.00 (0.99–1.01)	0.66	1.00 (0.99–1.01)	0.52	1.01 (1.00–1.01)	0.22
QRS length (ms)	1.01 (0.99–1.02)	0.51	1.01 (1.00–1.02)	0.11	1.00 (0.99–1.02)	0.51
Sokolow-Lyon index (mV) ($n = 124$)	0.55 (0.28–1.06)	0.08	0.51 (0.30–0.87)	0.01	0.59 (0.35–0.98)	0.04
Conduction disorders[d]	1.84 (0.68–5.00)	0.23	3.05 (1.20–7.76)	0.02	1.68 (0.75–3.76)	0.21
Bundle branch block, left bundle	0.9 (0.27–2.99)	0.87	1.47 (0.62–3.52)	0.38	1.06 (0.40–2.76)	0.91
Bundle branch block, right bundle	1.67 (0.7–3.99)	0.25	2.16 (1.05–4.47)	0.04	1.54 (0.75–3.17)	0.24
Fascicular block, left anterior	1.47 (0.54–4.04)	0.45	1.79 (0.81–3.96)	0.15	0.84 (0.32–2.20)	0.73
Fascicular block, left posterior	1.48 (0.47–4.69)	0.50	1.60 (0.55–4.69)	0.39	1.25 (0.44–3.58)	0.68
Heart block, first degree	1.58 (0.53–4.74)	0.41	1.87 (0.75–4.68)	0.18	0.94 (0.33–2.68)	0.90
ECG findings of pericarditis	0.68 (0.16–2.84)	0.59	1.08 (0.38–3.07)	0.89	0.67 (0.20–2.22)	0.52
ST-segment elevation, diffuse	0.73 (0.17–3.06)	0.67	1.16 (0.41–3.32)	0.78	0.73 (0.22–2.40)	0.60
PVC (all types)	1.56 (0.53–4.56)	0.42	1.75 (0.73–4.22)	0.21	1.21 (0.46–3.16)	0.70
PVC	1.13 (0.34–3.74)	0.84	1.41 (0.56–3.55)	0.46	0.95 (0.33–2.72)	0.93
Sinus mechanism	0.55 (0.21–1.48)	0.24	0.68 (0.28–1.62)	0.38	0.77 (0.31–1.87)	0.56
Normal sinus rhythm	0.39 (0.14–1.05)	0.06	0.56 (0.26–1.21)	0.14	0.58 (0.27–1.23)	0.15
Sinus tachycardia	1.62 (0.68–3.84)	0.28	1.39 (0.67–2.88)	0.38	1.46 (0.71–3.00)	0.30
Repolarization abnormalities	1.38 (0.58–3.29)	0.47	1.39 (0.67–2.88)	0.37	1.44 (0.70–2.94)	0.32
ST-segment depression, diffuse	0.68 (0.09–4.95)	0.70	0.45 (0.06–3.25)	0.43	1.64 (0.50–5.41)	0.42
ST-segment depression, regional	0.94 (0.11–7.73)	0.95	1.37 (0.33–5.68)	0.67	0.59 (0.08–4.33)	0.61
T wave inversions	1.74 (0.73–4.15)	0.21	1.34 (0.64–2.80)	0.44	1.43 (0.69–2.97)	0.34
Supraventricular arrhythmia[d]	2.86 (1.00–8.2)	0.05	2.40 (1.00–5.75)	0.05	2.24 (0.86–5.85)	0.10
Atrial fibrillation[d]	2.25 (0.66–7.64)	0.19	2.06 (0.76–5.54)	0.15	1.93 (0.67–5.54)	0.22
Uncategorized						
Premature atrial complex	2.84 (0.91–8.85)	0.07	1.76 (0.61–5.09)	0.29	1.74 (0.53–5.75)	0.36
Left ventricular hypertrophy	0.87 (0.26–2.95)	0.82	0.55 (0.17–1.77)	0.32	0.52 (0.16–1.71)	0.28
Low QRS voltage	4.50 (1.34–15.12)	0.02	2.57 (0.90–7.28)	0.08	2.77 (0.84–9.17)	0.10
P wave abnormality suggestive of LA enlargement	1.36 (0.54–3.40)	0.51	1.14 (0.49–2.67)	0.76	0.94 (0.41–2.20)	0.89
P wave abnormality suggestive of RA enlargement	N/A		N/A		0.01 (0–66336310)	0.67
Q waves, pathological	3.67 (1.46–9.22)	0.006	2.10 (0.90–4.89)	0.09	5.80 (2.78–12.12)	< 0.001

aHR: adjusted hazard ratio; CI: confidence interval; ECG: electrocardiogram; LA: left atrial; PVC: premature ventricular complex; QTcF: heart rate corrected QT interval using Fridericia's formula; RA: right atrial.

[a] Subdistribution hazards model.

[b] The P-values displayed have not been corrected for multiple testings, and require caution when analysing them.

[c] Cox proportional hazards model.

[d] When multiple eligible ECGs were available, ECGs without complete heart block or supraventricular arrhythmias were preferentially selected for this analysis, focusing on PR, QRS and QTc measurements. See Table 1 for cumulative incidence of arrhythmias in immune checkpoint inhibitor-associated myocarditis.

Table 4 Acute cellular rejection cohort baseline characteristics and outcomes ($n = 50$).

Recipient age (years)	51 (43—62)
Female recipient	18 (36)
Reason for transplant	
Dilated cardiomyopathy	4 (8)
Ischaemic cardiomyopathy	18 (36)
Amyloidosis	1 (2)
Restrictive cardiomyopathy	1 (2)
Congenital heart disease	4 (8)
Non-ischaemic cardiomyopathy, not otherwise specified	17 (34)
Hypertrophic cardiomyopathy	2 (4)
Other	3 (6)
Donor age (years)	29.0 (22.0—37.0)
Female donor	13 (26)
Known cardiac allograft vasculopathy	11 (22)
Induction therapy	
Basiliximab	26 (52)
Thymoglobulin	3 (6)
None	20 (40)
Other	1 (2)
Background/maintenance immunosuppressive regimen	
Prednisone + tacrolimus + mycophenolate	42 (84)
Prednisone + cyclosporine + mycophenolate	3 (6)
Other	5 (10)
Days from transplant to rejection	145 (26—283)
ACR grading scheme	
2R, moderate	46 (92)
3R, severe	4 (8)
Days from transplant to ECG	145 (28—283)
Days from biopsy to ECG	0 (0—1)
30-day all-cause mortality	0 (0)
Placement of pacemaker and/or defibrillator for ACR-related arrhythmias within 30 days of diagnosis	0 (0)
Placement of pacemaker without defibrillator for ACR-related arrhythmias within 30 days of diagnosis	0 (0)
Admitted during or as a result of ACR	29 (58.0)
Length of stay[a] (days) ($n = 29$)	12 (5—21)
Reduced LVEF at admission or during hospital stay for ACR (excluding pretransplant LVEF)[a] ($n = 28$)	4/28 (14.3)
In-hospital mortality[a] ($n = 29$)	0/29 (0)
Arrhythmias at any point during hospitalization (if applicable) or at presenting ECG[b]	
Supraventricular arrhythmia	6 (12)
Atrial fibrillation	3 (6)
Atrial flutter	2 (4)
Multifocal atrial tachycardia	1 (2)
Conduction disorder[c]	34 (68)
Bundle branch or fascicular blocks	33 (66)
First-degree heart block	6 (12)
Second-degree heart block	0 (0)
Third-degree heart block	0 (0)
ECG finding of pericarditis (PR depression or diffuse ST elevations)	2 (4)
Repolarization abnormalities (ST-segment or T wave changes)	33 (66)
PVCs (any type)	6 (12)
Ventricular arrhythmias (any type; sustained or non-sustained)	5 (10)
Life-threatening cardiac arrhythmias	1 (2)
Asystole	0 (0)
Pulseless electrical activity	0 (0)
Ventricular fibrillation	0 (0)
Ventricular tachycardia unspecified morphology, sustained	0 (0)
Ventricular tachycardia monomorphic, sustained	1 (2)
Ventricular tachycardia polymorphic, sustained	0 (0)
Ventricular tachycardia torsade de pointes, sustained	0 (0)
Third-degree heart block and/or life-threatening cardiac arrhythmia	1 (2)

Data are expressed as median (interquartile range) or number (%). ACR: acute cellular rejection; ECG: electrocardiogram; LVEF: left ventricular ejection fraction; PVC: premature ventricular complex.

[a] This refers to the subset of admitted patients.

[b] Please refer to Table A.2 for criteria/classification.

[c] This category includes the rhythms below; patients may experience more than one of these rhythms.

Table 5 Comparison of presenting electrocardiogram in immune checkpoint inhibitor-associated myocarditis and acute cellular rejection.

	ICI-myocarditis, presenting ECG	ACR (2R/3R), presenting ECG	P[a]
	($n = 125$)	($n = 50$)	
Heart rate (beats/min)	87.6 (71.3—104.6)	88.8 (80.4—110.2)	0.20
PR interval length (ms) ($n = 107$; $n = 48$)	161.3 (145.7—180.6)	153.2 (136.5—166.1)	0.01
QTcF length (ms) ($n = 122$; $n = 49$)	432.5 (405.4—462.1)	434.1 (393.5—460.1)	0.59
QRS length (ms) ($n = 125$; $n = 49$)	95.0 (85.3—122.3)	92.8 (85.5—103.2)	0.15
Sokolow-Lyon index ($n = 124$; $n = 50$)	1.240 (0.700—1.889)	1.421 (0.889—1.845)	0.40
Conduction disorders[b]	79 (63)	34 (68)	0.55
Bundle branch block, left bundle	20 (16)	0 (0)	0.003
Bundle branch block, non-specific	2 (2)	2 (4)	0.34
Bundle branch block, right bundle	43 (34)	27 (54)	0.02
Escape rhythm, ventricular	1 (1)	0 (0)	0.53
Fascicular block, left anterior	24 (19)	3 (6)	0.03
Fascicular block, left posterior	13 (10)	4 (8)	0.63
Heart block, first degree	18 (14)	5 (10)	0.44
Heart block, third degree	5 (4)	0 (0)	0.15
ECG findings of pericarditis	17 (14)	2 (4)	0.07
PR-segment depression	1 (1)	0 (0)	0.53
ST-segment elevation, diffuse	16 (13)	2 (4)	0.08
PVC (all types)	18 (14)	1 (2)	0.02
PVC	17 (14)	1 (2)	0.02
PVC bigeminy	2 (2)	0 (0)	0.37
Sinus mechanism	107 (85.6)	47 (94)	0.08
Sinus tachycardia	51 (40.8)	21 (42)	0.81
Repolarization abnormalities	53 (42)	33 (66)	0.005
ST-segment elevation, regional	8 (6)	0 (0)	0.07
ST-segment depression, diffuse	9 (7)	2 (4)	0.43
ST-segment depression, regional	7 (6)	3 (6)	0.92
T wave inversions	41 (33)	29 (58)	0.002
T wave notching	0 (0)	1 (2)	0.11
Supraventricular arrhythmia[b]	11 (9)	2 (4)	0.27
Atrial fibrillation	10 (8)	1 (2)	0.14
Atrial flutter	1 (1)	1 (2)	0.50
Uncategorized			
Premature atrial complex	8 (6)	0 (0)	0.07
Premature junctional complex	1 (1)	0 (0)	0.53
Left ventricular hypertrophy	21 (17)	10 (20)	0.62
Low QRS voltage	6 (5)	2 (4)	0.82
P wave abnormality suggestive of LA enlargement	29 (23)	14 (28)	0.51
P wave abnormality suggestive of RA enlargement	4 (3)	10 (20)	< 0.001
Q waves, pathological	19 (15)	4 (8)	0.20
Accelerated junctional rhythm	1 (1)	0 (0)	0.53

Data are expressed as median (interquartile range) or number (%). ACR: acute cellular rejection; ECG: electrocardiogram; ICI-myocarditis: immune checkpoint inhibitor-associated myocarditis; LA: left atrial; PVC: premature ventricular complex; QTcF: heart rate corrected QT interval using Fridericia's formula; RA: right atrial.

[a] Wilcoxon test for heart rate, PR interval length, QTcF length, QRS length and Sokolow-Lyon index; otherwise χ^2 test.

[b] When multiple eligible ECGs were available, ECGs 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 Table 4 for cumulative incidence of arrhythmias in ACR.

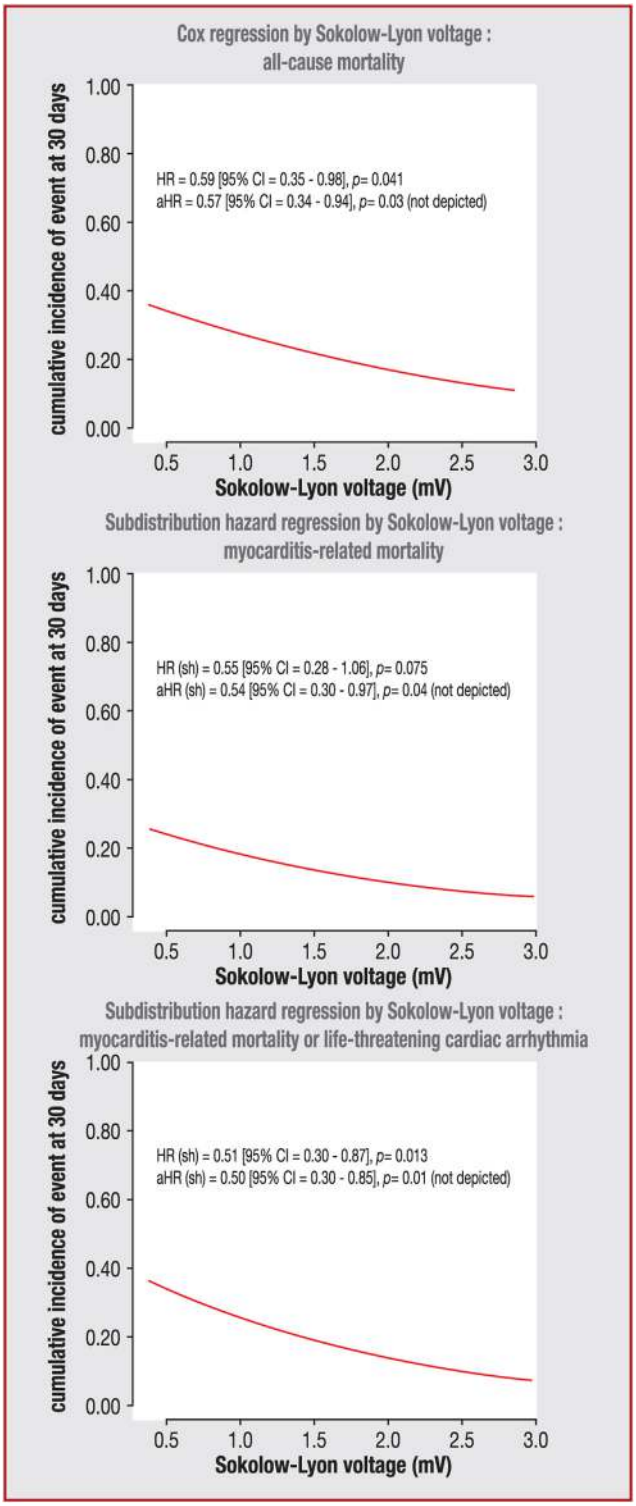

Figure 4. Model-estimated cumulative incidence of event at 30 days by Sokolow-Lyon index. aHR(sh): adjusted hazard ratio by subdistribution hazards model; CI: confidence interval; HR: hazard ratio; HR(sh): hazard ratio by subdistribution hazards model.

Conclusions

ICI-myocarditis manifests as diffuse alteration of the cardiac conduction system, represented by conduction blocks, a decrease in QRS voltage and the appearance of pathological Q waves on electrocardiogram. These features predict severe life-threatening cardiac arrhythmias and myocarditis-related death. Clinicians should prioritize identifying these electrocardiogram changes as part of a multimodal diagnostic workup for ICI-myocarditis. Patients with these features are at higher risk of adverse outcomes, and may benefit from more aggressive treatment and monitoring strategies.

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J.-E. S. Participation in advisory boards for the company BMS. Consultancy for the company AstraZeneca.

J. M. Served on advisory boards for the companies Bristol Myers Squibb, Takeda, Regeneron, Audentes, Decipher, Ipsen, Janssen, ImmunoCore, Boston Biomedical, Amgen, Myovant, Triple Gene/Precigen, Cytokinetics and AstraZeneca.

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The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2022.03.003.

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