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Electrocardiographic characteristics of bladder cancer patients receiving preoperative chemotherapy combined with immunotherapy

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Abstract

Objective: Patients treated with preoperative chemotherapy and immunotherapy for bladder cancer may be at increased risk of cardiotoxicity and electrophysiological abnormalities. This study aimed to analyze their electrocardiographic (ECG) alterations.

Methods: Patients with bladder cancer who were hospitalized and receiving tislelizumab plus nab-paclitaxel (TnP) were enrolled prospectively. ECG, cardiac biomarkers, and echocardiography were performed at baseline and the end of TnP.

Results: A total of 60 patients (76.7% males), including 30 muscle-invasive and 30 non-muscle-invasive bladder cancer, received three or four cycles of TnP, respectively. Hypertension was the commonest comorbidity (41.7%), and 25 patients (41.7%) were prescribed cardiovascular drugs. In comparison with baseline characteristics, cardiac troponin I (cTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were within normal ranges after TnP. However, echocardiographic parameter of left ventricular ejection fraction slightly decreased after TnP (62.81 ± 3.81% to 61.10 ± 4.37%, $p = .011$). The incidence of abnormal ECG increased from 65.0% at baseline to 76.7%, of which only a higher prevalence of fragmented QRS (fQRS) was observed (33.3% to 50.0%, $p = .013$; mainly in inferior leads). ECG parameters of QT dispersion (QTd) were prolonged significantly after the regimen (39.50 ± 11.37 to 44.20 ± 15.85 ms, $p = .019$).

Conclusion: In bladder cancer patients receiving preoperative chemotherapy combined with immunotherapy, the main ECG abnormality was fQRS and QTd, with relatively normal cardiac biomarkers and echocardiographic parameters. Regular ECG screening should be carried out carefully to detect potential cardiotoxicity in the long-term follow-up.

KEYWORDS
bladder cancer, cardio-oncology, electrocardiography, immunotherapy, preoperative therapy

1 | INTRODUCTION

Bladder cancer (BC) ranks among the 10 ten malignant tumors around the world; it can be classified into muscle-invasive BC (MIBC) and non-muscle-invasive BC (NMIBC) depending on the depth of tumor invasion (Richters et al., 2020). With the introduction of immune checkpoint inhibitors (ICIs), previous clinical studies have demonstrated that preoperative chemotherapy combined with immunotherapy could be an effective treatment option for BC patients (Singh et al., 2023).

However, ICIs may cause cardiovascular complications including myocarditis, arrhythmias, and atherosclerosis, which occur in about 1% of patients (Thuny et al., 2022). Our team found that most major adverse cardiovascular events and cardiovascular hospitalizations occurred during the first year after initiating ICI in cancer patients (Chan, Lakhani, et al., 2023). Specifically for bladder cancer, combining conventional cytotoxic chemotherapy with ICIs may further increase the incidence of adverse events (Funt et al., 2022). Ramamoorthy et al. found that BC patients have a higher risk of major adverse cardiovascular and cerebrovascular events than breast and prostate cancer patients (Ramamoorthy et al., 2023). Furthermore, according to a Survey, Epidemiology, and End Results database study, cardiac disease was the leading cause of long-term death for bladder cancer survivors, followed by the primary tumor itself (Kong et al., 2019).

As a result, effective cardiovascular surveillance strategies for patients with BC are essential to identify high-risk populations, implement protective interventions, and improve prognosis. As a rapid, non-invasive, and cost-effective diagnostic tool, the 2022 European Society of Cardiology (ESC) Guidelines on Cardio-Oncology recommend the 12-lead electrocardiogram (ECG) as a first-line risk assessment method to detect cardiovascular toxicity (Lyon et al., 2022), although the impact of full adherence to these guidelines on clinical practice remains to be elucidated (Tse et al., 2023). In the present study, we aimed to analyze the presence or absence of ECG abnormalities in BC patients receiving preoperative chemotherapy combined with immunotherapy.

2 | MATERIALS AND METHODS

2.1 | Study population

This was a retrospective analysis of two clinical trials (ClinicalTrials.gov identifiers: NCT04730219 and NCT04730232) between September 2020 and June 2022. Briefly, these two ongoing phase II studies were designed to determine the safety and efficacy of tislelizumab in combination with nab-paclitaxel for MIBC and NMIBC patients prior to cystectomy or transurethral resection biopsy at the Urology Department of the Second Hospital of Tianjin Medical University. The study received approval from the hospital's ethics committee. The inclusion criteria were as follows: (1) histopathologically diagnosed with BC and (2) treated with preoperative chemotherapy combined with immunotherapy (tislelizumab plus nab-paclitaxel (TnP)) every 21 days. In total, patients with MIBC and NMIBC received 3 and 4 cycles of TnP therapy, respectively; (3) underwent baseline and serial cardiovascular assessments (including ECG, cardiac biomarkers, and echocardiography). In particular, all patients were assessed on the first day of each cycle of TnP and before subsequent surgical treatment. Exclusion criteria: (1) incomplete clinical data; (2) poor-quality ECG; and (3) patients with uncontrolled or severe cardiovascular disease.

2.2 | Echocardiography

All patients underwent transthoracic echocardiography using a Philips IE33 ultrasound system equipped with an X5-1 (2.5–3.5 MHz) probe. Echocardiography was conducted by experienced cardiologists who were blinded to the clinical and ECG information and were measured based on current guidelines recommendation (Lang et al., 2015). The echocardiographic images were recorded in the following standard views: parasternal long-axis view, parasternal short-axis view, apical four-chamber view, apical three-chamber view, and apical two-chamber view. The biplane Simpson method was used to determine left ventricular ejection fraction (LVEF).

2.3 | ECG and definition of abnormal ECGs

A standard 12-lead ECG (25 mm/s, 10 mm/mV, 0.67–40 Hz bandpass filter; Shenzhen ECGMAC Medical Electronics Co., Ltd.) was recorded for enrolled patients before and after TnP.

The following automated ECG measurements were extracted: heart rate, PR interval, QRS duration (QRSD), QRS axis, QT interval, and Sokolow Lyon index (SLI). The following variables were measured manually: P-wave duration (PWD), P-wave amplitude (PWA), P-wave dispersion (Pd), QT dispersion (QTd), T-peak to T-end (Tp-Te), and QRS-wave amplitude (QRSWA) in each lead, and QRS transition zone on the precordial leads. Abnormal ECG was considered if any of the following features was present: sinus arrhythmia (sinus tachycardia and sinus bradycardia), atrial fibrillation, premature ventricular complex (PVC), conduction block (atrioventricular block and ventricular block), fragmented QRS (fQRS), pathological Q-wave, ST segment, or T-wave changes, prolonged QTc interval, clockwise rotation of QRS transitional zone (Chen et al., 2022), and low QRS voltage in limb and/or chest leads.

According to the ESC guidelines recommendation, the QTc interval is calculated using the Fridericia formula ($QTc = QT/RR^{1/3}$). QTc prolongation is defined as >450 ms for males and >460 ms for females (Lyon et al., 2022). Pathological Q-wave: Q-wave duration ≥40 ms, Q-wave amplitude ≥1/4 of the same lead R-wave (Delewi et al., 2013). QRSWA: the sum of absolute values of the maximum positive and negative wave amplitudes of the QRS-wave complex on each lead; if the QRS complex amplitudes of all six chest leads are less than 1.0 mV, it is defined as low QRS voltage (Kobayashi et al., 2017). fQRS was defined as: (1) a narrow QRS complex (<120 ms) with

additional R waves (R′); notches in the R or S waves; or the presence of more than one R′ in two contiguous leads; or (2) a wide QRS complex (≥120 ms) with more than two notches in the R or S waves (Das et al., 2008). Other methods for ECG measurement and specific definitions of abnormal ECG can refer to our previous publications (Chen et al., 2020; Liang et al., 2020).

To reduce measurement errors, all ECGs were transferred to a personal computer and measured manually after 400% magnification on the screen. ECG parameters were measured on three continuous heartbeats and the averages were calculated. All ECGs were analyzed and measured by two blinded and independent cardiologists (Z.C. and Y.Z.), further evaluated by a third senior reviewer (T.L.) if there was a significant disagreement.

2.4 | Statistical analysis

Continuous variables with normal distribution were presented as mean ± standard deviation (SD) and compared using paired *t*-test; otherwise, median, interquartile range, and Wilcoxon test were applied. Categorical variables were expressed as frequencies and percentages and analyzed by McNemar's test. Laboratory and echocardiographic observations with less than 10% missing values were imputed as mean values. A p value <.05 was considered statistically significant. The analysis was performed by using Statistical Package for the Social Sciences (SPSS) version 26.0.

3 | RESULTS

3.1 | Baseline characteristics

This study included a cohort of 60 patients diagnosed with BC, with a mean age of 66.4 ± 10.2 years. Twenty-five (41.7%), eight (13.3%), and five (8.3%) patients suffered from hypertension, diabetes mellitus, and coronary artery disease, respectively. Additionally, 25 patients (41.7%) were receiving treatment with cardiovascular drugs. Specifically, 23 patients (38.3%) were taking

TABLE 1 Baseline characteristics of included patients.

Characteristics	Total BC ($n = 60$)	MIBC ($n = 30$)	NMIBC ($n = 30$)	p value
Female, *n*%	14 (23.3)	7 (23.3)	7 (23.3)	.619
Age at diagnosis, year, mean ± SD	66.4 ± 10.2	66.7 ± 10.6	66.0 ± 9.9	.773
BMI, kg/m^2, mean ± SD	25.0 ± 3.5	24.4 ± 3.6	25.7 ± 3.3	.164
Systolic pressure, mmHg	131 (127, 140)	134 (128, 144)	130 (125, 135)	.084
Diastolic pressure, mmHg	80 (75, 83)	80 (70, 84)	79 (75, 81)	.734
Medical history, *n*%				
Hypertension	25 (41.7)	12 (40.0)	13 (43.3)	.500
Diabetes mellitus	8 (13.3)	4 (13.3)	4 (13.3)	.647
Dyslipidemia	3 (5)	1 (3.3)	2 (6.7)	.500
Renal insufficiency	2 (3.3)	2 (6.7)	0 (0.0)	.246
History of CVD				
Coronary artery disease	5 (8.3)	3 (10.0)	2 (6.7)	.500
Ischemic stroke	5 (8.3)	3 (10.0)	2 (6.7)	.500
Arrhythmias	4 (6.7)	3 (10.0)	1 (3.3)	.306
Cardiovascular medications, *n*%				
Antihypertensive drugs	23 (38.3)	12 (40.0)	11 (36.7)	.500
ACEI/ARBs	8 (13.3)	6 (20.0)	2 (6.7)	.500
β-Blocker	5 (8.3)	2 (6.7)	3 (10.0)	.500
CCBs	13 (13.3)	5 (16.7)	8 (26.7)	.266
Antidiabetic drugs	7 (11.7)	4 (13.3)	3 (10.0)	.500
Antiplatelet drugs	4 (6.7)	1 (3.3)	3 (10.0)	.306
Statins	1 (1.7)	0 (0.0)	1 (3.3)	.500
Smoking, *n* (%)	23 (38.3)	14 (46.7)	9 (30.0)	.144
Alcohol consumption, *n* (%)	11 (18.3)	5 (16.7)	6 (20.0)	.500
Family history with CVD, *n* (%)	1 (1.7)	0 (0.0)	1 (3.3)	.500
Family history with tumor, *n* (%)	2 (3.3)	0 (0.0)	2 (6.7)	.246
Other cancer, *n*%	5 (8.3)	2 (6.7)	4 (13.3)	.306

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CVD, cardiovascular disease; NMIBC, non-muscle-invasive bladder cancer.

TABLE 2 Laboratory variables change in included patients before and after TnP.

Variables	Reference range	Pre-TnP	Post-TnP	*p* value
cTnI, ng/mL	0–0.020	0.011 (0.011, 0.014)	0.013 (0.011, 0.013)	.367
NT-proBNP, ng/L	0–125	148.0 (30.4, 170.4)	146.9 (23.8, 187.6)	.735
CKMB, U/L	0–16	11.55 (7.53, 13.96)	9.83 (6.93, 11.21)	.176
CK, U/L	0–190	72.94 (49.30, 82.95)	115.08 (52.30, 115.08)	.008
D-dimer, ng/mL	0–500	796.3 (293.9, 783.5)	613.0 (281.1, 683.4)	.622
Albumin, g/L	40–55	42.4 (39.6, 45.0)	43.1 (40.9, 46.1)	.143
ALT, U/L	<35	25.5 (11.3, 23.4)	24.4 (13.6, 24.8)	.083
Creatinine, μmol/L	46–92	81.8 (67.8, 84.4)	78.9 (67.2, 84.2)	.749
Potassium, mmol/L	3.5–5.3	4.2 (3.9, 4.5)	4.2 (3.9, 4.6)	.636
FG, mmol/L	4.1–5.9	5.6 (4.9, 5.9)	5.6 (4.7, 5.9)	.501
WBC, $\times 10^9$/L	3.5–9.5	6.74 ± 2.19	6.53 ± 2.38	.385
HGB, g/L	115–150	135.1 ± 18.2	129.3 ± 17.0	.006
Platelets, $\times 10^9$/L	125–350	238 ± 72	250 ± 76	.026

Abbreviations: ALT, alanine aminotransferase; cTnI, cardiac troponin I; CKMB, creatine kinase–myocardial band; FG, fasting glucose; HGB, hemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide; TnP, tislelizumab plus nab-paclitaxel; WBC, white blood cell.

TABLE 3 Echocardiographic parameters change in patients before and after TnP.

	Pre-TnP	Post-TnP	*p* value
LAD, mm	36.53 ± 4.11	38.25 ± 8.32	.128
RVAWT, mm	3.48 ± 0.40	3.50 ± 0.33	.743
RVEDD, mm	20.73 ± 2.09	20.71 ± 3.42	.972
LVEDD, mm	47.58 ± 3.73	47.67 ± 4.28	.847
LVEF, %	62.81 ± 3.81	61.10 ± 4.37	.011
E/A	0.70 ± 0.19	0.73 ± 0.17	.451
E/e′	10.63 ± 3.24	10.94 ± 3.02	.436

Abbreviations: E/A: The ratio of early and late diastolic left ventricular filling peak velocity; E/e′, the ratio of early diastolic left ventricular filling peak velocity and early peak mitral annular velocity; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; RVAWT, right ventricular anterior wall thickness; RVEDD, right ventricular end-diastolic dimension; TnP, tislelizumab plus nab-paclitaxel.

antihypertensive agents, seven patients (11.7%) were taking antidiabetic agents, and four patients (6.7%) were taking antiplatelet agents. Among these patients, 30 individuals with MIBC underwent three cycles of TnP, while the remaining 30 NMIBC patients received four cycles of TnP, and no significant difference in baseline characteristics between the two subgroups was observed (Table 1).

3.2 | Laboratory test

Detailed laboratory test results are shown in Table 2 and Table S1. No significant changes in cardiac troponin I (cTnI), N-terminal pro-brain natriuretic peptide (NT-proBNP) were observed after TnP administration compared to baseline. However, creatine kinase was increased (72.94 (49.30–82.95) U/L to 115.08 (52.30–115.08) U/L, $p = .008$), hemoglobin was decreased ((135.1 ± 18.2) g/L to (129.3 ± 17.0) g/L, $p = .006$), and platelets ((238 ± 72) × 10^9/L to (250 ± 76) × 10^9/L, $p = .026$) were all within normal ranges.

3.3 | Echocardiography

Among the echocardiographic findings, all patients had a preserved LVEF (all ≥50%) around the treatment, but a slight decrease in mean LVEF was observed from (62.75 ± 3.98) % at baseline to (61.05 ± 4.03) % after TnP ($p = .010$) (Table 3; Table S2).

3.4 | Electrocardiography

The incidence of abnormal ECG rose from baseline 65.0% to 76.7% at the end of TnP, with fQRS prevalence increasing significantly (33.3% to 50.0%, $p = .039$), and almost all fQRS occurred on the inferior leads (Table 4). A similar difference in fQRS was also seen in MIBC patients (Table S3). A typical case of emerging fQRS is shown in Figure 1.

The changes in ECG parameters are detailed in Table 4 and Table S3. Following TnP, the PWD (108.03 ± 10.32 to 104.07 ± 12.33 ms, $p = .019$), QRSD (94.4 ± 12.39 to 92.63 ± 12.37 ms, $p = .009$), and Tp-Te (85.17 ± 12.83 to 77.67 ± 10.29 ms, $p < .05$) were considerably shortened, while QTd (39.50 ± 11.37 to 44.20 ± 15.85 ms, $p = .019$) increased significantly, which was more pronounced in the MIBC group than in the NMIBC group (Figure 2).

TABLE 4 ECG changes in patients during TnP.

	Pre-TnP	Post-TnP	*p* value
Abnormal ECG, *n* (%)	39 (65)	46 (76.7)	.118
ST-T changes, *n* (%)	6 (10.0)	7 (11.7)	1.000
ST changes, *n* (%)	3 (5.0)	1 (1.7)	.625
T-wave changes, *n* (%)	5 (8.3)	8 (13.4)	.250
QTc prolongation, *n* (%)	9 (15.0)	3 (5.0)	.070
fQRS, *n* (%)	20 (33.3)	30 (50.0)	.013
Inferior fQRS, *n* (%)	20 (33.3)	28 (46.7)	.039
Pathological Q wave, *n* (%)	1 (1.7)	2 (3.3)	1.000
Low QRS voltage, *n* (%)	4 (6.7)	4 (6.7)	1.000
Sinus arrhythmia, *n* (%)	8 (13.3)	6 (10.0)	.727
Atrial fibrillation, *n* (%)	1 (1.7)	2 (3.3)	1.000
PVC, *n* (%)	0	2 (3.3)	.500
First-degree AV block, *n* (%)	4 (6.7)	6 (10.0)	.500
Intraventricular block, *n* (%)	4 (6.7)	3 (5.0)	1.000
ECG parameters			
HR (bpm)	73.07 ± 11.01	74.02 ± 10.37	.493
PWD (ms)	108.03 ± 10.32	104.07 ± 12.33	.019
PRI (ms)	173.53 ± 30.37	178.37 ± 32.77	.246
QRS axis (°)	30.72 ± 31.99	31.10 ± 33.30	.816
QRSD (ms)	94.4 ± 12.39	92.63 ± 12.37	.009
QTc (ms)	419.47 ± 37.40	412.95 ± 26.46	.054
QTd (ms)	39.50 ± 11.37	44.20 ± 15.85	.019
Tp-Te (ms)	85.17 ± 12.83	77.67 ± 10.29	<.05
SLI (mV)	1.70 ± 0.70	1.68 ± 0.70	.695
iCEB	4.23 ± 0.61	4.23 ± 0.53	.886

Abbreviations: fQRS, fragmented QRS; HR, heart rate; iCEB, index of cardio-electrophysiological balance; PRI, PR interval; PVC, premature ventricular complex; PWD, P-wave duration; QRSD, QRS duration; QRSWA, QRS-wave amplitude; QTd, QT dispersion; QTI, QT interval; QTc, corrected QT interval; SLI, Sokolow–Lyon index; TpTe, T-peak to T-end; TnP, tislelizumab plus nab-paclitaxel.

4 | DISCUSSION

This study evaluated cardiovascular changes using echocardiography and ECG in patients with bladder cancer receiving preoperative chemotherapy and immunotherapy. We found that hypertension was the most common comorbidity (41.7%), and aberrant ECGs increased from 65.0% at baseline to 76.7% after treatment, which was mainly due to a higher proportion of fQRS. Among ECG parameters, PWD, QRSD, and Tp-Te were significantly shortened, but PWA, Pd, and QTd increased after the regimen. In addition, cTnI, NT-proBNP, and echocardiographic parameters were within normal limits.

With great advancements in anti-tumor therapy and extension of survival, CVD is becoming an important issue for cancer survivors (Chan, Satti, et al., 2023; Zhang, Wei, et al., 2023). In a retrospective study of 1638 patients with BC by Barone et al., hypertension (59.9%), CVD (23.4%), and diabetes mellitus (22.4%) were the most common comorbidities (Barone et al., 2023). Another study from France found that the patients with MIBC who received cisplatin-based neoadjuvant chemotherapy had a median age of 79 years old, and the prevalence of hypertension, atherosclerosis, and smoking were 36%, 13%, and 66%, respectively (Dumont et al., 2023). These findings were consistent with our results, suggesting a high burden of CVD and risk factors, as well as the necessity for timely intervention by clinicians.

Our previous studies have shown that the incidence of abnormal ECG in patients with diffuse large B-cell lymphoma and breast cancer increased by 12% (36% to 48%) and 22% (43% to 66%), respectively, after anthracycline-based chemotherapy (Chen et al., 2020; Liang et al., 2020). Similar changes were also observed in the present study. However, a small sample study from China revealed that the prevalence of abnormal ECGs decreased by 10% (46% to 36%) following nab-paclitaxel-containing therapy in breast cancer (Wang et al., 2022). Another prospective study found that 41 cancer patients (38.68%) developed various ECG abnormalities among 106 patients receiving ICI therapy (Zhang, Chen, et al., 2023). These differences may be related to differences in population, comorbidities, and cancer therapies and require more epidemiological studies.

Notably, the main increase in abnormal ECG was fQRS (33.3% to 50.0%, $p = .041$), and nearly all of these occurred in inferior leads. As a marker of abnormal ventricular depolarization and

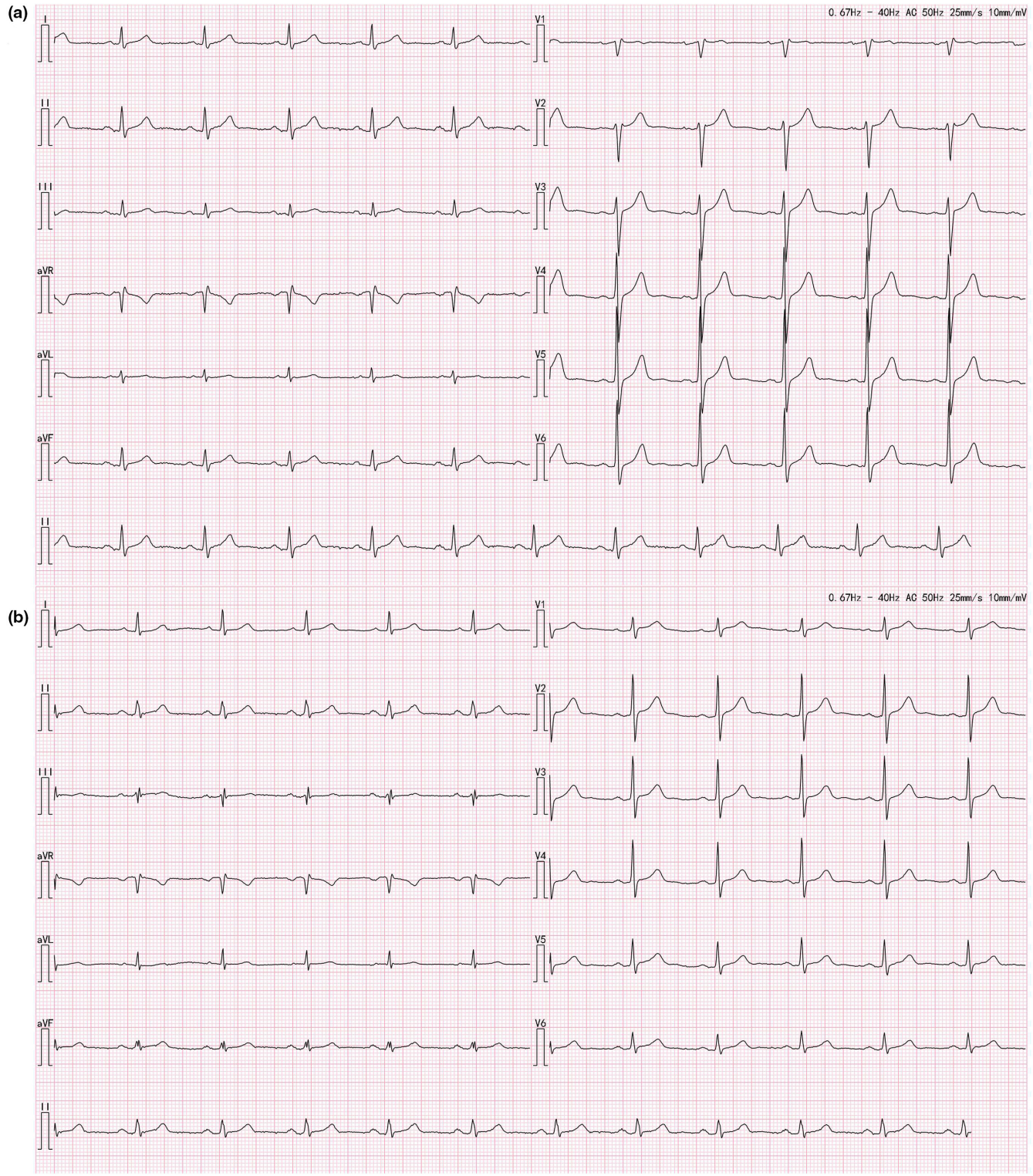

FIGURE 1 An example of ECG changes in a 67-year-old man. (a) Normal ECG at baseline. (b) An emerging fQRS on the inferior leads (II, III, and aVF) after preoperative therapy.

myocardial fibrosis, the proportion of fQRS was also increased significantly after chemotherapy in patients with DLBCL (15.8% to 28.9%, $p = .041$) and breast cancer (26.6% to 53.1%, $p < .01$; Chen et al., 2020; Das et al., 2008; Liang et al., 2020). However, the clinical significance of fQRS may vary depending on its different distribution in the coronary artery territory. A large general population study from Finland found that the incidence of fQRS was 19.7%, with 15.7%, 0.8%, and 2.9% in the inferior, lateral, and anterior leads, respectively. Only lateral fQRS was associated with a higher risk of all-cause mortality, arrhythmia, and cardiogenic death (Terho et al., 2014). Another study in heart failure patients with preserved ejection fraction showed that both inferior and

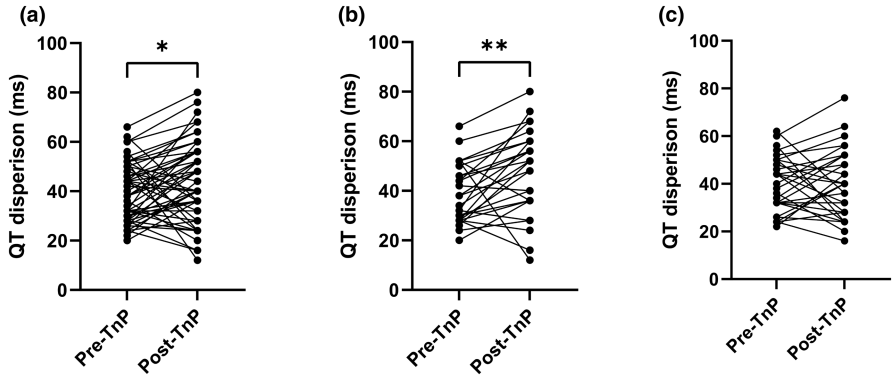

FIGURE 2 QT dispersion (QTd) change during TnP. (a) QTd increased in the total patients with BC after the therapy ($p = .019$). Subgroup analyses showed that QTd only increased in (b) patients with MIBC ($p = .009$), but not in (c) patients with NMIBC (*$p < 0.05$; **$p < 0.01$).

anterior/lateral fQRS were associated with a higher-risk cardiovascular and all-cause mortality (Sung et al., 2023). The prognostic value of fQRS in cancer populations will be the subject of further investigation.

QTd is measured as the change between the maximum and minimum QT interval within a 12-lead ECG, and reflects the regional heterogeneity of ventricular repolarization. As a traditional ECG predictor of ventricular arrhythmias, several studies have shown that QTd was associated with a greater risk of malignant arrhythmias in patients with heart failure or myocardial infarction (Bazoukis et al., 2020). However, Cosgun et al. found no distinct relationship between QTd and SYNTAX score-assessed coronary artery disease severity in patients with stable angina pectoris (Cosgun et al., 2021). Furthermore, it has been reported that QTd prolonged significantly in patients with gastrointestinal cancer and non-Hodgkin lymphoma following chemotherapy (Kuittinen et al., 2010; Oztop et al., 2004). Another research showed that ICI combination treatment significantly increased QTd in patients with advanced melanoma (31 ± 14 ms vs. 50 ± 14 ms, $p < .0001$), whereas ICI monotherapy had no effect on QTd (Pohl et al., 2020). Our results supported the findings mentioned above and appeared to emphasize the potential cardiotoxicity caused by ventricular repolarization instability.

The underlying mechanisms of abnormalities in ventricular depolarization and repolarization reflected by fQRS and QTd are not yet fully elucidated in BC patients treated with nab-paclitaxel and tislelizumab. Conventional microtubule inhibitors, such as paclitaxel and docetaxel, have been associated with an increased risk of reversible asymptomatic sinus bradycardia, conduction block, and myocardial ischemia, possibly due to abnormal calcium handling and histamine release induced by vehicle cremophor (Al-Mahayri et al., 2021). Nab-paclitaxel is a novel nanoparticle albumin-bound paclitaxel with an improved safety than traditional forms (Henderson & Bhatia, 2007). However, there are no reports regarding the effects of nab-paclitaxel on ECG parameters. On the other hand, ECG abnormalities in patients with ICI-associated myocarditis have been well described, with cardiac inflammation and fibrosis playing an important role (Zlotoff et al., 2021), but the exact mechanism of ECG alteration in asymptomatic patients treated with short-term ICI is currently unknown. In a preclinical study, Vincenzo et al. found that 10 days of ICI treatment could increase myocardial fibrosis and induce pro-inflammatory cytokine storm through NLRP-3 and MyD-88 pathways (Quagliariello et al., 2022). Another basic research demonstrated that short-term ICI therapy in mice induces T-cell-mediated plaque inflammation and worsens plaque progression (Poels et al., 2020). The same phenomenon may also occur in elderly cancer patients with comorbidities who often have subclinical atherosclerosis, ultimately leading to myocardial ischemia and fibrosis. We speculate that these factors may partly account for the increased fQRS and QTd in BC patients who received preoperative chemotherapy and immunotherapy.

Moreover, we also found a slight impairment of LVEF in BC patients, but none of them meet the definition of cancer therapy-related cardiovascular toxicity according to current guidelines (Lyon et al., 2022). Interestingly, changes in fQRS, QTd, and LVEF were more significant in patients with MIBC than NMIBC, despite similar baseline characteristics and the fact that NMIBC patients received one more cycle of TnP therapy. Future studies are warranted to investigate the correlation among myocardial histological changes, cardiac function, and electrocardiographic characteristics using advanced imaging techniques such as CMR and PET-CT.

This study has several limitations. First, as a single-center study, the sample was limited. Second, there was a lack of long-term follow-up. Finally, the ability of different ECG biomarkers to predict adverse outcomes was not investigated. Future studies with larger sample sizes and long-term follow-up are needed to determine the relationship between abnormal ECG parameters and clinical outcomes.

5 | CONCLUSION

In summary, ECG parameters including fQRS and QTd were significantly altered in BC patients receiving preoperative chemotherapy combined with immunotherapy. Regular ECG monitoring should be carried out carefully to detect potential cardiotoxicity on the follow-up.

AUTHOR CONTRIBUTIONS

Tong Liu, Hai-Long Hu, and Zi-Liang Chen contributed to the conception and design of the research. Zi-Liang Chen and Kai-Peng Jia

performed the data analyses, interpreted the data, and wrote the manuscript. Zi-Liang Chen, Kai-Peng Jia, Yi Zheng, Nan Zhang, and Xin Wang contributed to the data collection. Tong Liu and Zhi-Wei Zhang contributed to obtaining financing. Gary Tse, Hai-Long Hu, and Tong Liu contributed to critical revision of the manuscript. All authors read and approved the final draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was conducted in accordance with the declaration of Helsinki.

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REFERENCES

Al-Mahayri, Z. N., AlAhmad, M. M., & Ali, B. R. (2021). Current opinion on the pharmacogenomics of paclitaxel-induced toxicity. *Expert Opinion on Drug Metabolism & Toxicology*, *17*(7), 785–801. https://doi.org/10.1080/17425255.2021.1943358

Barone, B., Finati, M., Cinelli, F., Fanelli, A., Del Giudice, F., De Berardinis, E., Sciarra, A., Russo, G., Mancini, V., D'Altilia, N., Ferro, M., Porreca, A., Chung, B. I., Basran, S., Bettocchi, C., Cormio, L., Imbimbo, C., Carrieri, G., Crocetto, F., & Busetto, G. M. (2023). Bladder cancer and risk factors: Data from a multi-institutional long-term analysis on cardiovascular disease and cancer incidence. *Journal of Personalized Medicine*, *13*(3), 512. https://doi.org/10.3390/jpm13030512

Bazoukis, G., Yeung, C., Wui Hang Ho, R., Varrias, D., Papadatos, S., Lee, S., Ho Christien Li, K., Sakellaropoulou, A., Saplaouras, A., Kitsoulis, P., Vlachos, K., Lampropoulos, K., Thomopoulos, C., Letsas, K. P., Liu, T., & Tse, G. (2020). Association of QT dispersion with mortality and arrhythmic events—A meta-analysis of observational studies. *Journal of Arrhythmia*, *36*(1), 105–115. https://doi.org/10.1002/joa3.12253

Chan, J. S. K., Lakhani, I., Lee, T. T. L., Chou, O. H. I., Lee, Y. H. A., Cheung, Y. M., Yeung, H. W., Tang, P., Ng, K., Dee, E. C., Liu, T., Wong, W. T., Tse, G., & Leung, F. P. (2023). Cardiovascular outcomes and hospitalizations in Asian patients receiving immune checkpoint inhibitors: A population-based study. *Current Problems in Cardiology*, *48*(1), 101380. https://doi.org/10.1016/j.cpcardiol.2022.101380

Chan, J. S. K., Satti, D. I., Dee, E. C., Sharma, G., Virani, S. S., Liu, T., & Tse, G. (2023). Association between psychological distress and cardiovascular health amongst cancer survivors in the United States: Findings from nationally representative data. *European Journal of Preventive Cardiology*, *30*(16), e74–e77. https://doi.org/10.1093/eurjpc/zwad162

Chen, Z., Lu, K., Zhou, L., Liu, D., Li, X., Han, X., Tao, H., Tse, G., Zhang, H., & Liu, T. (2020). Electrocardiographic characteristics of diffuse large B-cell lymphoma patients treated with anthracycline-based chemotherapy. *Journal of Electrocardiology*, *60*, 195–199. https://doi.org/10.1016/j.jelectrocard.2020.04.024

Chen, Z., Yuan, M., Aro, A. L., Tse, G., Li, G., & Liu, T. (2022). Association between electrocardiographic QRS transition zone and mortality from all causes and cardiovascular diseases: A systematic review and meta-analysis. *Journal of Electrocardiology*, *73*, 62–67. https://doi.org/10.1016/j.jelectrocard.2022.05.012

Cosgun, M., Erdal, E., Gunes, Y., Sincer, I., & Mansiroglu, A. K. (2021). Evaluation of electrocardiographic ventricular repolarization parameters in stable coronary artery disease. *Experimental Biomedical Research*, *4*(2), 141–147. https://doi.org/10.30714/j-ebr.2021267977

Das, M. K., Suradi, H., Maskoun, W., Michael, M. A., Shen, C., Peng, J., Dandamudi, G., & Mahenthiran, J. (2008). Fragmented wide QRS on a 12-lead ECG: A sign of myocardial scar and poor prognosis. *Circulation. Arrhythmia and Electrophysiology*, *1*(4), 258–268. https://doi.org/10.1161/CIRCEP.107.763284

Delewi, R., Ijff, G., van de Hoef, A., Hirsch, A., Robbers, L. F., Nijveldt, R., van der Laan, A. M., van der Vleuten, P. A., Lucas, C., Tijssen, J. G. P., van Rossum, A. C., Zijlstra, F., & Piek, J. J. (2013). Pathological Q Waves in Myocardial Infarction in Patients Treated by Primary PCI. *JACC: Cardiovascular Imaging*, *6*(3), 324–331. https://doi.org/10.1016/j.jcmg.2012.08.018

Dumont, C., Aregui, A., Hauchecorne, M., Lefèvre, M., Aussedat, Q., Reignier, P.-L., Gauthier, H., Hennequin, C., Fossey-Diaz, V., Xylinas, E., Pachev, A., Desgrandchamps, F., Masson-Lecomte, A., & Culine, S. (2023). Safety and efficacy of preoperative chemotherapy for muscle-invasive bladder cancer in elderly patients. *World Journal of Urology*, *41*(10), 2715–2722. https://doi.org/10.1007/s00345-023-04561-2

Funt, S. A., Lattanzi, M., Whiting, K., Al-Ahmadie, H., Quinlan, C., Teo, M. Y., Lee, C. H., Aggen, D., Zimmerman, D., McHugh, D., Apollo, A., Durdin, T. D., Truong, H., Kamradt, J., Khalil, M., Lash, B., Ostrovnaya, I., McCoy, A. S., Hettich, G., … Rosenberg, J. E. (2022). Neoadjuvant Atezolizumab with gemcitabine and cisplatin in patients with muscle-invasive bladder cancer: A multicenter, single-arm, phase II trial. *Journal of Clinical Oncology*, *40*(12), 1312–1322. https://doi.org/10.1200/jco.21.01485

Henderson, I. C., & Bhatia, V. (2007). Nab-paclitaxel for breast cancer: A new formulation with an improved safety profile and greater efficacy. *Expert Review of Anticancer Therapy*, *7*(7), 919–943. https://doi.org/10.1586/14737140.7.7.919

Kobayashi, A., Misumida, N., Aoi, S., & Kanei, Y. (2017). Low QRS voltage on presenting electrocardiogram predicts multi-vessel disease in anterior ST-segment elevation myocardial infarction. *Journal of Electrocardiology*, *50*(6), 870–875. https://doi.org/10.1016/j.jelectrocard.2017.06.012

Kong, J., Diao, X., Diao, F., Fan, X., Zheng, J., Yan, D., Huang, J., Qin, H., & Lin, T. (2019). Causes of death in long-term bladder cancer survivors: A population-based study. *Asia-Pacific Journal of Clinical Oncology*, *15*(5), e167–e174. https://doi.org/10.1111/ajco.13156

Kuittinen, T., Jantunen, E., Vanninen, E., Mussalo, H., Nousiainen, T., & Hartikainen, J. (2010). Late potentials and QT dispersion after high-dose chemotherapy in patients with non-Hodgkin lymphoma. *Clinical Physiology and Functional Imaging*, *30*(3), 175–180. https://doi.org/10.1111/j.1475-097X.2009.00920.x

Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F. A., Foster, E., Goldstein, S. A., Kuznetsova, T., Lancellotti, P., Muraru, D., Picard, M. H., Rietzschel, E. R., Rudski, L.,

Spencer, K. T., Tsang, W., & Voigt, J.-U. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart Journal Cardiovascular Imaging*, *16*(3), 233–270. https://doi.org/10.1093/ehjci/jev014

Liang, X., Wang, Y., Yin, X., Gong, X., Pan, S., Chen, Z., & Geng, X. (2020). Electrocardiographic characteristics of breast cancer patients treated with chemotherapy. *Cardiology Research and Practice*, *2020*, 6678503. https://doi.org/10.1155/2020/6678503

Lyon, A. R., López-Fernández, T., Couch, L. S., Asteggiano, R., Aznar, M. C., Bergler-Klein, J., Boriani, G., Cardinale, D., Cordoba, R., Cosyns, B., Cutter, D. J., de Azambuja, E., de Boer, R. A., Dent, S. F., Farmakis, D., Gevaert, S. A., Gorog, D. A., Herrmann, J., Lenihan, D., … van der Pal, H. J. H. (2022). 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the international cardio-oncology society (IC-OS). *European Heart Journal*, *43*(41), 4229–4361. https://doi.org/10.1093/eurheartj/ehac244

Oztop, I., Gencer, M., Okan, T., Yaren, A., Altekin, E., Turker, S., & Yilmaz, U. (2004). Evaluation of cardiotoxicity of a combined bolus plus Infusional 5-fluorouracil/Folinic acid treatment by echocardiography, plasma troponin I level, QT interval and dispersion in patients with gastrointestinal system cancers. *Japanese Journal of Clinical Oncology*, *34*(5), 262–268. https://doi.org/10.1093/jjco/hyh047

Poels, K., van Leent, M. M. T., Boutros, C., Tissot, H., Roy, S., Meerwaldt, A. E., Toner, Y. C., Reiche, M. E., Kusters, P. J., Malinova, T., Huveneers, S., Kaufman, A. E., Mani, V., Fayad, Z. A., de Winther, M. P., Marabelle, A., Mulder, W. J., Robert, C., Seijkens, T. T., & Lutgens, E. (2020). Immune checkpoint inhibitor therapy aggravates T cell-driven plaque inflammation in atherosclerosis. *JACC CardioOncology*, *2*(4), 599–610. https://doi.org/10.1016/j.jaccao.2020.08.007

Pohl, J., Mincu, R. I., Mrotzek, S. M., Hinrichs, L., Michel, L., Livingstone, E., Zimmer, L., Wakili, R., Schadendorf, D., Rassaf, T., & Totzeck, M. (2020). ECG changes in melanoma patients undergoing cancer therapy-data from the ECoR registry. *Journal of Clinical Medicine*, *9*(7), 2060. https://doi.org/10.3390/jcm9072060

Quagliariello, V., Passariello, M., Di Mauro, A., Cipullo, C., Paccone, A., Barbieri, A., Palma, G., Luciano, A., Buccolo, S., Bisceglia, I., Canale, M. L., Gallucci, G., Inno, A., De Lorenzo, C., & Maurea, N. (2022). Immune checkpoint inhibitor therapy increases systemic SDF-1, cardiac DAMPs fibronectin-EDA, S100/calgranulin, galectine-3, and NLRP3-MyD88-chemokine pathways. *Frontiers in Cardiovascular Medicine*, *9*, 930797. https://doi.org/10.3389/fcvm.2022.930797

Ramamoorthy, V., Chan, K., Appunni, S., Zhang, Z., Ahmed, M. A., McGranaghan, P., Saxena, A., & Rubens, M. (2023). Prevalence and trends of perioperative major adverse cardiovascular and cerebrovascular events during cancer surgeries. *Scientific Reports*, *13*(1), 2410. https://doi.org/10.1038/s41598-023-29632-7

Richters, A., Aben, K. K. H., & Kiemeney, L. A. L. M. (2020). The global burden of urinary bladder cancer: An update. *World Journal of Urology*, *38*(8), 1895–1904. https://doi.org/10.1007/s00345-019-02984-4

Singh, A., Osbourne, A. S., & Koshkin, V. S. (2023). Perioperative immunotherapy in muscle-invasive bladder cancer. *Current Treatment Options in Oncology*, *24*(9), 1213–1230. https://doi.org/10.1007/s11864-023-01113-z

Sung, K.-T., Chang, S.-H., Chi, P.-C., Chien, S.-C., Lo, C.-I., Lin, C.-F., Huang, W. H., Yun, C. H., Tsai, C. T., Su, C. H., Hou, C. J., Yeh, H. I., Tsao, C. H., Kuo, J. Y., & Hung, C.-L. (2023). QRS fragmentation in preserved ejection fraction heart failure: Functional insights, pathological correlates, and prognosis. *Journal of the American Heart Association*, *12*(6), e028105. https://doi.org/10.1161/JAHA.122.028105

Terho, H. K., Tikkanen, J. T., Junttila, J. M., Anttonen, O., Kenttä, T. V., Aro, A. L., Kerola, T., Rissanen, H. A., Reunanen, A., & Huikuri, H. V. (2014). Prevalence and prognostic significance of fragmented QRS complex in middle-aged subjects with and without clinical or electrocardiographic evidence of cardiac disease. *The American Journal of Cardiology*, *114*(1), 141–147. https://doi.org/10.1016/j.amjcard.2014.03.066

Thuny, F., Naidoo, J., & Neilan, T. G. (2022). Cardiovascular complications of immune checkpoint inhibitors for cancer. *European Heart Journal*, *43*(42), 4458–4468. https://doi.org/10.1093/eurheartj/ehac456

Tse, G., Shao, Q., Liu, J., & Zhang, Y. (2023). The potential impact of the 2022 ESC cardio-oncology guidelines on clinical practice in China. *JACC CardioOncology*, *5*(1), 153–155. https://doi.org/10.1016/j.jaccao.2023.01.003

Wang, W., Wang, L., Chang, J.-Y., Hu, F., Yan, J.-Y., Zhang, J., Liang, Y. P., Zhang, H. W., Wu, H. P., & Cai, H.-F. (2022). Cardiotoxicity monitoring of pyrotinib in combination with nab-paclitaxel, doxorubicin, and cyclophosphamide in HER2-positive breast cancer: A single-armed clinical trial. *Gland Surgery*, *11*(4), 742–750. https://doi.org/10.21037/gs-22-161

Zhang, C., Chen, Z., Qin, S., Zhu, Y., Shu, L., & Zuo, Z. (2023). Incidence of adverse cardiovascular events associated with immune checkpoint inhibitors and risk factors for left ventricular dysfunction: A single-center prospective clinical study. *Frontiers in Cardiovascular Medicine*, *10*, 1052699. https://doi.org/10.3389/fcvm.2023.1052699

Zhang, N., Wei, Z., Zhang, Y., Zhang, Q., Chen, Z., Tse, G., Li, G., Liu, T., & Wu, S. (2023). Association of Life's essential 8 with incident atherosclerotic cardiovascular disease in cancer patients: The Kailuan prospective cohort study. *European Journal of Preventive Cardiology*, *30*(17), e78–e80. https://doi.org/10.1093/eurjpc/zwad256

Zlotoff, D. A., Hassan, M. Z. O., Zafar, A., Alvi, R. M., Awadalla, M., Mahmood, S. S., Zhang, L., Chen, C. L., Ederhy, S., Barac, A., Banerji, D., Jones-O'Connor, M., Murphy, S. P., Armanious, M., Forrestal, B. J., Kirchberger, M. C., Coelho-Filho, O. R., Rizvi, M. A., Sahni, G., … Neilan, T. G. (2021). Electrocardiographic features of immune checkpoint inhibitor associated myocarditis. *Journal for Immunotherapy of Cancer*, *9*(3), e002007. https://doi.org/10.1136/jitc-2020-002007

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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