

Corrected QT Interval Variability as a Predictor of Malignant Ventricular Arrhythmia Due to Anthracyclines in Breast Cancer

Variabilidad del intervalo QT corregido como predictor de arritmia ventricular maligna por antraciclinas en cáncer de mama

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ABSTRACT

Background: One of the most common cardiotoxic effects of anthracyclines is malignant ventricular arrhythmia. Corrected QT interval (QTc) variability has emerged as a potential electrocardiographic predictor.

Objective: The aim of this study was to determine the influence of QTc variability on the onset of malignant ventricular arrhythmia in patients with breast cancer treated with anthracyclines.

Methods: A prospective, longitudinal, observational study was conducted at Lenin Hospital in Holguín (Cuba) from June 2023 to June 2025. A total of 150 patients with breast cancer treated with anthracyclines were included. QTc was measured at baseline, after each treatment cycle, and at 3 and 12 months. Descriptive and inferential statistics were used, including multivariate logistic regression.

Results: Mean age was 55.3 ± 9.8 years, and mean body mass index (BMI) was 32.4 ± 2.1 kg/m². Eighty-one percent of patients had at least one cardiovascular risk factor. QTc showed a progressive increase from baseline (418 ± 19 ms) to post-cycle 4 (463 ± 26 ms). The intra-subject QTc variability (coefficient of variation) was $15.3 \pm 4.2\%$. There was a significant positive correlation between the number of risk factors and QTc prolongation ($\rho = 0.55$; $r^2 = 0.30$; $p < 0.001$). Obesity ($\beta = 24.7$ ms) and hypertension ($\beta = 15.2$ ms) were the strongest independent predictors of QTc prolongation. Twenty-five patients (16.7%) developed malignant ventricular arrhythmia during follow-up. In the multivariate analysis, QT variability was independently associated with malignant ventricular arrhythmia (adjusted OR = 5.90; 95% CI 2.41–14.46; $p < 0.001$).

Conclusions: QTc interval variability during anthracycline therapy is an early and independent marker of risk for malignant ventricular arrhythmia. Obesity and hypertension enhance this effect. Serial QTc interval assessment and variability calculation could improve risk stratification in cardiooncology.

Key words: Ventricular arrhythmia - Anthracyclines - Cardiotoxicity - Breast cancer - Risk factors - QT interval

RESUMEN

Introducción: Uno de los efectos cardiotóxicos más frecuentes de las antraciclinas es la arritmia ventricular maligna. La variabilidad del intervalo QT corregido (QTc) emerge como un predictor electrocardiográfico potencial.

Objetivo: Determinar la influencia de la variabilidad del QTc en la aparición de arritmia ventricular maligna en pacientes con cáncer de mama tratadas con antraciclinas.

Material y métodos: Se realizó un estudio observacional longitudinal prospectivo en el Hospital Lenin de Holguín (Cuba) de junio de 2023 a junio de 2025. Se incluyeron 150 pacientes con cáncer de mama tratadas con antraciclinas. Se midió el QTc basal, post-cada ciclo, a los 3 y 12 meses. Se utilizó estadística descriptiva e inferencial, incluyendo regresión logística multivariante.

Resultados: La edad media fue $55,3 \pm 9,8$ años y el índice de masa corporal (IMC) promedio de $32,4 \pm 2,1$ kg/m². El 81,3% presentó al menos un factor de riesgo cardiovascular. El QTc mostró un incremento progresivo desde el basal (418 ± 19 ms) hasta el post-ciclo 4 (463 ± 26 ms). La variabilidad intra-sujeto del QTc (coeficiente de variación) fue del $15,3 \pm 4,2\%$. Existió correlación positiva significativa entre el número de factores de riesgo y la prolongación del QTc ($\rho = 0,55$; $r^2 = 0,30$; $p < 0,001$). La obesidad ($\beta = 24,7$ ms) y la hipertensión arterial (HTA) ($\beta = 15,2$ ms) constituyeron los predictores independientes más fuertes del incremento del QTc. Veinticinco pacientes (16,7%) desarrollaron arritmia ventricular maligna durante el seguimiento. En el análisis multivariante, la variabilidad del QT se asoció de forma independiente con la arritmia ventricular maligna (OR ajustado = 5,90; IC95% 2,41-14,46; $p < 0,001$).

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Conclusiones: La variabilidad del intervalo QTc durante el tratamiento con antraciclinas constituye un marcador precoz e independiente de riesgo de arritmia ventricular maligna. La obesidad y la HTA potencian este efecto. La medición seriada del QTc y el cálculo de su variabilidad podrían mejorar la estratificación del riesgo en cardiooncología.

Palabras clave: Arritmia ventricular - Antraciclinas - Cardiotoxicidad - Cáncer de mama - Factores de riesgo - Intervalo QT

INTRODUCTION

Cancer, characterized by uncontrolled cell proliferation and tissue invasion, is an ancient disease that has accompanied humankind since its origins, with records dating back three or four million years. (1) By 2030, there are projected to be more than 20 million new cases and 9.8 million cancer deaths worldwide, surpassed only by cardiovascular diseases (more than 17 million); in the United States, deaths will exceed 2 million. (2) In Cuba, in 2023, malignant tumors were the second leading cause of death (crude rate of 246.0/100.000 inhabitants, 25 199 deaths), only preceded by cardiovascular diseases and together, they accounted for 48.67% of overall mortality. In Holguín, 2300 deaths from malignant tumors were recorded (rate of 241.7/100 000 inhabitants), the second leading cause of death behind cardiovascular diseases. (3)

New cancer therapies have increased survival rates, but at the cost of increasing the risk of cardiovascular events due to cardiotoxicity, (4) defined as cardiovascular conditions resulting directly or indirectly from anticancer treatment. (5) This cardiotoxicity can be acute or subacute—including ventricular repolarization abnormalities, corrected QT interval (QTc) changes, supraventricular or ventricular arrhythmias, coronary syndromes, pericarditis, and myocarditis, occurring from the onset of treatment to the first year post-treatment—or chronic. (6)

In breast cancer, treatment regimens include anthracyclines, which are highly effective but limited by cardiotoxicity. (7,8) Chemotherapy can induce arrhythmias through multifactorial pathogenesis: primary arrhythmias due to potassium channel inhibition (QTc prolongation and torsade de pointes [TdP]), or secondary arrhythmias due to structural damage that leads to ischemia, inflammation, and arrhythmias. (9)

QTc interval prolongation is an established risk factor for malignant ventricular arrhythmias (MVA): TdP, sustained/non-sustained ventricular tachycardia, ventricular fibrillation, and sudden cardiac death, raising growing concern about cancer-related cardiotoxicity. (10,11) Currently, there are limited data on the incidence of serious QTc-related events in cancer patients. In the non-cancer population, it ranges from 2.5 events per million years and 12.5% with antiarrhythmic drugs. (12) Drugs such as anthracyclines, despite their specificity, prolong QTc interval, alter repolarization, and increase the risk of MVA and sudden death. (13)

Cancer patients are particularly prone to QTc

prolongation due to multiple risk factors and comorbidities: (12) advanced age, diabetes mellitus, left ventricular hypertrophy, and ischemic heart disease, common conditions in this population and that increase susceptibility to repolarization abnormalities. (14,15)

The European Society of Cardiology Cardio-Oncology Guideline, (16) adopted by the Provincial Cardiology Service at Vladimir Ilich Lenin Hospital in Holguín, establishes a monitoring protocol for anthracycline therapy that includes a baseline electrocardiogram to assess QTc, but does not require its repetition in subsequent cycles, regardless of the patient's cardiovascular risk.

A review of the literature reveals a gap in the systematization of electrical cardiotoxicity prediction and in the analysis of the dynamic relationship between QTc interval variability, cardiovascular risk factors, and the onset of MVA during anthracycline treatment. Current protocols do not include serial electrocardiographic follow-up after each cycle nor do they incorporate the integrated assessment of comorbidities as modulators of arrhythmic risk. Validated tools are needed for clinical decision-making to stratify individual risk of serious arrhythmias. It is essential that cardiologists and electrophysiologists understand the association between each anticancer agent and specific arrhythmias for an early identification of drug-induced arrhythmias, in order to treat them effectively, and improve the survival of these patients.

OBJECTIVE

The aim of this study was to determine the influence of QTc interval variability on the occurrence of MVA in patients with breast cancer treated with anthracyclines at Vladimir Ilich Lenin Hospital in Holguín from June 2023 to June 2025.

METHODS

Study Design and Population

A prospective, longitudinal, observational study was conducted at Vladimir Ilich Lenin University Hospital. The study population consisted of 150 female patients diagnosed with breast cancer and undergoing chemotherapy with anthracyclines, meeting the inclusion and exclusion criteria.

Inclusion criteria: Adult patients (age ≥ 18 years) with a histopathological diagnosis of breast cancer, scheduled to begin a chemotherapy regimen including doxorubicin (adriamycin), with a left ventricular ejection fraction (LVEF) $\geq 50\%$ confirmed by baseline echocardiography, and who signed an informed consent form.

Exclusion criteria: Patients with known history of structural heart disease, coronary artery disease, congenital channelopathies, sustained atrial or ventricular arrhythmias on the baseline ECG, use of medications that prolong the

QTc interval, uncorrected hypokalemia or hypomagnesemia, or end-stage renal disease.

A total of 150 female patients were included, with a mean age of 55.3 ± 9.8 years (range: 32–75 years). Demographic variables such as age and body mass index (BMI) and cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking) were collected using a standardized questionnaire at the onset the study.

Follow-up

Of the 150 patients included, 145 completed the 12-month follow-up (retention rate of 96.7%). The 5 losses (3.3%) were due to relocation to another province ($n = 2$), treatment discontinuation ($n = 2$), and death from a non-cardiovascular cause ($n = 1$). Given the low percentage of losses, no data imputation was performed, and the analysis is based on the cases available at each time point.

Chemotherapy and Intervention Protocol

Drug: doxorubicin (Adriamycin, Pfizer Inc., New York, NY, USA).

Dose: 60 mg/m² of body surface area per cycle.

Administration: diluted in 500 mL 5% dextrose, infused intravenously over 60 minutes.

Regimen: Four cycles were administered, with a 21-day interval between each cycle.

Electrocardiographic evaluations and QTc measurements.

Timing of recordings: ECGs were performed at 7 time points: baseline (pre-chemotherapy), at the end of each of the 4 cycles, and 3 months and 12 months post-treatment.

QT correction and analysis: The QT interval was corrected for heart rate (QTc) using the Fridericia formula:

$QTc = QT \text{ (sec)} / \text{cube root of the RR interval (sec)}$. Prolonged QTc was defined as >470 ms.

Definition of malignant ventricular arrhythmia (MVA): MVA was defined as the documented presence of at least one of the following events during follow-up: sustained ventricular tachycardia (duration ≥ 30 seconds or requiring intervention), non-sustained ventricular tachycardia (≥ 3 beats, heart rate ≥ 100 bpm, duration <30 seconds) in the context of symptoms or electrical instability, TdP, or ventricular fibrillation. Detection was performed using a 12-lead ECG (if the event occurred during consultation), scheduled 24-hour Holter monitoring (performed in all patients one month post-cycle 4), or continuous monitoring during unscheduled hospitalizations due to palpitations or syncope. All events were independently adjudicated by two cardiologists of the team.

QTc variability metrics: Three parameters were calculated to quantify the temporal variability of repolarization:

- Maximum ΔQTc : Maximum difference (in ms) between any post-treatment QTc and the baseline value.
- QTc coefficient of variation (QTV): Calculated as (standard deviation of each patient's 7 QTc measurements / mean of those 7 measurements) $\times 100\%$. It represents the temporal instability of repolarization.
- Absolute maximum QTc: The highest value recorded throughout the follow-up period.

Definitions

Complex PCI is defined as that involving the treatment of multiple vessels, unprotected left main coronary artery approach, intervention on a venous bypass graft, management of a true bifurcation, or treatment of lesions with severe calcification requiring calcium ablation techniques or thrombotic lesions. Ad hoc PCI is defined as PCI performed immediately after diagnostic coronary angiography, while planned PCI is performed as a scheduled intervention at a later time after coronary angiography. CIN was defined as an increase of ≥ 0.5 mg/dL or $\geq 25\%$ of baseline serum creatinine within 48–72 hours after the procedure.

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Statistical Analysis

The analysis was performed using SPSS software v.28.0 (IBM Corp., Armonk, NY, USA), with a significance level of $\alpha = 0.05$ (two-sided).

Descriptive statistics: mean $\pm$ standard deviation (SD) was used for normally distributed variables or median and interquartile range (IQR) for non-normally distributed variables, and frequencies and percentages were used for categorical variables.

Inferential statistics: The Shapiro-Wilk test was used for normality. Group comparisons: Student's t-test or the Mann-Whitney U test was used to compare 2 groups and one-way ANOVA or the Kruskal-Wallis test for ≥ 3 groups. Repeated measures were assessed using ANOVA for repeated-measures or mixed linear models. Categorical associations were evaluated with the chi-square or Fisher's exact tests, and Pearson or Spearman coefficients were used for correlation.

Multivariate models: Multiple linear regression was performed to identify independent predictors of maximum ΔQTc . Multivariate binary logistic regression (stepwise method) was implemented to identify factors associated with the occurrence of MVA, including QT variability (dichotomized: QTV $\geq 15\%$ vs. $<15\%$), age, obesity, hypertension, and diabetes as covariates. Crude and adjusted odds ratios (OR) are reported with their 95% confidence intervals (95% CI). The goodness of fit was assessed using the Hosmer-Lemeshow test and Nagelkerke's R².

Ethical Considerations

The study was approved by the Ethics Committee of Vladimir Ilich Lenin University Hospital and was conducted in accordance with the Declaration of Helsinki. (17) All participants signed a written informed consent form, guaranteeing confidentiality, the right to withdraw without penalty, and the absence of additional risks arising from the research.

RESULTS

Table 1 shows the distribution of patients according to their cardiovascular risk profile. The cohort had a mean age of 55.3 ± 9.8 years and mean BMI of 32.4 ± 2.1 kg/m², falling within the range for Class I obesity. Obesity was the most prevalent cardiovascular risk factor (45.3%), followed by hypertension (34.0%). Stratification by cardiovascular risk factor (CVRf) burden revealed that 26.7% of the patients had no risk factors, while the majority (73.3%) had at least one, and more than a quarter (26.7%) had three or more, indicating a high baseline cardiovascular risk profile prior to exposure to anthracyclines.

Table 2 shows the evolution of QTc over the course of the study. A progressive and sustained electrical deterioration was observed, characterized by a significant increase in QTc from baseline to post-cycle 4, with partial recovery at 12 months, although values did not return to baseline levels. The mean maximum

Δ QTc was 38.2 ± 12.1 ms. The intra-subject QTV was $15.3 \pm 4.2\%$, reflecting significant electrical instability during follow-up.

It is important to note that the intra-subject QTV of 15.3% reflects the standard deviation of each patient's 7 QTc measurements expressed as a percentage of their mean QTc (temporal instability), and not a direct 15% increase from baseline value. The mean percentage increase from baseline was approximately 9% (38 ms out of 418 ms).

Table 3 shows the correlation between the CVRF burden and QTc prolongation. A positive and significant correlation was identified between the number of CVRFs and the magnitude of the QTc value attained ($p = 0.55$; 95% CI: 0.43–0.65). The number of CVRFs explained approximately 30% of QTc variability (coefficient of determination $r_s^2 = 0.30$; $p < 0.001$). Patients with ≥ 3 CVRFs had a significantly greater maximum Δ QTc (40 ± 15.7 ms) than those with 1–2 CVRFs (25 ± 10.3 ms) or no CVRFs (0 ± 5.1 ms) ($p < 0.001$ for both comparisons)

Table 1. Distribution of patients by cardiovascular risk profile

Characteristic	Total (n=150)
Age (years), mean $\pm$ SD	55.3 $\pm$ 9.8
BMI (kg/m ²), mean $\pm$ SD	32.4 $\pm$ 2.1
HTN, n (%)	51 (34.0)
Obesity, n (%)	68 (45.3)
Diabetes mellitus, n (%)	42 (28.0)
Dyslipidemia, n (%)	49 (32.7)
Smoking, n (%)	29 (19.3)
0 CVRF, n (%)	40 (26.7)
1–2 CVRF, n (%)	70 (46.6)
≥ 3 CVRF, n (%)	40 (26.7)

BMI: body mass index; CVRF: cardiovascular risk factors; HTN: hypertension; SD: standard deviation

A multiple linear regression model was performed to identify the independent effect of each CVRF on the maximum Δ QTc (dependent variable). Table 4 shows that obesity was the strongest independent predictor of QTc interval prolongation, with an unstandardized β coefficient of 24.7 ms (standardized $\beta = 0.42$; $p < 0.001$). Hypertension also made a significant contribution ($\beta = 15.2$ ms; $p < 0.001$). The model as a whole explained 35% of Δ QTc maximum variability ($R^2 = 0.35$; adjusted $R^2 = 0.33$; $p < 0.001$).

Among the 150 patients, 25 (16.7%) experienced at least one episode of MVA during follow-up. The incidence was significantly higher in the group with high QT variability (QTV $\geq 15\%$). In the multivariate logistic regression analysis (Table 5), QT variability (QTV $\geq 15\%$) remained an independent predictor of MVA, with an adjusted OR of 5.90 (95% CI 2.41–14.46; $p < 0.001$), after adjusting for age, obesity, hypertension, and diabetes. Obesity also showed a significant independent association (OR = 2.20; 95% CI: 1.02–4.75; $p = 0.045$). The model showed good fit (Hosmer-Lemeshow: $p = 0.418$) and explained 32% of the outcome variability (Nagelkerke $R^2 = 0.32$).

DISCUSSION

The analyzed cohort consists predominantly of patients in their 50s, consistent with numerous international reports. Osorio (18) notes that age is the most important risk factor for breast cancer: two out of every three cases occur in women aged 50 and older, and more than 75% are diagnosed after menopause. Abdel-Qadir (19) highlights that the highest incidence of chemotherapy-associated cardiovascular events is concentrated in the fifth and sixth decades of life, particularly in breast and hematologic cancers—a stage marked by an increase in comorbidities and subclinical cardiovascular abnormalities, which heightens susceptibility to iatrogenic damage. (16) In Cuba, the rapid aging of the population makes this issue particularly relevant, as reduced myocardial reserve and

Table 2. Patient distribution according to QTc interval variability during treatment and follow-up. For definitions, see "QTc Variability Metrics" in Methods

Time of evaluation	QTc (ms) Mean $\pm$ SD (range)	Δ QTc vs. baseline (ms) * Mean $\pm$ SD	QTV among patients (%) † Median (IQR)	p-value ‡
Baseline (pre-treatment)	418 $\pm$ 19 (380–458)	—	4.5 (3.8–5.2)	Reference
Post-Cycle 1	425 $\pm$ 20 (385–468)	+7 $\pm$ 4.1	4.7 (4.0–5.4)	0.045
Post-Cycle 2	435 $\pm$ 22 (392–479)	+17 $\pm$ 6.3	5.1 (4.3–5.9)	<0.001
Post-Cycle 3	450 $\pm$ 24 (403–498)	+32 $\pm$ 8.9	5.3 (4.5–6.1)	<0.001
Post-Cycle 4	463 $\pm$ 26 (412–512)	+45 $\pm$ 11.5	5.6 (4.8–6.4)	<0.001
3 months post-treatment	445 $\pm$ 23 (399–491)	+27 $\pm$ 9.7	5.2 (4.4–6.0)	<0.001
12 months post-treatment	438 $\pm$ 21 (394–484)	+20 $\pm$ 8.2	4.8 (4.1–5.5)	<0.001

IQR: interquartile range; QTc: corrected QT; Δ QTc: difference in QTc; QTV: QTc coefficient of variation; SD: standard deviation;

*Absolute difference from baseline.

† Coefficient of variation among patients at each time point.

‡ Comparison vs. baseline using ANOVA for repeated measures.

Table 3. Correlation between groups of cardiovascular risk factors (CVRF) and QTc prolongation

CVRF Group	n	QTc (ms) Mean $\pm$ SD	Δ QTc vs. Baseline (ms)	p-value (vs. 0 CVRF)	Spearman's correlation (r_s)	Coefficient of Determination (r_s^2)
0 factors	40	418 $\pm$ 19	+0	Reference	—	—
1–2 factors	70	443 $\pm$ 24	+25	<0.01	0.45	0.20
≥ 3 factors	40	458 $\pm$ 31	+40	<0.001	0.67	0.45
TOTAL	150				0.55 (95% CI 0.43–0.65)	0.30

CVRF: cardiovascular risk factors; QTc: corrected QT; SD: standard deviation

Table 4. Multiple linear regression model to predict maximum Δ QTc (increase from baseline)

Variable	β Coefficient (unstandardized)	Standard error	Standardized β	t-value	p-value	95% CI for β
Constant (β_0)	418.3	4.2	—	99.6	<0.001	—
Obesity	24.7	3.1	0.42	7.97	<0.001	18.6 – 30.8
Hypertension	15.2	2.8	0.28	5.43	<0.001	9.7 – 20.7
Diabetes	8.9	3.5	0.13	2.54	0.012	2.0 – 15.8
Dyslipidemia	6.3	3.2	0.10	1.97	0.051	-0.03 – 12.6
Smoking	4.1	2.9	0.07	1.41	0.160	-1.6 – 9.8

Model $R^2 = 0.35$; adjusted $R^2 = 0.33$; $p < 0.001$.**Table 5.** Factors associated with the occurrence of malignant ventricular arrhythmias (MVAs). Multivariate logistic regression analysis

Variable	Crude OR (95% CI)	Adjusted OR* (95% CI)	p-value
QT variability (QTV $\geq 15\%$)	7.57 (3.12–18.38)	5.90 (2.41–14.46)	<0.001
Age (per 10 years)	1.38 (0.91–2.09)	1.21 (0.76–1.93)	0.425
Obesity (BMI ≥ 30 kg/m ²)	2.85 (1.18–6.88)	2.20 (1.02–4.75)	0.045
Hypertension	2.41 (1.02–5.69)	1.78 (0.78–4.06)	0.172
Diabetes mellitus	1.67 (0.68–4.10)	1.25 (0.51–3.06)	0.628

*Model adjusted for all variables in the table. Hosmer-Lemeshow test: $p = 0.418$. Nagelkerke $R^2 = 0.32$.

BMI: body mass index; QTV: QTc coefficient of variation.

alterations in the electrical conduction system create a proarrhythmic substrate. It is therefore crucial to understand this impact on our population.

López (20) suggests an association between overweight, obesity, and metabolic syndrome and an increased risk of breast cancer in postmenopausal women—a finding consistent with this study. The high prevalence of obesity (45.3%) and hypertension (34.0%) in our series reflects a population with increased cardiovascular risk.

Progressive prolongation of the QTc interval between cycles of chemotherapy is a cardinal sign of anthracycline-induced electrical toxicity. This study reveals a significant increase, with mean values >460 ms by the fourth cycle and an initial increase of +7 ms that becomes more pronounced. Previous reports describe average increases of 35–50 ms after four or more cycles, especially in patients with risk factors,

which indicates oxidative stress, mitochondrial damage, and alterations in ion channels in ventricular myocytes. (21) QTc variability, quantified by the intra-subject coefficient of variation (15.3%), reflects the temporal instability of repolarization and constitutes a more dynamic marker than mere absolute prolongation. In our study, this variability was strongly associated with the occurrence of MVA, even after adjusting for confounding factors (adjusted OR = 5.90), suggesting that electrical instability, beyond the absolute QTc value, is a relevant predictor of arrhythmias.

The incidence of MVA in our series (16.7%) is consistent with reports from pharmacovigilance studies and oncology cohorts. Salem et al. (22), in an analysis of the WHO's VigiBase database, described a progressive increase in reports of ventricular arrhythmias associated with anticancer drugs, although with absolute incidences below 5% in the general population.

Our slightly higher incidence may be explained by intensive monitoring (scheduled Holter monitoring, serial ECGs) and the inclusion of non-sustained ventricular tachycardia in the definition of MVA, as well as by the high-risk profile of our cohort.

The burden of CVRFs in our population was high: only 26.7% of patients had no risk factors. While Zamorano et al. (23) reported only 22% with ≥ 3 CVRFs in Europe, our results show 26.7% in that category, reflecting significant exposure to chronic degenerative diseases. Consistent with our findings, Gerodias et al. (24) observed in 341 patients with anthracycline-induced cardiotoxicity, that those with comorbidities (especially HTN and atrial fibrillation) were 12.37 times more likely to experience cardiotoxicity.

Multivariate analysis identified obesity as the main independent predictor of QTc prolongation ($\beta = 24.7$ ms). Consistent with our results, Dykiert found in 81 adults with overweight or grade I obesity, significantly greater QT dispersion in obese individuals. (25) Hypertension also showed a significant independent effect ($\beta = 15.2$ ms). Dyslipidemia showed a trend that did not reach statistical significance ($p = 0.051$), suggesting that its contribution might be more modest or mediated by other factors, an aspect requiring confirmation in studies with greater statistical power.

Damage caused by anthracyclines, especially doxorubicin, is dose-dependent and mediated by oxidative stress, mitochondrial dysfunction, and inflammation, which impair myocardial architecture and electrical function, explaining QTc prolongation and the predisposition to lethal arrhythmias. In agreement with our findings, Martínez Riverón, in 2024, demonstrated in patients treated with taxanes that QTc prolongation and QTc dispersion are among the electrocardiographic variables showing significant variation. (10) Mazur (26) found a high incidence of sustained ventricular tachycardia (56.6%) in 23 patients with anthracycline-induced cardiomyopathy, which is also consistent with our findings.

In the logistic regression model, QTc variability remained a significant independent predictor of MVA (adjusted OR = 5.90), while obesity also showed an independent effect (OR = 2.20). Hypertension and diabetes lost statistical significance in the multivariate analysis, suggesting that part of their effect may be mediated by QTc variability or obesity.

The literature supports including QTc assessment in standardized protocols for cardiovascular surveillance in cancer patients, especially in those with multiple comorbidities. Preventive interventions—optimal control of hypertension, diabetes, and obesity, plus cardioprotective pharmacological strategies, such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors—can mitigate QTc progression and reduce adverse events. (27) In practice, this profile requires a comprehensive pre-chemotherapy evaluation (blood pressure, BMI, blood glucose, and harmful habits) and early intervention.

Combining QTc variability with the number of CVRFs and the cumulative dose of anthracyclines allows for effective risk stratification, which should be incorporated into clinical protocols for decisions regarding dose modification, cardioprotective therapies, and post-treatment follow-up.

Study Limitations

Several limitations should be acknowledged. First, the case series design, though longitudinal, lacks a control group, which limits the ability to establish causality. Second, the definition of MVA included non-sustained ventricular tachycardia, which may have increased the incidence compared with studies that consider only sustained or symptomatic events. Third, although a multivariate analysis was performed, variables such as the exact cumulative dose or the use of other concomitant medications—which could act as residual confounders—were not included. Finally, sample size, while adequate for the primary analyses, precludes subgroup analyses by cancer subtypes or specific chemotherapy regimens.

CONCLUSIONS

QTc interval variability during treatment with anthracyclines constitutes an early and independent marker of risk for malignant ventricular arrhythmias, even after adjusting for classic cardiovascular risk factors. Obesity and hypertension potentiate this effect. The implementation of serial QTc measurements and the calculation of its variability (intra-subject coefficient of variation) in cardio-oncological monitoring protocols could improve risk stratification and enable earlier preventive interventions, particularly in populations with a high burden of comorbidities.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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