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Original Article

Predictive Value of Bazett-Corrected QTc for Chemotherapy-Induced Cardiotoxicity in Breast Cancer: A Retrospective Cohort Study

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Abstract

Background: Cardiotoxicity remains a major concern in breast cancer patients receiving anthracycline-based chemotherapy. Meanwhile, prolongation of the QTc interval has been associated with an increased risk of *torsades de pointes*; however, the clinical evidence for its role as a predictor of subclinical cardiotoxicity remains limited. This study aims to evaluate the association between Bazett-corrected QTc and the incidence of subclinical left ventricular dysfunction, as measured by strain echocardiography.

Methods: This single-center retrospective cohort study was conducted at Dr. Mohammad Hoesin General Hospital, Indonesia (January 2022–December 2023). Female breast cancer patients aged ≥18 years who received anthracycline or non-anthracycline chemotherapy and completed baseline and third-cycle echocardiography were included. QTc was measured from 12-lead ECGs before and after chemotherapy using Bazett's formula. Subclinical cardiotoxicity was defined as a >15% relative reduction in Global Longitudinal Strain (GLS) from baseline. Logistic regression and Receiver Operating Curve (ROC) analyses assessed the predictive value of baseline QTcB.

Results: In 32 breast cancer patients on anthracycline therapy (mean age 49.5 ± 9.0 years), 59.4% developed subclinical cardiotoxicity. Prolonged baseline QTcB, older age, and obesity were significantly associated with subclinical cardiotoxicity ($p < 0.05$). In multivariate analysis, QTcB remained an independent predictor (OR = 21.09; 95% CI: 0.979–454.4; $p = 0.05$). ROC analysis showed moderate discrimination (Area Under Curve [AUC] = 0.717; 95% CI: 0.50–0.92; $p = 0.04$).

Conclusions: Prolonged QTc appears to be a promising predictor of subclinical cardiotoxicity with fair diagnostic accuracy. However, it should be considered alongside other modalities. Further studies with larger populations are needed to control for other risk factors.

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Keywords: QTc, cardiotoxicity, breast cancer.

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Introduction

Advances in early detection and optimization of chemotherapy regimens have significantly improved the survival of breast cancer patients. Anthracyclines are one of the preferred neoadjuvant and adjuvant therapies. However, their use often leads to cardiotoxic effects, known as Cancer Therapy-Related Cardiac Dysfunction (CTRCD). The CTRCD definition from the British Society of Echocardiography (BSE) is a reduction in Left Ventricular Ejection Fraction (LVEF) of more than 10 absolute percentage points to below 50%. Probable subclinical cardiotoxicity is defined as a decline in LVEF of more than 10 absolute percentage points to a value of 50% or higher, accompanied by a relative decrease in Global Longitudinal Strain (GLS) of more than 15%. Possible subclinical cardiotoxicity is indicated by either a reduction in LVEF of less than 10 percentage points to a value below 50% or a relative reduction in GLS exceeding 15% from baseline.[1] Subclinical LV dysfunction can occur in up to 42% of patients undergoing treatment, and its presence is associated with a 3.5-fold increased risk of death. Despite routine echocardiographic monitoring, the need for sensitive biomarkers of early cardiotoxicity remains critical.[2]

Earlier CTRCD onset detection by Electrocardiogram (ECG) is expected to reduce examination costs while improving performance and non–invasiveness.[3] Previously, QT prolongation on ECG was allegedly associated with an increased risk of fatal arrhythmias such as *torsades de pointes* and cardiovascular mortality, including in the subset of chemotherapy patients. The Bazett-corrected QT interval (QTcB) is used widely in clinical practice and pharmacological regulatory guidance, with a QTc >500 ms or a change >60 ms considered clinically significant.[4] A cohort study of more than 59,000 cancer patients showed that although QTcB is a sensitive marker, its association with mortality is confounded by age and underlying health conditions, especially when the QTc is ≥500 ms. In the context of breast cancer therapy, a prospective study evaluating the EC-Doc (epirubicin, cyclophosphamide, and docetaxel) regimen reported statistically significant QTc prolongation after epirubicin-cyclophosphamide cycles, which normalized after docetaxel administration.[5] Despite these findings, the predictive value of QTcB for CTRCD in patients receiving EC-Doc remains unclear. This study aimed to evaluate the association between the Bazett-corrected QTc interval and the incidence of cardiotoxicity and to establish QTcB as a potential early marker for CTRCD..

Methods

This study was carried out at Dr. Mohammad Hoesin General Hospital in Palembang, Indonesia. It was a single-center retrospective cohort study from January 2022 to December 2023. The study aimed to determine whether baseline QTc prolongation, corrected by Bazett's formula, could predict the risk of developing subclinical cardiotoxicity in women with breast cancer who received chemotherapy.

Study Population

This study included women aged 18 or older who had been diagnosed with breast cancer and undergone chemotherapy containing anthracycline (doxorubicin) and non-anthracycline (trastuzumab, carboplatin, vincristine) during the study period. Initially, a total of 50 breast cancer patients with complete baseline echocardiographic data, including QTcB measurements, were included. Patients with incomplete medical records were excluded, yielding a final sample of 32 patients. Patients were only part of the study if they had a baseline 12-lead ECG done before their first chemotherapy cycle and completed baseline data before chemotherapy and after the third cycle of chemotherapy, followed by a 3rd cycle of chemotherapy follow–up echocardiography between January 2022 and December 2023. Patients with pre-existing extensive arrhythmias, electrolyte imbalances (hypokalemia/hyperkalemia), or those on medication (amiodarone, macrolide, fluoroquinolone, antipsychotic, and SSRI) known to affect their QT interval were not included in this study (Figure 1).

QTc Interval Assessment

Baseline QTcB values were obtained within one week before the first chemotherapy infusion, and the latest QTcB values were measured within 4 hours after the chemotherapy infusion on the 3rd cycle. QTc intervals were calculated from standard 12-lead ECGs and corrected for heart rate using Bazett's formula ($QTc = QT/\sqrt{RR}$). The change in QTcB (ΔQTcB) was defined as the difference between the most recent and baseline QTcB values (ΔQTcB = QTcB latest– QTcB baseline).

ECG recordings were performed using a portable ECG device (KardiaMobile™ 6L, AliveCor®, Mountain View, California, USA) with a 300 Hz sampling frequency and 14-bit resolution, capable of obtaining signals from two primary leads. Data were extracted from lead II, representing the

direction of the cardiac electrical vector. Each patient received detailed instructions for performing the acquisition with the KardiaMobile™ 6L recorder. ECG acquisition lasted approximately 3 minutes, and the recorded data were wirelessly transmitted to a preinstalled smartphone application (AliveCor® Kardia), which stored the data locally and simultaneously uploaded it to the cloud system. All ECG recordings were reviewed and interpreted by qualified cardiologists in accordance with European Society of Cardiology (ESC) and the U.S. Food and Drug Administration (FDA) guidelines, with QTc > 480 ms in women considered prolonged.

Cardiotoxicity Measures

CTRCD was defined according to the recommendations of the BSE. CTRCD was categorized into two groups: cardiotoxicity and subclinical cardiotoxicity. This study identified subclinical cardiotoxicity based on GLS assessment, defined as a relative reduction in GLS >15% from baseline. The utility of GLS as an echocardiographic marker for detecting early cardiotoxicity during or following anthracycline-based chemotherapy before more prominent symptoms or drops in ejection fraction appear has been described in previous studies.[6]

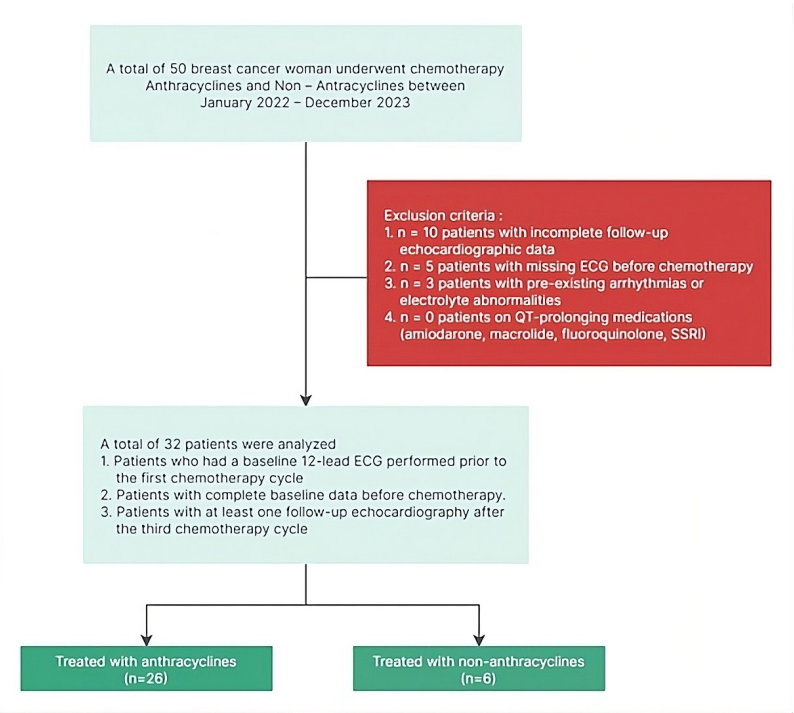

Figure 1. Study population.

Outcome Measures

The primary outcome was to evaluate the predictive value of QTcB for the development of CTRCD using Receiver Operating Characteristic (ROC) curve analysis and logistic regression modeling. Secondary outcomes included the incidence of CTRCD within 1 year of chemotherapy initiation. This study also evaluates patients' characteristics, including age, major comorbidities (diabetes, hypertension, coronary artery disease, chronic kidney disease, obesity), and laboratory parameters.

Statistical Analysis

Patient demographics and clinical characteristics were analyzed using descriptive statistics. Bivariate analysis was performed to assess associations between categorical variables using the Chi-square test. Variables with significant associations were further analyzed using binary logistic regression to identify the most significant predictors of CTRCD. The predictive value of baseline QTcB for CTRCD was evaluated using Receiver Operating Characteristic (ROC) curve analysis to determine the Area Under the Curve (AUC) and 95% confidence intervals. Model performance was assessed through sensitivity, specificity, Nagelkerke's R^2, and overall accuracy. p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 26.0 (IBM Corp).

Ethical Consideration

All data were retrieved from hospital records and were anonymized to ensure confidentiality. No personal identifying information was used or stored during the study.

Results

Patient Characteristics

A total of 32 breast cancer patients were included in the analysis, with a mean age of 49.5 ± 9.0 years. Most participants were younger than 65 years (90.6%) and had no major comorbidities such as diabetes (25%), hypertension (15.6%), or coronary artery disease (3.1%). Baseline cardiac function showed a mean Ejection Fraction (EF) of 62.16 ± 6.4%, which decreased slightly to 62.4 ± 9.1% after the third chemotherapy cycle. The mean GLS at baseline was −14.9 ± 7.4, and −16.2 ± 7.9 after the third cycle, indicating minimal average change. Regarding QTc intervals (Bazett-corrected), the majority of patients (68.8%) had normal QTc, while 31.3% exhibited prolonged QTc intervals. Most participants (81.3%) received anthracycline-based chemotherapy, and 59.4% were classified as having subclinical cardiotoxicity, whereas no patients developed overt clinical cardiotoxicity during the observation period. According to the HFA-ICOS risk score, most patients were categorized as low risk (81.3%), with 6.3% in the moderate-risk group and 12.3% in the high-risk group. (Table 1).

Bazett-Corrected QT Interval Changes

The QTcB values increased from baseline to the most recent measurement, with the latest value showing greater central tendency (median and mean approximately 458.5 ms) compared with the baseline value of approximately 439.2 ms. However, the number of evaluable cases slightly decreased due of missing follow-up data at the end of the third cycle (n = 4). The interquartile range for the latest measurement is notably wide, spanning 391-530 ms, indicating substantial variability among individuals. The reported change in QTc (ΔQTc) reveals an average increase of 7 units, with a substantial range from -48 to 114. This variation indicates that while some individuals experienced a shortening of the QTc interval, others encountered a marked prolongation (Table 2).

Relationship between cumulative chemotherapy doses and the incidence of subclinical cardiotoxicity. Patients who developed subclinical cardiotoxicity received a higher proportion of doxorubicin (57.6%) compared to those without cardiotoxicity (42.3%), with a median cumulative dose of 330 mg/m² (range: 50–5280 mg/m²). In contrast, trastuzumab exposure was more common among patients without subclinical cardiotoxicity (66.6%) than among those with cardiotoxicity (33.3%), with a median cumulative dose of 3520 mg/m² (range: 1760–5280 mg/m²). All patients who received docetaxel (100%) developed subclinical cardiotoxicity, with a median cumulative dose of 654 mg/m² (range: 400–1064 mg/m²). Meanwhile, carboplatin (median 4000 mg/m²; range: 2000–6000 mg/m²) and vincristine (median 10 mg/m²; range: 10–10 mg/m²) were only administered to patients without evidence of subclinical cardiotoxicity (Table 3).

Association between QTcB and CTRCD

Bivariate analysis was performed to examine

Table 1. Baseline characteristics.

Characteristics	N (%)/ Median [IQR] or Mean ± SD
Age	49.5 ± 9.0
<65 year	29 (90.6%)
≥65 year	3 (9.4%)
Diabetes	
No	24 (75%)
Yes	8 (25%)
Hypertension	
No	27 (84.4%)
Yes	5 (15.6%)
Chronic Kidney Disease	
No	3 (9.4%)
Yes	29 (90.6%)
CAD	
No	31 (96.9%)
Yes	1 (3.1%)
Obese	

No	24 (75%)
Yes	8 (25%)
Potassium Ion (mmol/L)	4.1 ± 1.19
No	29 (90.6%)
Yes	3 (9.4%)
Ureum (mg/dl)	17.7 ± 6.7
No	18 (56.3%)
Yes	14 (43.8%)
Creatinin (mg/dl)	0.72 ± 0.12
No	29 (90.6%)
Yes	3 (9.4%)
EF baseline	62.16 ± 6.4
EF After 3rd Chemo	62.47 ± 9.1
GLS Baseline	14.9 ± 7.4
GLS After 3rd Chemo	16.2 ± 7.9
QTc (Bazzet)	
Normal	22 (68.8%)
Prolonged	10 (31.3%)
Cancer Related Therapy	
Not Related Anthracycline	6 (18.8%)
Related Anthracycline	26 (81.3%)
Subclinical Cardiotoxicity	
No	13 (40.6%)
Yes	19 (59.4%)
Cardiotoxicity	
No	0 (0%)
Yes	0 (0%)
HFA ICOS Risk Score	
Low	26 (81.3%)
Moderate	2 (6.3%)
High	4 (12.3%)
Very High	0 (0%)

CAD: Coronary Artery Disease, EF: Ejection Fraction, QTc: Bazett-corrected QT interval.

the association between clinical variables and the incidence of subclinical cardiotoxicity among breast cancer patients receiving anthracycline-based chemotherapy. The results showed that age, obesity, and baseline QTcB were significantly associated with subclinical cardiotoxicity. Patients aged ≥65 years were more likely to develop subclinical cardiotoxicity compared to younger patients ($p = 0.01$). Similarly, obesity demonstrated a significant association ($p = 0.001$), with a higher proportion of obese patients found in the cardiotoxicity group. Moreover, baseline QTcB prolongation was significantly associated with subclinical cardiotoxicity ($p = 0.04$), suggesting a potential role as a predictive marker of early cardiac dysfunction (Table 4).

In contrast, other comorbid conditions, including diabetes mellitus, hypertension, chronic kidney disease, coronary artery disease, renal function parameters (urea and creatinine), EF dysfunction, and cancer therapy type, did not show significant differences between patients with and without subclinical cardiotoxicity (all $p > 0.05$) (Table 4). These findings indicate that although patients presented with varying clinical profiles, most comorbidities were not significantly different between groups. The significant predictors identified were older age, obesity, and prolonged baseline QTcB, highlighting their potential importance in early risk stratification for chemotherapy-induced cardiotoxicity.

Table 2. Baseline and after chemotherapy 3rd cycle QTcB.

Measure	N	Median [IQR] or Mean ± SD
QTcB Baseline	32	439.19 ± 42.5
QTcB Latest	28	458.50 [391 – 530]
ΔQTc (Latest − Baseline)	28	7 [-48 – 114]

QTc/QtcB: Bazett-corrected QT interval, SD: Standard Deviation.

Table 3. Chemotherapy cumulative doses and subclinical cardiotoxicity occurrence.

Variable	Subclinical Cardiotoxicity		Median [IQR] or Mean ± SD
	No n (%)	Yes n (%)	
Doxorubicin Cumulative Dosed (mg/m²)	11 (42.3%)	15 (57.6%)	330 [50 – 5280]
Trastuzumab Cumulative dosed (mg/m²)	2 (66.6%)	1 (33.3%)	3520 [1760 – 5280]
Docetaxel Cumulative dosed (mg/m²)	0 (0%)	3 (100%)	654 [400 – 1064]
Carboplatin Cumulative dosed (mg/m²)	2 (100%)	0 (0%)	4000 [2000 – 64]
Vincristine Cumulative dosed (mg/m²)	1 (100%)	0 (0%)	10 [10 – 10]

IQR: Interquartile Range, SD: Standard Deviation.

Multivariate logistic regression analysis was performed to identify independent predictors of subclinical cardiotoxicity. The model demonstrated strong predictive performance (χ^2 = 32.476, p < 0.001; Nagelkerke R^2 = 0.86), indicating that approximately 86% of the variability in subclinical cardiotoxicity incidence was explained by the included variables. Among the predictors, baseline QTcB was positively associated with subclinical cardiotoxicity (B = 3.049; Odds Ratio [OR] = 21.09; 95% CI: 0.979–454.4; p = 0.05), indicating that patients with prolonged baseline QTcB were more likely to develop subclinical cardiotoxic ity. In contrast, age (p = 0.678) and obesity (p = 0.99) were not significantly associated with subclinical cardiotoxicity in the adjusted model. (Table 5).

Predictors of CTRCD

ROC curve analysis was performed to evaluate the predictive value of several clinical variables for CTRCD. Among all predictors analyzed, baseline QTcB demonstrated moderate discriminative ability, with an AUC of 0.717 (95% CI: 0.50–0.92, p = 0.040), indicating statistically significant predictive value for CTRCD. Although sensitivity was relatively low (26.3%), specificity was 61.5%, suggesting that QTcB prolongation could serve as an early marker for identifying patients at higher risk of cardiotoxicity. In addition, obesity was significantly associated with CTRCD (AUC 0.711, 95% CI: 0.533–0.888, p = 0.046), suggesting that obesity may be associated with increased susceptibility to CTRCD. Other clinical parameters, such as age, diabetes mellitus, hypertension, Chronic Kidney Disease (CKD), Coronary Artery Disease (CAD), and baseline ejection fraction, demonstrated AUC values below 0.6 and were not statistically significant, indicating limited predictive performance (Table 6).

Discussion

In this study of 32 breast cancer patients (mean age 49.5 ± 9.0 years), 59.4% developed subclinical but not clinical cardiotoxicity. Most patients received anthracycline-based chemotherapy and were categorized as low risk according to HFA-ICOS criteria. Older age, obesity, and prolonged baseline QTcB were significantly associated with subclinical cardiotoxicity, with QTcB identified as an independent predictor (OR = 21.09; p = 0.05). These results align with studies by Upshaw *et al.* Poovorawan *et al.* and Serrano *et al.* who found that older age and higher Body Mass Index (BMI) were associated with increased risk of anthracycline cardiotoxicity.[7–9] The overall comorbidity pattern was comparable to that reported by Kuroda and Serrano, although diabetes was slightly more prevalent.[8,10] Notably, our study revealed a higher rate of subclinical cardiotoxicity than the symptomatic incidence typically reported,

Table 4. Bivariate analysis of factors associated with subclinical ccardiotoxicity.

Variable	Subclinical Cardiotoxicity		P-value
	No (n = 13)	Yes (n = 19)	
Age			
<65 year	12 (92.3%)	17 (89.5%)	**0.01***
≥65 year	1 (7.7%)	2 (10.5%)	
Diabetes			
No	10 (76.9%)	14 (73.7%)	0.83
Yes	3 (23.1%)	5 (26.3%)	
Hypertension			
No	12 (92.3%)	15 (78.9%)	0.28
Yes	1 (7.7%)	4 (21.1%)	
Chronic Kidney Disease			
No	0 (0%)	3 (15.8%)	0.17
Yes	13 (100%)	16 (84.2%)	
CAD			
No	12 (92.3%)	19 (100%)	0.06
Yes	1 (7.7%)	0 (0%)	
Obese			
No	13 (100%)	11 (57.9%)	**0.001***
Yes	0 (0%)	8 (42.1%)	
Potassium Ion (mmol/L)			
No	11 (84.6%)	18 (94.7%)	0.356
Yes	2 (15.4%)	1 (5.3%)	
Ureum (mg/dl)			
No	10 (76.9%)	8 (42.1%)	0.06
Yes	3 (23.1%)	11 (57.9%)	
Creatinin (mg/dl)			
No	13 (100%)	16 (84.2%)	0.195
Yes	0 (0%)	3 (15.8%)	
Baseline QTcB			
Normal	8 (61.5%)	14 (73.7%)	**0.04***
Prolonged	5 (38.5%)	5 (26.3%)	
Cancer Related Therapy			
Not Related Anthracycline	2 (15.4%)	4 (21.1%)	0.68
Related Anthracycline	11 (84.6%)	15 (78.9%)	
EF Dysfunction			
No	12 (92.3%)	16 (84.2%)	0.45
Yes	1 (7.7%)	3 (15.8%)	
HFA ICOS Risk Score			
Low	11 (84.6%)	15 (78.9%)	0.46
Moderate	0 (0%)	2 (10.5%)	
High	2 (15.4%)	2 (10.5%)	
Very High	0 (0%)	0 (0%)	

CAD: Coronary Artery Disease, EF: Ejection Fraction, QTc:B Bazett-corrected QT interval.

Table 5. Multivariate regression analysis of factors associated with subclinical ccardiotoxicity.

Variable	B	P-value	OR (Exp B)	95% CI
Baseline QTcB	3.049	0.05	21.09	0.979 – 454.4
Age	-3.421	0.678	0.033	0.033 –0.00
Obese	-21.429	0.99	0.001	0.00 – 0.00

$\chi^2 = 32.476$, $p < 0.001$; Nagelkerke $R^2 = 0.86$; CI: Confidence Interval.

underscoring the importance of early detection before overt dysfunction develops.

Anthracycline chemotherapy can lead to QTc interval prolongation, reflecting early myocardial repolarization abnormalities that may precede overt structural or functional cardiac injury.[3] In this study, a significant increase in QTcB values was observed from baseline to post-chemotherapy, with the median QTcB rising from approximately 439.2 ms to 458.5 ms. Veronese *et al.*'s findings were similar to our study. It demonstrates a statistically significant prolongation of the QTc interval after the AC phase of chemotherapy (doxorubicin and cyclophosphamide) compared to baseline values (439.7 ± 33.2 ms vs. 472.5 ± 36.3 ms, $p = 0.001$). There was also a significant increase in the QTc interval after the final (T) phase compared to baseline (467.9 ± 42.6 ms vs. 439.7 ± 33.2 ms; $p < 0.001$). The wide interquartile range (391–530 ms) and large variation in ΔQTc (−48 to 114 ms) observed in this study further highlight considerable individual variability in QTc response to chemotherapy. Such heterogeneity suggests that while some patients may experience QTc shortening, others are predisposed to marked prolongation, potentially reflecting differences in myocardial sensitivity or drug metabolism.[11]

Cardiotoxicity varies according to the type of chemotherapy. Type I CTRCD, typically caused by anthracyclines such as doxorubicin, is dose-dependent and characterized by irreversible myocardial cell damage, whereas Type II CTRCD, associated with anti-HER2 therapy, is generally non–dose-dependent and often reversible.[1] In our study, the median cumulative doxorubicin dose, 330 [50 – 5280] mg/m^2, might be similar in patients with subclinical cardiotoxicity. Veronese *et al.* observed QTc prolongation and elevated troponin levels even at lower doxorubicin doses (240 mg/m^2) during ACT chemotherapy regimens. These results underscore that cardiotoxicity can occur even at modest anthracycline exposures.[11] Chan *et al.* showed in a large population-based study that QTc ≥500 ms and delta QTc >60 ms were associated with increased all-cause mortality in cancer patients, but this association was attenuated in the presence of comorbidities such as renal dysfunction and electrolyte imbalance.[4] Based on

Table 6. ROC curve (AUC) analysis for predictors of CTRCD.

Variable	AUC (95% CI)	Std. Error	Sensitivity (%)	Specificity (%)	Accuracy (%)	P-value
Age	0.553 (0.344 – 0.761)	0.106	10.5%	92.3%	43%	0.618
Diabetes Mellitus	0.516 (0.31 – 0.722)	0.105	26.3%	76.9%	46.8%	0.878
Hypertension	0.567 (0.365 – 0.768)	0.103	21%	92.3%	50%	0.527
CKD	0.421 (0.222 – 0.620)	0.102	88,89	7.1%	53%	0.454
CAD	0.462 (0.253 – 0.670)	0.107	5%	92%	39.3%	0.715
Obese	0.711 (0.533 – 0.888)	0.090	42%	92%	63%	0.046*
Pottasium	0.449 (0.241 – 0.658)	0.107	5%	84.6%	37.5%	0.631
Ureum	0.674 (0.483 – 0.865)	0.098	57.9%	76%	65.6%	0.099
Creatinin	0.579 (0.380 – 0.778)	0.102	15.7%	92.8%	48%	0.454
Cancer Therapy	0.472 (0.267 – 0.677)	0.105	78.9%	15%	53.1%	0.788
QTcB Baseline	0.717 (0.50 – 0.92)	0.108	26.3%	61.5%	40.6%	0.040*
EF dysfunction	0.442 (0.23 – 0.64)	0.106	15.7%	92.3%	46.8%	0.589

CKD: Chronic Kidney Disease, CAD: Coronary Artery Disease, EF: Ejection Fraction, QTc:B Bazett-corrected QT interval.

BSE 2020, recommendations for the frequency of echocardiography during chemotherapy with anthracycline and anti-HER2 are every 2–3 cycles of chemotherapy.[1] Kuroda *et al.* further demonstrated that cumulative anthracycline dose is not an absolute predictor of CTRCD, as patients with similar cumulative doses exhibited different outcomes. This variability suggests that individual susceptibility, including pre-existing comorbidities such as hypertension, dyslipidemia, or diabetes, inflammation, and drug type, with doxorubicin posing a higher risk than epirubicin.[10]

ROC analysis demonstrated that baseline QTcB had moderate predictive ability for subclinical cardiotoxicity (AUC = 0.717, 95% CI: 0.50–0.92, p = 0.04), with an accuracy of 59.4%, specificity of 61.5%, and sensitivity of 26.3%. Obesity also showed significant predictive value (AUC = 0.711, p = 0.046), whereas age, comorbidities, and baseline EF were not predictive (AUC < 0.6). EF was not sensitive enough in detecting minimal impairment of the myocardium until the cardiac dysfunction became moderate to severe.[14] Murtaza Makasarwala *et al.* found that a prolonged baseline QTc interval (>450 ms) predicted cardiotoxicity in patients treated with trastuzumab.[13] Kinoshita *et al.* found that QTc and Activation Recovery Interval (ARIc) were both prolonged in patients who subsequently developed CTRCD, with ARIc correlating strongly with reduced left ventricular ejection fraction (LVEF; r = –0.56, p < 0.001).[3] Puppe *et al.* further highlighted epirubicin-induced QTc prolongation during anthracycline therapy.[5] This emphasizes that early electrical alterations in cardiac repolarization, reflected by QTc prolongation, may serve not only as a repolarization metric but also as an early harbinger of impaired myocardial mechanics.

Multimodal assessment is particularly crucial in breast cancer patients receiving anthracyclines, where structural cardiac changes often lag behind electrophysiologic disturbances. The QTcB modality must be accompanied by other modalities. Its accuracy can be compromised by heart rate variability, autonomic tone, and inter-individual susceptibility to ion channel alterations. Additionally, systemic inflammatory status and tumor characteristics appear to modulate cardiotoxic risk.[15] In QTc as a predictive tool for cardiovascular mortality, the Bazett formula had the poorest performance among mathematical methods; it was the only formula that significantly predicted CV events and mortality (hazard ratios of 2.05-2.92) in both hospital-based and population-based cohorts, compared with the Framingham and Fridericia formulas.[4] ESC recommends integrating biomarkers (NT-proBNP, troponin), ECG changes, and imaging (GLS) into CTRCD surveillance strategies to enhance early detection and guide timely cardioprotective interventions.[12]

This study has several limitations. First, its retrospective design and single-center setting limit the ability to establish causal relationships and may reduce generalizability to broader populations. Second, the sample size was relatively small, which may have limited the statistical power to detect significant associations, particularly in multivariate analysis. Third, confounding factors such as comorbidities were not fully controlled. Lastly, although baseline QTcB demonstrated a promising predictive value for subclinical cardiotoxicity, it should be interpreted alongside other diagnostic modalities, such as strain imaging and biomarker assessment. Future prospective multicenter studies with larger sample sizes and extended follow-up are warranted to validate these results and establish clinically applicable QTc thresholds for early detection.

Conclusion

Bazett-corrected QTc interval shows promise as a sensitive, non-invasive indicator for subclinical cardiotoxicity in breast cancer patients undergoing chemotherapy. Its integration into clinical practice may facilitate earlier recognition of cardiac injury. Nonetheless, QTc should be interpreted in combination with other risk factors and modalities to enhance diagnostic accuracy. Larger prospective studies using standard QTc thresholds and validated outcomes are essential to confirm its prognostic utility and to develop comprehensive, evidence-based cardio-oncology surveillance algorithms.

List of Abbreviations

ARIc	Activation Recovery Interval
AUC	Area Under Curve
BMI	Body Mass Index
BSE	British Society of Echocardiography
CI	Confidence Interval
CKD	Chronic Kidney Disease
CTRCD	Cancer Therapy–Related Cardiac Dysfunction
EC-Doc	Epirubicin, Cyclophosphamide, and Docetaxel
ECG	Electrocardiogram
EF	Ejection Fraction

ESC	European Society of Cardiology
FDA	U.S. Food and Drug Administration
GLS	Global Longitudinal Strain
IQR	Interquartile Range
LV	Left Ventricular
NLR	Neutrophil-to-Lymphocyte Ratio
OR	Odds Ratio
QTc	Bazett-corrected QT interval
QTcB	Bazett-corrected QT interval
ROC	Receiver Operating Curve

Ethical Clearance

All data were retrieved from hospital records and were anonymized to ensure confidentiality. No personal identifying information was used or stored during the study.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

AET, MRF, IP, and ML : Conceptualization
SB, ML, ZRS, and JAP : Methodology
ML, FS, VA : Statistical analysis
ML : Writing original draft
AET : Writing review editing

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Conflict of Interest

There is no conflict of interest in this study.

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Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, AI was used to assist with paraphrasing, and improving language clarity. The authors reviewed and edited all content generated by the tool.

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