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Original Article

Development and validation of a predictive model for cancer therapy-related cardiac dysfunction in breast cancer patients using echocardiographic indicators

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Abstract: Objective: This study aimed to develop and validate a predictive model for cancer therapy-related cardiac dysfunction (CTRCD) in breast cancer patients undergoing chemotherapy, targeted therapy, or immunotherapy. Methods: A retrospective analysis was conducted on 506 patients treated at Hunan Provincial People's Hospital (2018-2023). Results: Clinical and imaging biomarkers, including NT-proBNP ($P < 0.001$), left ventricular ejection fraction (LVEF; $P = 0.003$), and left atrial diameter (LA; $P = 0.012$), were evaluated. Lasso-Cox regression identified eight significant predictors (all $P < 0.05$), which were incorporated into a nomogram. The model exhibited excellent discrimination in both the training (AUC 0.82, 95% CI 0.78-0.86) and validation cohorts (AUC 0.79, 95% CI 0.74-0.83). Time-dependent ROC curves demonstrated consistent predictive accuracy at 4 weeks (AUC 0.80, $P < 0.001$), 8 weeks (AUC 0.81, $P < 0.001$), and 12 weeks (AUC 0.79, $P = 0.002$). Calibration curves indicated good agreement (Hosmer-Lemeshow test $P = 0.34$), and decision curve analysis confirmed the model's clinical utility (net benefit > 15% across threshold probabilities). Conclusion: This validated tool facilitates early CTRCD risk stratification (C-index 0.80, $P < 0.001$), supporting personalized monitoring of cardiotoxicity.

Keywords: Cancer therapy-related cardiac dysfunction, breast cancer, left ventricular ejection fraction, left atrial diameter, predictive model

Introduction

Breast cancer is one of the most prevalent malignancies affecting women globally. Recent epidemiological data from the International Agency for Research on Cancer of the World Health Organization indicate that approximately 2.3 million new breast cancer cases were diagnosed in 2022, accounting for 11.6% of all newly reported cancer cases worldwide [1]. These statistics not only underscore the substantial disease burden of breast cancer but also highlight its significant public health implications. While geographical variations in incidence rates exist, breast cancer has become the leading cause of cancer-related mortality among women in many developed countries, with incidence rates increasing with age [2]. According to data from the American Cancer Society, the median age at diagnosis in high-income countries is 61 years, while patients in low- and middle-income countries tend to be diagnosed at younger ages [3].

Contemporary management of breast cancer includes multimodal treatment approaches, such as surgical intervention, radiation therapy, systemic chemotherapy, and molecularly targeted therapies. Chemotherapy remains a cornerstone of treatment regimens [4]. Despite the well-documented efficacy of chemotherapeutic agents - particularly anthracyclines (e.g., doxorubicin) and targeted therapies like trastuzumab - in improving survival outcomes, these treatments are often associated with significant cardiotoxic side effects [5]. Chemotherapy-induced cardiovascular complications include heart failure, cardiac arrhythmias, and progressive decline in left ventricular ejection fraction (LVEF), with severe cases leading to

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irreversible cardiac dysfunction [6]. The pathophysiology of cancer therapy-related cardiac dysfunction (CTRCD) is multifactorial, involving complex interactions between drug toxicity, baseline cardiovascular status, genetic predisposition, and comorbid conditions [7]. Current diagnostic strategies for CTRCD rely on isolated clinical parameters such as LVEF measurements or circulating biomarkers like NT-proBNP [8]. However, the limitations of single-parameter assessments highlight the need for integrated predictive models that incorporate multiple diagnostic modalities to enhance early detection and optimize treatment decisions.

Several biomarkers have shown promise in early identification and risk stratification of CTRCD. NT-proBNP, a well-established marker of myocardial stress, is widely used in heart failure diagnosis and management [9, 10]. Elevated NT-proBNP levels correlate strongly with progressive cardiac dysfunction, particularly in the context of ventricular remodeling and heart failure [11]. In cancer therapy, serial monitoring of NT-proBNP provides a valuable tool for detecting subclinical cardiotoxicity, with early elevations helping to identify high-risk patients who may benefit from timely interventions. LVEF, the conventional measure of left ventricular systolic function, has traditionally played a central role in CTRCD monitoring [12]. While it provides critical information on cardiac contractility, its clinical utility is limited by the delayed detection of significant changes, which often become apparent only after substantial myocardial damage [13]. This latency is particularly problematic for breast cancer patients receiving cardiotoxic regimens like anthracyclines and trastuzumab, where subtle LVEF alterations may delay the recognition of clinically significant cardiac injury. In contrast, left atrial (LA) diameter, an emerging echocardiographic parameter, offers complementary value by reflecting both cardiac filling dynamics and chronic pressure loading [14]. Evidence suggests that LA enlargement is strongly associated with progressive cardiac dysfunction, heart failure, and increased cardiovascular risk [15]. Compared to LVEF, changes in LA diameter are more temporally sensitive, often detecting abnormalities in the early stages of cardiac impairment [16]. Furthermore, the technical feasibility and non-invasive nature of LA diameter assessment via routine echocardiography enhance its potential for widespread clinical use. Although existing studies have suggested the prognostic value of LA diameter in predicting CTRCD, developing comprehensive predictive models incorporating this parameter remains an active area of investigation.

The primary objective of this study is to develop and rigorously validate a multivariate predictive model for accurate CTRCD risk assessment in breast cancer patients undergoing systemic therapies. By integrating key clinical and imaging parameters - NT-proBNP, LVEF, and LA diameter - and employing advanced statistical methods, such as Lasso-Cox regression for optimal variable selection, this study aims to provide clinicians with a robust tool for risk stratification. The construction of a clinically accessible nomogram will facilitate the translation of complex biomarker data into practical risk assessments, enabling more informed therapeutic decisions and personalized patient management strategies.

Methods and materials

Sample size calculation

According to the study by Fawzy et al. [16], the incidence of Cancer Therapy-Related Cardiac Dysfunction (CTRCD) in breast cancer patients following chemotherapy was 25.5%. Using the formula $N = Z^2 \times [P \times (1 - P)]/E^2$, where $P = 0.255$, $Z = 1.96$, and $E = 0.05$, the required sample size was calculated to be 292 patients. After accounting for a 10% margin of error, the final required sample size was 321. The actual sample size was determined based on available clinical data.

General information

This retrospective study analyzed clinical data from 506 breast cancer patients treated at Hunan Provincial People's Hospital between January 2018 and December 2023. The study was approved by the Hunan Provincial People's Hospital's Medical Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: (1) Female patients aged 18 to 75 years with a pathologically confirmed diagnosis of breast cancer [17]. (2) Patients undergoing or scheduled to begin chemothera-

py, targeted therapy, or immunotherapy, with a defined treatment plan. (3) Clinical staging of breast cancer at stage II or III according to the TNM classification. (4) Availability of complete clinical data.

Exclusion criteria: (1) History of significant cardiovascular disease, including heart failure, coronary artery disease, myocardial infarction, or severe arrhythmias. (2) Presence of other malignancies or recent cancer treatments. (3) Pregnancy or lactation. (4) Use of medications that could interfere with cardiac function assessment, such as long-term antibiotics, antivirals, or immunosuppressants.

Definition of CTRCD

Cancer Therapy-Related Cardiac Dysfunction (CTRCD) is defined as a reduction in left ventricular ejection fraction (LVEF) of more than 10%, resulting in an LVEF below the normal threshold of 53% [16].

Collection of clinical data

Baseline clinical data included age, body mass index (BMI), hypertension, diabetes, smoking history, hyperlipidemia, and family history of cardiovascular disease. Breast cancer subtypes (e.g., Luminal A, Luminal B [-], Luminal B [+], HER2 overexpression, and Triple-Negative Breast Cancer [TNBC]) and the expression status of hormone receptors (ER, PR) and HER2 were recorded. Tumor staging (T and N stages) and treatment regimens - specifically the use of trastuzumab in combination with anthracyclines - were documented. Cardiac function indicators, including NT-proBNP, LVEF, LA diameter, E/A ratio, and E/e' ratio, were assessed prior to initiation of cancer therapy.

Ultrasound examination

All patients underwent two-dimensional speckle-tracking echocardiography (2D-STE) using the PHILIPS EPIQ7C system with an X5-1 probe (1-5 MHz). Patients were examined in the left lateral decubitus position with ECG monitoring. Standard cardiac views were recorded over at least four consecutive cardiac cycles and analyzed offline using the QLAB workstation.

LVEF was measured using the Simpson's biplane method from apical four-chamber views. LA diameter was measured during ventricular diastole to capture the maximal internal dimension.

The E/A ratio was determined via pulsed-wave Doppler by assessing the early diastolic (E wave) and atrial contraction (A wave) velocities.

The E/e' ratio was calculated by combining E wave velocity with tissue Doppler-derived e' velocity to estimate left ventricular filling pressure.

Laboratory tests

Prior to treatment, 5 mL of peripheral blood was collected in sterile tubes and processed promptly. Serum was separated by centrifugation and used for biochemical analyses. CK-MB and NT-proBNP levels were measured using the Beckman Coulter AU5800 analyzer, with reagent kits provided by the manufacturer to ensure reliability and consistency.

Patient grouping

A total of 506 patients were enrolled. Based on CTRCD status, patients were randomly divided into training and validation cohorts at a 7:3 ratio using the R programming language. The training cohort included 354 patients (92 with CTRCD and 262 without), while the validation cohort included 152 patients (30 with CTRCD and 122 without).

Follow-up

All patients underwent routine follow-up within three months after treatment. Patients who developed cardiac symptoms - such as chest discomfort, chest pain, or dyspnea - were allowed to return earlier for necessary clinical evaluations. Follow-up duration was recorded in weeks.

Outcome measures

Primary outcome: Independent prognostic factors for CTRCD were identified using Cox proportional hazards regression analysis. Based on these factors, a predictive model was developed and visualized using a nomogram.

Secondary outcome: Lasso-Cox regression was employed for variable selection to identify key

predictors significantly associated with CTRCD. The proportional hazards (PH) assumption was tested using Schoenfeld residuals. Cumulative incidence function (CIF) curves were generated for NT-proBNP, LVEF, and LA to evaluate their impact on CTRCD development and improve risk stratification.

To assess model performance and clinical applicability, time-dependent Receiver Operating Characteristic (ROC) curves, calibration curves, and Decision Curve Analysis (DCA) were employed at multiple time points (e.g., 4, 8, and 12 weeks). These metrics evaluated the model's discrimination, calibration, accuracy, and net clinical benefit, identifying the optimal prediction strategy.

Statistical analysis

Statistical analyses were performed using SPSS version 27.0 and R version 4.3.3. Categorical variables were expressed as percentages and compared using the chi-square test. Continuous variables were tested for normality using the Kolmogorov-Smirnov (K-S) test. Normally distributed data were analyzed using independent sample t-tests and reported as mean ± standard deviation (Mean ± SD), while non-normally distributed data were analyzed using the Mann-Whitney U test and reported as median (P50) and interquartile range (IQR). Univariate and multivariate Cox regression analyses were conducted to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to identify independent risk factors for CTRCD. Statistical modeling and visualization were carried out in R using the following packages: glmnet for LASSO regression, survival for Cox regression and proportional hazards assumption testing, rms for restricted cubic splines and nomogram construction, timeROC for time-dependent ROC curve analysis, pec for calibration curve evaluation, and rmda for decision curve analysis. All statistical tests were two-sided, and a *p*-value < 0.05 was considered statistically significant.

Results

Comparison of baseline characteristics and cardiac function indices between training and validation groups

Training group: Patients with a BMI < 22.9 were significantly more prevalent in the CTRCD group (P = 0.032). The combination of trastuzumab and anthracyclines was strongly associated with CTRCD occurrence (P < 0.001). Additionally, higher proportions of patients with Luminal A and Luminal B (-) breast cancer subtypes were observed in the CTRCD group (P = 0.005 and P = 0.018, respectively). HER2-positive status was also significantly correlated with CTRCD (P = 0.021). In terms of cardiac function indices, NT-proBNP levels were significantly elevated (P < 0.001), LVEF was markedly reduced (P < 0.001), and left atrial (LA) diameter was significantly decreased (P < 0.001).

Validation group: The proportion of patients with a BMI < 22.9 was significantly higher in the CTRCD group (P = 0.006). Similarly, trastuzumab combined with anthracyclines was significantly associated with CTRCD (P < 0.001). The proportions of patients with Luminal A and Luminal B (-) subtypes were elevated in the CTRCD group (P = 0.018 and P = 0.005, respectively), and HER2-positive patients were more prevalent (P = 0.026). Cardiac indices revealed significantly increased NT-proBNP levels (P < 0.001), decreased LVEF (P < 0.001), and reduced LA diameter (P < 0.001) (**Table 1**).

Lasso-Cox regression for screening prognostic factors of CTRCD in the training group

All 22 variables were included in the Lasso-Cox regression analysis for variable selection. Eight variables with non-zero coefficients were identified at a lambda.min of 0.020733: hyperlipidemia, trastuzumab combined with anthracyclines, breast cancer subtype, tumor stage, CK-MB, NT-proBNP, LVEF, and LA diameter (**Figure 1**).

Univariate Cox regression risk assessment of feature variables in the training group

Univariate Cox regression analysis of nine feature variables (selected via Lasso-Cox regression) identified significant associations with CTRCD risk. Patients without hyperlipidemia exhibited a lower risk (hazard ratio [HR] = 0.585, P = 0.042), while those receiving trastuzumab and anthracycline combination therapy showed a significantly reduced risk (HR = 0.392, P = 0.001). Among breast cancer subtypes, patients with Luminal B (+) subtype had a significantly increased risk (HR = 3.211, P < 0.001), whereas Luminal B (-) and HER2-overexpressing subtypes showed no statisti-

Table 1. Baseline data of patients in the training and validation groups

Indicator	Training Group (n = 354)		*P*-value	Validation Group (n = 152)		*P*-value
	CTRCD (n = 92)	N-CTRCD (n = 262)		CTRCD (n = 30)	N-CTRCD (n = 122)	
Age						
≥ 50 years	48 (52.17)	150 (57.25)	0.399	14 (46.67)	61 (50.00)	0.744
< 50 years	44 (47.83)	112 (42.75)		16 (53.33)	61 (50.00)	
BMI (kg/m^2)						
~22.9	41 (44.57)	112 (42.75)	0.032	16 (53.33)	37 (30.33)	0.006
23-24.9	35 (38.04)	128 (48.85)		8 (26.67)	72 (59.02)	
≥ 25	16 (17.39)	22 (8.40)		6 (20.00)	13 (10.66)	
Hypertension						
Yes	9 (9.78)	30 (11.45)	0.660	8 (26.67)	16 (13.11)	0.068
No	83 (90.22)	232 (88.55)		22 (73.33)	106 (86.89)	
Diabetes						
Yes	10 (10.87)	32 (12.21)	0.732	5 (16.67)	13 (10.66)	0.361
No	82 (89.13)	230 (87.79)		25 (83.33)	109 (89.34)	
Smoking History						
Yes	24 (26.09)	69 (26.34)	0.963	9 (30.00)	31 (25.41)	0.609
No	68 (73.91)	193 (73.66)		21 (70.00)	91 (74.59)	
Hyperlipidemia						
Yes	18 (19.57)	30 (11.45)	0.050	5 (16.67)	20 (16.39)	0.971
No	74 (80.43)	232 (88.55)		25 (83.33)	102 (83.61)	
Family History of Cardiac Disease						
Yes	11 (11.96)	24 (9.16)	0.440	3 (10.00)	14 (11.48)	0.818
No	81 (88.04)	238 (90.84)		27 (90.00)	108 (88.52)	
Trastuzumab + Anthracycline						
Yes	17 (18.48)	17 (6.49)	< 0.001	9 (30.00)	9 (7.38)	< 0.001
No	75 (81.52)	245 (93.51)		21 (70.00)	113 (92.62)	
Breast Cancer Subtype						
Luminal A	33 (35.87)	126 (48.09)	0.005	10 (33.33)	51 (41.80)	0.018
Luminal B (-)	11 (11.96)	45 (17.18)		4 (13.33)	24 (19.67)	
Luminal B (+)	17 (18.48)	17 (6.49)		9 (30.00)	9 (7.38)	
HER2+	15 (16.30)	42 (16.03)		3 (10.00)	16 (13.11)	
TNBC	16 (17.39)	32 (12.21)		4 (13.33)	22 (18.03)	
ER						
Positive	61 (66.30)	188 (71.76)	0.325	23 (76.67)	84 (68.85)	0.401
Negative	31 (33.70)	74 (28.24)		7 (23.33)	38 (31.15)	
PR						
Positive	61 (66.30)	188 (71.76)	0.325	23 (76.67)	84 (68.85)	0.401
Negative	31 (33.70)	74 (28.24)		7 (23.33)	38 (31.15)	
HER2						
Positive	32 (34.78)	59 (22.52)	0.021	12 (40.00)	25 (20.49)	0.026
Negative	60 (65.22)	203 (77.48)		18 (60.00)	97 (79.51)	
Ki-67						
≥ 20%	42 (45.65)	91 (34.73)	0.063	12 (40.00)	48 (39.34)	0.948
< 20%	50 (54.35)	171 (65.27)		18 (60.00)	74 (60.66)	
Tumor Staging						
Stage II	54 (58.70)	136 (51.91)	0.261	16 (53.33)	68 (55.74)	0.812
Stage III	38 (41.30)	126 (48.09)		14 (46.67)	54 (44.26)	

T Staging						
T0	19 (20.65)	42 (16.03)	0.245	4 (13.33)	18 (14.75)	0.064
T1	11 (11.96)	46 (17.56)		12 (40.00)	21 (17.21)	
T2	27 (29.35)	74 (28.24)		5 (16.67)	43 (35.25)	
T3	24 (26.09)	51 (19.47)		6 (20.00)	22 (18.03)	
T4	11 (11.96)	49 (18.70)		3 (10.00)	18 (14.75)	
N Staging						
N0	20 (23.26)	55 (23.40)	0.724	5 (18.52)	28 (25.00)	0.847
N1	44 (51.16)	115 (48.94)		13 (48.15)	54 (48.21)	
N2	22 (25.58)	65 (27.66)		9 (33.33)	30 (26.79)	
CK-MB (U/L)	18.00 (4.00)	18.00 (4.00)	0.343	18.03 ± 3.20	18.10 ± 2.81	0.919
NT-proBNP (pg/mL)	187.50 (29.25)	160.00 (38.75)	< 0.001	186.50 (32.25)	162.00 (41.00)	0.006
LVEF (%)	56.10 (6.80)	62.40 (6.02)	< 0.001	56.10 (7.30)	62.10 (5.80)	< 0.001
LA (mm)	31.50 (4.00)	28.00 (4.00)	< 0.001	30.33 ± 3.83	28.28 ± 2.73	0.009
E/A	1.10 (0.30)	1.20 (0.30)	0.172	1.10 (0.28)	1.10 (0.30)	0.761
E/e'	7.53 ± 1.21	7.70 ± 1.18	0.230	7.55 ± 1.26	7.69 ± 1.20	0.575

Note: BMI, Body Mass Index; CTRCD, Cancer Therapy-Related Cardiac Dysfunction; HER2, Human Epidermal Growth Factor Receptor 2; ER, Estrogen Receptor; PR, Progesterone Receptor; LVEF, Left Ventricular Ejection Fraction; LA, Left atrial inner diameter; E/A, E/A Ratio; E/e', E/e' Ratio; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; CK-MB, Creatine Kinase-MB.

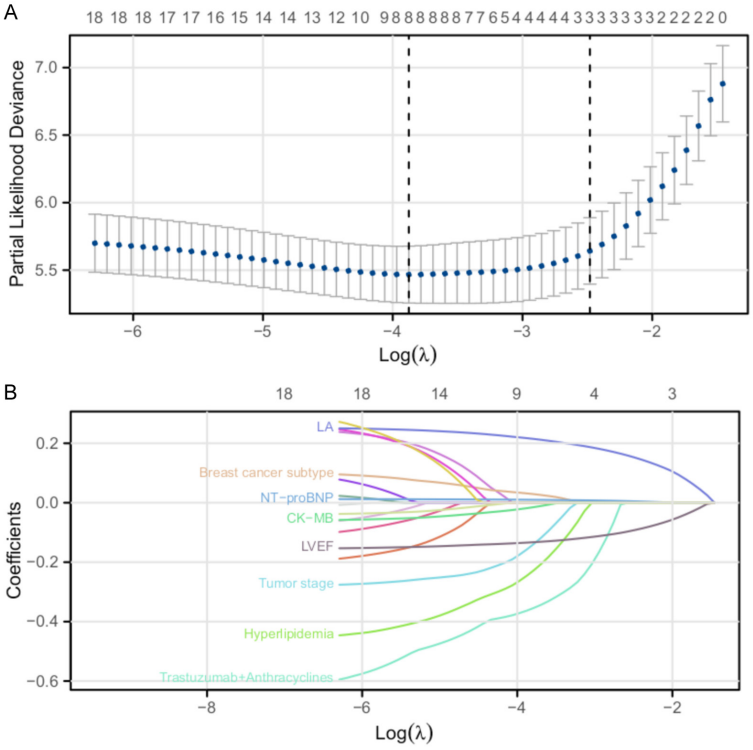

Figure 1. Variable selection results of Lasso-Cox regression analysis. A: The relationship between partial likelihood deviance and log(λ), showing the deviation changes at different lambda values; B: The changes in regression coefficients for each variable at different lambda values. Note: NT-proBNP, N-terminal pro B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LA, left atrial inner diameter.

cally significant differences (P = 0.958 and P = 0.319, respectively). TNBC patients had a higher risk (HR = 1.856, P = 0.045). Tumor stage and CK-MB changes did not significantly affect CTRCD occurrence (P = 0.211 and P = 0.231, respectively). Elevated NT-proBNP was associated with an HR of 1.021 (P < 0.001), reduced LVEF with an HR of 0.806 (P < 0.001), and increased LA diameter with an HR of 1.372 (P < 0.001) (**Table 2**).

Schoenfeld residuals test results using PH assumption test

PH assumption was evaluated for five variables using the Schoenfeld residuals test. Hyperlipidemia, trastuzumab plus anthracycline therapy, breast cancer subtype, and LA diameter met the PH assumption (all P > 0.05). However, NT-proBNP and LVEF exhibited significant deviations (both P < 0.001), indicating that these variables did not satisfy the PH assumption (**Figure 2**).

Stratified analysis of NT-proBNP, LVEF, and LA using CIF curves

CIF curves were generated for six variables, with stratified analyses performed for NT-proBNP, LVEF, and LA. NT-proBNP and LVEF

Table 2. Univariate Cox regression analysis results for the five key variables selected by Lasso-Cox regression

Indicator	Beta	SE	*P* Value	HR	Lower	Upper
Hyperlipidemia						
Yes						
No	-0.536	0.264	0.042	0.585	0.349	0.981
Trastuzumab Anthracyclines						
Yes						
No	-0.999	0.270	< 0.001	0.368	0.217	0.624
Breast Cancer Subtype						
Luminal A						
Luminal B (-)	-0.018	0.351	0.958	0.982	0.493	1.953
Luminal B (+)	1.167	0.302	< 0.001	3.211	1.777	5.805
HER2 Overexpression	0.313	0.315	0.319	1.368	0.738	2.534
Triple-Negative Breast Cancer	0.618	0.308	0.045	1.856	1.015	3.393
Tumor stage						
II						
III	-0.245	0.213	0.252	0.783	0.515	1.190
CK-MB (U/L)	-0.043	0.036	0.231	0.958	0.894	1.027
NT-proBNP (pg/mL)	0.021	0.003	< 0.001	1.021	1.015	1.028
LVEF (%)	-0.215	0.026	< 0.001	0.806	0.766	0.848

Note: NT-proBNP, N-terminal pro B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LA, Left atrial internal diameter; CK-MB, Creatine Kinase-MB.

significantly influenced the 12-week CIF (both P < 0.001). Although LA diameter showed no significant deviation in the Schoenfeld test, stratification was conducted due to its continuous nature. Cutoff points for NT-proBNP, LVEF, and LA were determined using the surv_cutpoint function from the survival package, followed by stratified analyses (**Figure 3**).

Risk assessment of key variables using multivariate cox regression analysis

Multivariate Cox regression analysis indicated that hyperlipidemia was not significantly associated with CTRCD risk (HR = 0.774, P = 0.343). Among breast cancer subtypes, TNBC patients exhibited a significantly increased risk (HR = 1.898, P = 0.041), while Luminal A, Luminal B (-), Luminal B (+), and HER2-overexpressing subtypes showed no significant differences. NT-proBNP emerged as a key risk factor; levels < 172 were associated with a significantly reduced CTRCD risk (HR = 0.273, P < 0.001). LVEF was strongly associated with CTRCD, with levels < 56.5% significantly increasing risk (HR = 3.626, P < 0.001). LA diameter ≥ 32 mm was also a significant risk factor (HR = 0.413, P < 0.001) (**Table 3**).

Prognostic analysis of NT-proBNP, LVEF, and LA using restricted cubic spline plots

Restricted cubic spline analysis revealed significant associations between NT-proBNP, LVEF, and LA diameter with CTRCD risk **Figure 4**). Elevated NT-proBNP levels showed a nonlinear positive association with CTRCD risk (P-overall < 0.001, P-nonlinear < 0.001), with HR exhibiting significant peak changes (**Figure 4A**). LVEF was negatively correlated with CTRCD risk (P-overall < 0.001), with HR decreasing monotonically as LVEF increased, suggesting a linear trend (P-nonlinear = 0.926) (**Figure 4B**). Increased LA diameter was positively correlated with CTRCD risk (P-overall < 0.001), with HR consistently rising with higher LA values and a predominantly linear association (P-nonlinear = 0.112) (**Figure 4C**).

Prognostic model based on breast cancer subtype, NT-proBNP, LVEF, and LA

A nomogram was constructed using NT-proBNP, LVEF, and LA diameter in the training group to predict CTRCD occurrence. Point allocation indicated that LVEF and LA diameter contributed substantially to the prognostic score, with

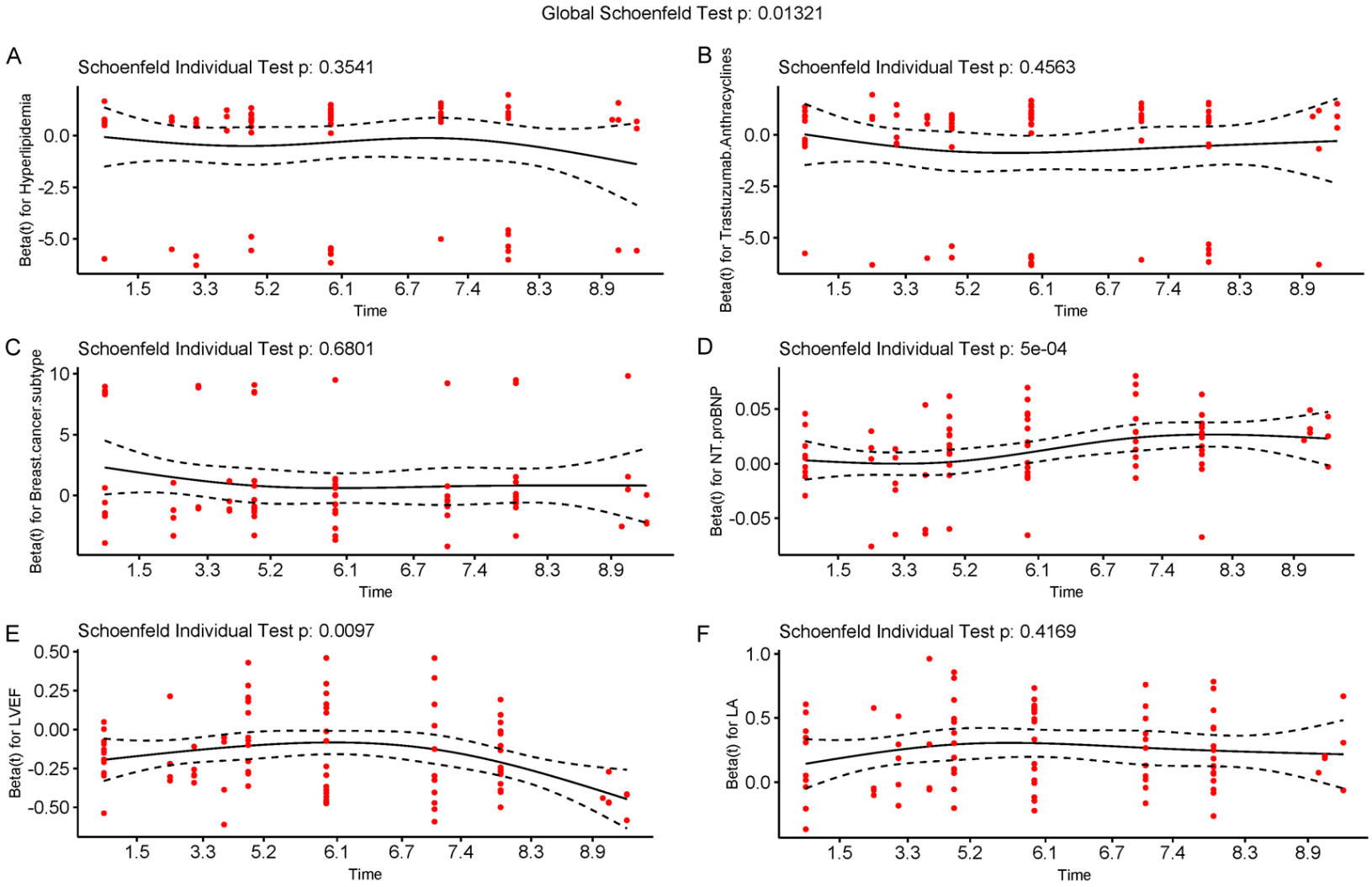

Figure 2. PH assumption test results based on Schoenfeld residuals. A: The relationship between the Schoenfeld residual difference and the time of the hyperlipidemia variables; B: The relationship between the Schoenfeld residue of Trastuzumab Anthracyclines and the time; C: The relationship between the Schoenfeld residual and the time of the breast cancer classification; D: The relationship between the Schoenfeld residue of NT-proBNP and the time; E: The relationship between the Schoenfeld residuals of LVEF and the time; F: The relationship of the Schoenfeld residue of the LA on the time. Note: NT-proBNP, N-terminal pro B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LA, left atrial inner diameter.

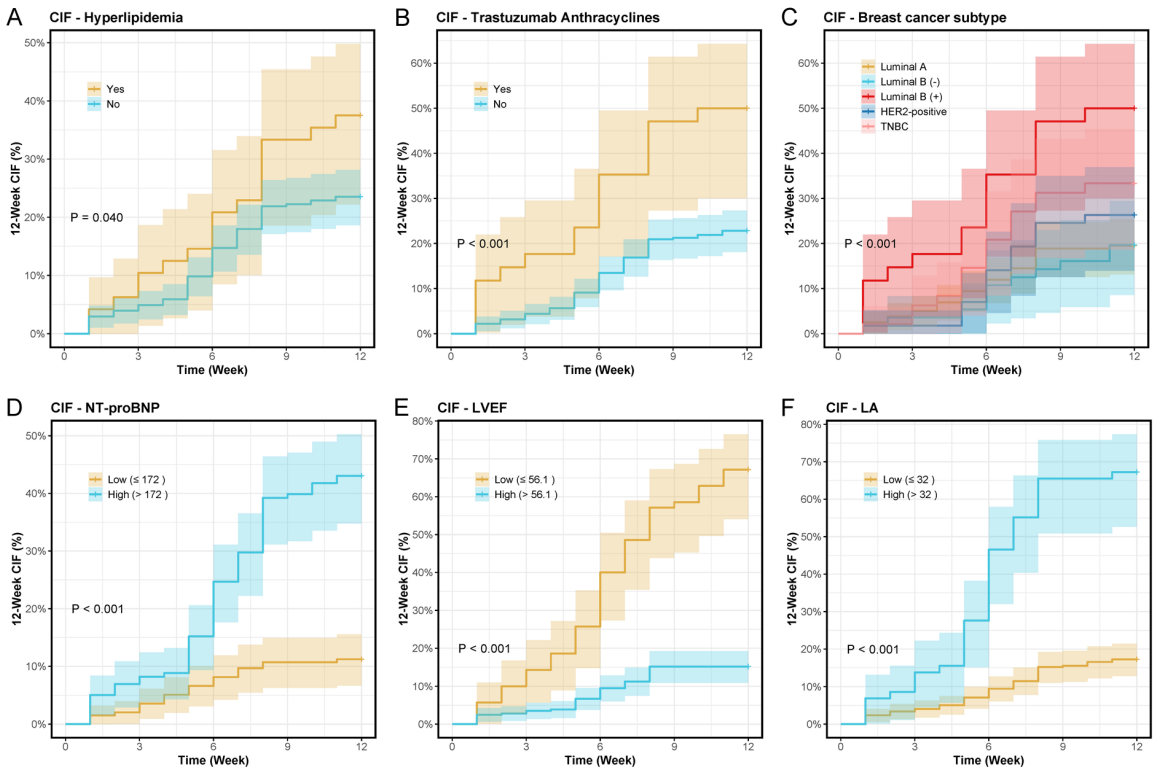

Figure 3. CIF curves for NT-proBNP, LVEF, and LA. A: CIF curve between hyperlipidemia and those without hyperlipidemia; B: The CIF curve of the Trastuzumab Anthracyclines; C: CIF curve of different subtypes of breast cancer classification; D: CIF curve after NT-proBNP stratification; E: The CIF curve after LVEF stratification; F: CIF curve after LA stratification. Note: CIF, Cumulative Incidence Function; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LA, left atrial inner diameter.

LVEF having the greatest impact, while NT-proBNP had a relatively smaller effect (**Figure 5**).

Evaluation of predictive value for CTRCD at 4, 8, and 12 weeks using time-dependent ROC curves

Time-dependent ROC curves assessed the model's predictive accuracy for CTRCD at 4, 8, and 12 weeks. In the training group, area under the curve (AUC) values were 0.871, 0.851, and 0.807, respectively. In the validation group, AUC values were 0.821, 0.784, and 0.833, demonstrating robust predictive performance across time intervals (**Figure 6**).

Comparison of predicted and observed outcomes

Calibration curves were used to evaluate the model's ability to predict survival probabilities at 4, 8, and 12 weeks. In the training group, predicted and observed survival probabilities showed high concordance, with curves closely approaching the diagonal line, particularly at 12 weeks. In the validation group, curves exhibited slight deviations but maintained reasonable predictive accuracy, confirming the model's reliability across time points (**Figure 7**).

Net benefit of the model using decision curve analysis

DCA assessed the net benefit of the model for predicting CTRCD at 12 weeks. In the training group, the overall risk model and LVEF demonstrated substantial net benefits, particularly at higher threshold probabilities, outperforming the "all positive" and "all negative" models. In contrast, breast cancer subtype, NT-proBNP, and LA showed flatter curves, especially at lower thresholds. In the validation group, the risk model and LA diameter exhibited strong net benefits, while breast cancer subtype, LVEF, and NT-proBNP had more modest effects. These results confirm the model's consistent performance and broad applicability (**Figure 8**).

Table 3. Results of multivariate Cox regression analysis

Indicator	Beta	SE	*P* Value	HR	Lower	Upper
Hyperlipidemia						
Yes						
No	-0.180	0.274	0.510	0.835	0.488	1.428
Trastuzumab Anthracyclines						
Yes						
No	-1.173	0.741	0.114	0.310	0.072	1.323
Breast Cancer Subtype						
Luminal A						
Luminal B (-)	-0.269	0.354	0.447	0.764	0.382	1.530
Luminal B (+)	-0.603	0.801	0.451	0.547	0.114	2.627
HER2 Overexpression	0.272	0.316	0.390	1.312	0.706	2.439
Triple-Negative Breast Cancer	0.477	0.311	0.125	1.611	0.876	2.960
NT-proBNP (pg/mL)						
≥ 172						
< 172	-1.310	0.250	< 0.001	0.270	0.165	0.440
LVEF (%)						
≥ 56.5						
< 56.5	1.271	0.226	< 0.001	3.563	2.288	5.548
LA (mm)						
≥ 32						
< 32	-1.097	0.223	< 0.001	0.334	0.216	0.517

Note: HR, Hazard Ratio; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LA, left atrial inner diameter.

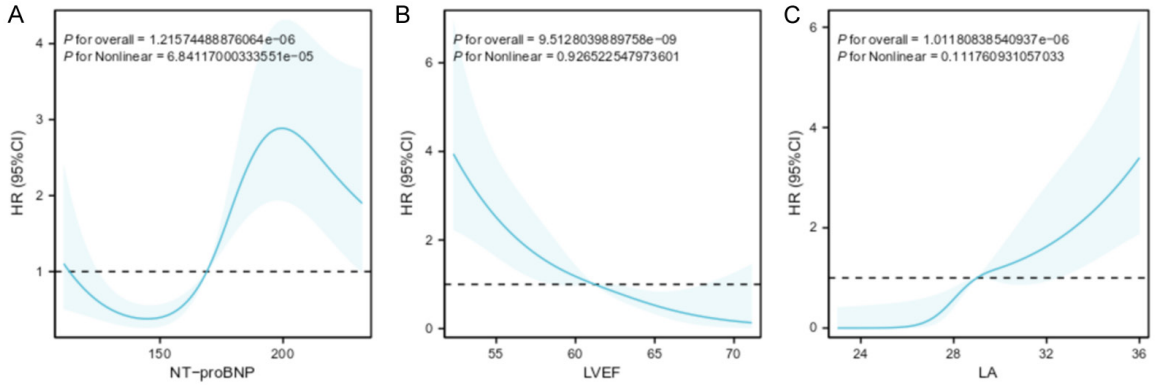

Figure 4. Restricted cubic spline analysis of NT-proBNP, LVEF, and LA. A: Restricted cubic spline analysis of NT-proBNP's impact on CTRCD risk; B: Restricted cubic spline analysis of LVEF's impact on CTRCD risk; C: Restricted cubic spline analysis of LA's impact on CTRCD risk. Note: HR, Hazard Ratio; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LA, left atrial inner diameter.

Discussion

This study constructed and validated a risk prediction model for CTRCD in breast cancer patients, utilizing clinical and imaging parameters. Through Lasso-Cox regression analysis, eight key variables were identified: hyperlipidemia, trastuzumab combined with anthracyclines, breast cancer subtype, tumor stage, CK-MB, NT-proBNP, LVEF, and LA diameter. A nomogram, constructed based on multivariate Cox regression results, demonstrated high predictive accuracy in both the training and validation cohorts, providing an effective tool for clini-

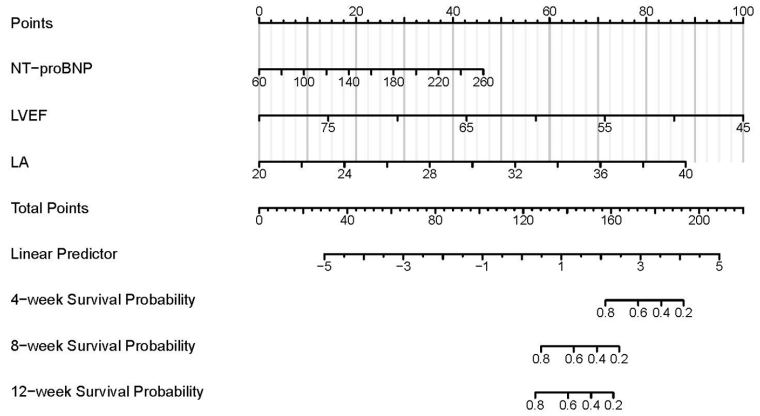

Figure 5. Nomogram prediction model based on NT-proBNP, LVEF, and LA. Note: NT-proBNP, N-terminal pro B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LA, left atrial inner diameter.

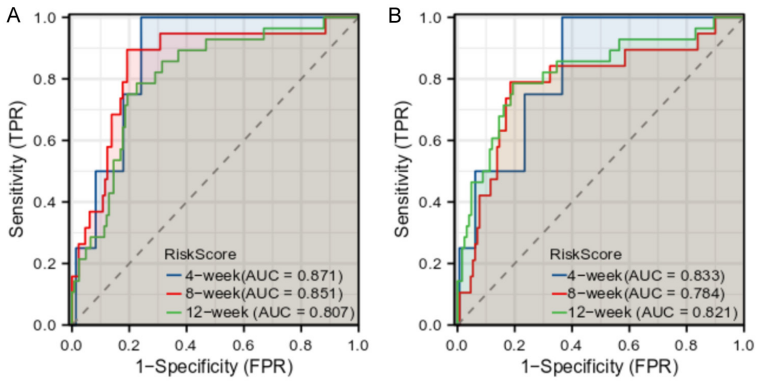

Figure 6. Time-Dependent ROC curve evaluation of the model's predictive ability in the training and validation groups. A: Time-dependent ROC curves for the training group predicting CTRCD at 4, 8, and 12 weeks, along with their corresponding AUC values; B: Time-dependent ROC curves for the validation group predicting CTRCD at 4, 8, and 12 weeks, along with their corresponding AUC values. Note: CTRCD, Cancer Therapy-Related Cardiac Dysfunction; AUC, Area Under the Curve; ROC, Receiver Operating Characteristic.

cal risk assessment. The model's prognostic performance at 4, 8, and 12 weeks was validated by time-dependent ROC curves, calibration curves, and decision curve analysis, confirming its reliability and clinical utility.

The proposed CTRCD prediction model holds substantial clinical significance, particularly for the early detection of cardiac dysfunction in breast cancer patients receiving antitumor therapy [18]. CTRCD significantly impacts long-term survival and quality of life, with notable inter-individual variability in its occurrence. By integrating three critical prognostic indicators - NT-proBNP, LVEF, and LA diameter - the model allows clinicians to identify high-risk patients with greater precision, enabling timely modifications to therapeutic strategies to prevent or delay CTRCD onset.

Hyperlipidemia is closely linked to increased cardiovascular risk and may exacerbate cardiac dysfunction through several mechanisms [19]. It promotes atherosclerosis, reducing coronary blood flow and causing myocardial ischemia; facilitates excessive lipid deposition in the heart and surrounding vessels, increasing cardiac workload; and disrupts fatty acid metabolism, triggering oxidative stress and inflammatory responses in cardiomyocytes, thereby accelerating myocardial damage [20]. These mechanisms may render breast cancer patients more vulnerable to chemotherapy-induced cardiac injury, particularly with anthracyclines, thus elevating CTRCD risk. However, in our multivariate analysis, hyperlipidemia did not retain independent prognostic significance when adjusted for NT-proBNP, LVEF, and LA diameter. Kosalka et al. [21] observed an increased CTRCD risk (RR = 2.2-2.4) in patients with both obesity and dyslipidemia, but dyslipidemia alone lacked independent predictive value. Similarly, Bostany et al. [22] suggested that the direct cardiotoxicity of anthracyclines may overshadow the influence of metabolic factors, with hyperlipidemia failing to emerge as a significant predictor in multivariable models. A meta-analysis by Pinho et al. [23] further supported this, finding no significant association between dyslipidemia and CTRCD after adjusting for confounders (OR = 0.89, P = 0.28). Araújo et al. [24] reported that lipid parameters, such as total cholesterol and LDL-C, contributed minimally to predicting anthracycline-induced cardiotoxicity, whereas inflammatory markers (e.g., C-reactive protein)

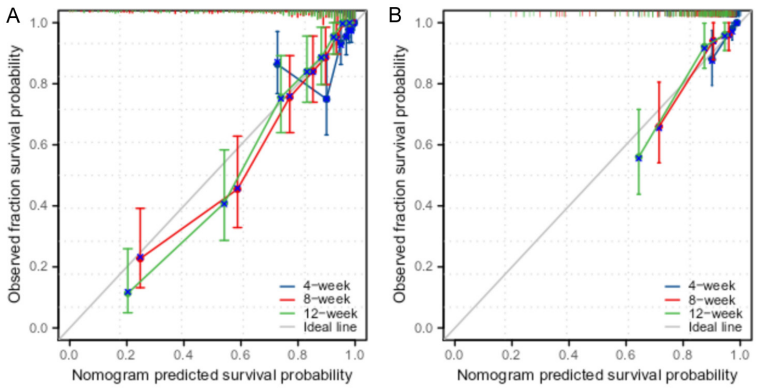

Figure 7. Calibration curves in the training and validation groups. A: Calibration curves in the training group, showing the comparison of predicted survival probabilities at 4, 8, and 12 weeks with actual observed survival probabilities; B: Calibration curves in the validation group, showing the comparison of predicted survival probabilities at 4, 8, and 12 weeks with actual observed survival probabilities.

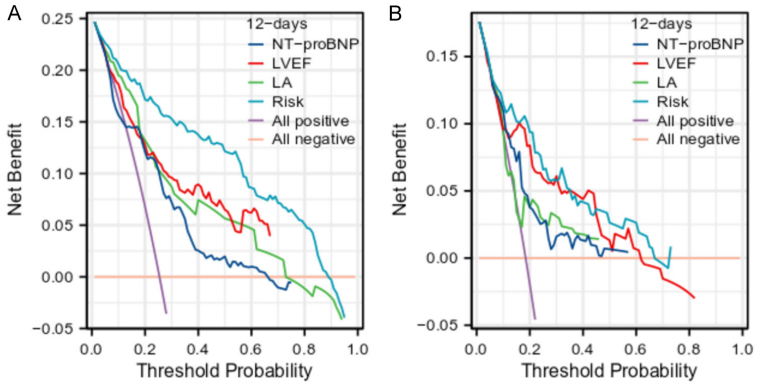

Figure 8. Decision curve analysis in the training and validation groups. A: Decision curve analysis in the training group, showing the relationship between net benefit and threshold probability for different models; B: Decision curve analysis in the validation group, showing the relationship between net benefit and threshold probability for different models. Note: NT-proBNP, N-terminal pro B-type Natriuretic Peptide; LVEF, Left Ventricular Ejection Fraction; LA, left atrial inner diameter.

and clinical factors (e.g., BMI) provided greater predictive value. The predominant role of chemotherapeutic agents, especially anthracyclines, in driving cardiac injury, combined with patient and treatment heterogeneity, likely accounts for hyperlipidemia's limited independent prognostic role. Consequently, while hyperlipidemia influences overall cardiac health and may contribute to cardiovascular disease risk, its specific impact on CTRCD appears secondary in this context.

Our study also identified the combination of trastuzumab and anthracyclines, breast cancer subtype, and tumor stage as significant prognostic indicators. This regimen, a standard treatment for HER2-positive breast cancer, exerts a synergistic therapeutic effect: trastuzumab targets the HER2 receptor to inhibit cancer cell proliferation and metastasis, while anthracyclines induce cytotoxic effects through DNA damage [25]. Breast cancer subtypes - hormone receptor-positive (HR +), HER2-positive, and TNBC - not only guide treatment decisions but also correlate with varying CTRCD risks [26]. HER2-positive patients, frequently treated with trastuzumab, face an elevated risk of cardiac dysfunction, such as reduced LVEF [27]. Lee et al. [28] reported that in HER2-positive patients receiving radiotherapy and trastuzumab, higher cardiac radiation doses (e.g., V25 Gy ≥ 3%) significantly increased CTRCD risk, suggesting additive cardiotoxic effects inherent to subtype-specific regimens. The link between HER2 overactivation and cardiac dysfunction may involve signaling pathway cross-talk, such as HER2-mediated phosphorylation events that promote cardiomyocyte apoptosis and functional decline [29]. Tumor stage further influences treatment outcomes, with advanced or metastatic breast cancer often exhibiting greater drug resistance and heterogeneity, which complicates therapeutic efficacy [30]. As tumor stage progresses, therapeutic resistance may further diminish treatment effectiveness. However, these factors' significance was attenuated in multivariate Cox regression, likely due to complex interactions among variables once confounders were controlled. This finding emphasizes the need to evaluate multiple factors collectively in clinical practice, rather than relying solely on individual indicators or therapeutic approaches.

Although CK-MB is a marker of myocardial injury, its prognostic value diminished in multivari-

ate analyses due to influences from underlying diseases, tumor types, treatment regimens (e.g., trastuzumab and chemotherapy), and other cardiac risk factors [31]. These interactions may obscure CK-MB's statistical significance, limiting its ability to fully capture all mechanisms of cardiotoxicity.

In breast cancer patients, particularly those undergoing chemotherapy and radiotherapy, cardiac function may be compromised, leading to elevated NT-proBNP levels. NT-proBNP, a marker indicative of increased cardiac workload, myocardial injury, or heart failure, is a key predictor of CTRCD. A prospective study by Andersson et al. [32] demonstrated that NT-proBNP levels > 276.5 pg/mL independently predicted trastuzumab-related cardiotoxicity with 100% sensitivity, confirming a strong correlation with cardiotoxicity development during treatment. Elevated NT-proBNP typically signals the onset of cardiac dysfunction, establishing it as an effective early marker for CTRCD risk assessment in this study.

Changes in LVEF often reflect underlying cardiac injury during breast cancer treatment, particularly with anthracyclines [33]. Anthracyclines, such as doxorubicin, are notably cardiotoxic, potentially reducing LVEF through direct myocardial damage or fibrosis. A decline in LVEF is frequently an early indicator of CTRCD, and when LVEF falls below a critical threshold, it signifies significant impairment in cardiac pumping capacity, predicting serious complications [34]. Additionally, antitumor therapies, particularly chemotherapy and targeted treatments like anthracyclines and trastuzumab, may impair diastolic function, resulting in LA enlargement [35]. An increased LA diameter typically reflects compromised diastolic function and heightened cardiac workload; as left ventricular filling pressures rise, the heart's pumping efficiency deteriorates, exacerbating CTRCD risk [36]. Furthermore, an enlarged LA is associated with atrial fibrillation, a major risk factor for heart failure, which increases the likelihood of cardiotoxic events. Tan et al. [37] found that changes in left atrial reservoir strain (LASr) were strongly correlated with cardiotoxicity risk, suggesting that impaired LA function may serve as an early marker, particularly following anthracycline treatment. Electrophysiological remodeling of the LA is closely linked to atrial fibrillation. Additional research [38] has shown that an increased LA diameter elevates CTRCD risk by adversely affecting atrial function and exacerbating cardiac workload, reinforcing its role as an independent prognostic indicator. Thus, LA enlargement not only reflects structural cardiac alterations but also serves as an early signal of dysfunction, making it a valuable marker for CTRCD risk evaluation.

Notably, NT-proBNP, LVEF, and LA demonstrated significant associations with CTRCD in breast cancer patients receiving antitumor therapy. Although hyperlipidemia may influence cardiac health through mechanisms like atherosclerosis and increased workload, it did not emerge as an independent prognostic factor in our multivariate analysis. In contrast, breast cancer subtype is closely tied to the cardiotoxic risk of specific treatment regimens, while NT-proBNP, LVEF, and LA serve as critical indicators of myocardial injury and cardiac dysfunction, offering clinicians valuable early warnings. Esmaeilzadeh et al. [39] reported that integrating global longitudinal strain, LVEF, and NT-proBNP into a single model significantly improved CTRCD diagnostic accuracy (AUC = 0.893), outperforming individual indicators. By incorporating hyperlipidemia and breast cancer subtype, our study not only reinforces the importance of established markers but also enhances the model's applicability, providing new insights for individualized cardioprotective strategies.

Despite the promising predictive performance of our CTRCD risk model in both training and validation cohorts, several limitations must be acknowledged. First, the retrospective, single-center design may introduce selection bias and limit the model's external generalizability. Second, the relatively small sample size, particularly in the validation cohort, may impact the robustness and universality of the findings. Future studies should validate the model in large-scale, multicenter prospective trials. Additionally, while the model incorporated multiple variables (NT-proBNP, LVEF, LA, etc.), other potential influencing factors - such as tumor treatment modalities, genetic background, and lifestyle - were not considered. Future research could explore additional biomarkers, such as global longitudinal strain, cardiac magnetic res-

onance imaging, or plasma proteomics, to further enhance model accuracy. Moreover, developing dynamic assessment tools that incorporate longitudinal data may enable more precise, real-time evaluation of CTRCD risk, thereby optimizing individualized treatment decisions.

Conclusion

The CTRCD prediction model, developed through Lasso-Cox regression and nomogram analysis, comprehensively integrates clinical and imaging indicators to accurately assess the risk of cardiac dysfunction in breast cancer patients during antitumor therapy. Its robust performance in both training and validation cohorts underscores its potential as a clinical tool for early identification of high-risk patients, facilitating timely interventions to mitigate CTRCD.

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Disclosure of conflict of interest

None.

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