Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Analysis of Cardiotoxicity and Risk Factors of Breast Cancer Chemotherapy Drugs: A Five-Year Single-Centre Retrospective Study in Early Breast Cancer

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Objective: To investigate the cardiotoxicity of breast cancer (BC) chemotherapy drugs and analyse their risk factors.

Methods: Through the electronic medical record system, the data of 415 patients with early BC (EBC) who had undergone a complete chemotherapy cycle were retrospectively collected within 5 years from the beginning of chemotherapy. Baseline clinical, biochemical and echocardiographic data were retrospectively extracted for comparative analysis.

Results: The incidence of cardiotoxic events in patients with EBC receiving trastuzumab-targeted therapy was as high as 23%, which was significantly higher than that in the conventional chemotherapy group ($P = 0.006$). The incidence of cardiotoxicity in patients receiving conventional chemotherapy combined with targeted therapy increased year by year. The use of anthracyclines or trastuzumab significantly increased the risk of cardiotoxicity, especially when the two drugs were used in combination, showing a significant synergistic effect ($P < 0.001$). An anthracycline exposure cycle >4, radiotherapy, use of trastuzumab, abnormal myocardial zymogram and elevated troponin I (TnI) levels were identified as risk factors for cardiotoxicity. The Tei index increased over time ($P < 0.001$), indicating progressive subclinical cardiac dysfunction. The Tei index of patients after 4 courses of chemotherapy differed from that before chemotherapy ($P < 0.05$). High-sensitivity cardiac TnI (hs-cTnI) and brain-type natriuretic peptide (BNP) increased over time. Further comparison showed that the levels of hs-cTnI ($P < 0.05$) and BNP ($P < 0.05$) differed between T4 and T0. The Tei index had a certain predictive value for early cardiotoxicity, with an area under the curve (AUC) of 0.867.

Conclusion: In patients with EBC, cumulative anthracycline use of >4 cycles, trastuzumab use and radiotherapy independently increased 5-year cardiotoxicity (adjusted odds ratio >3), whereas a Tei index of >0.40 predicted early subclinical injury with an AUC of 0.867. The cardiotoxicity associated with targeted therapy drugs, represented by trastuzumab, is mostly asymptomatic left ventricular ejection fraction reduction and shows a synergistic effect with anthracyclines. During chemotherapy, the Tei index was more accurate in evaluating myocardial injury.

Keywords: chemotherapy, breast cancer, cardiotoxicity, risk factors, predictors

Received: 8 January 2025
Accepted: 10 July 2025
Published: 30 July 2025

Introduction

Breast cancer (BC) is a malignant tumour that occurs in breast epithelial cells. According to the latest *Cancer Statistics 2024*, breast cancer remains the most commonly diagnosed cancer among women worldwide, accounting for approximately 30% of all new female cancer cases.[1] The *Global Burden of Disease Study 2023* reports that BC incidence continues to rise globally, with over 2.3 million new cases annually.[2] Despite advances in treatment, BC has the highest mortality rate among female cancers, with over 685,000 deaths annually worldwide.[3]

In China, the number of new BC cases ranks fourth, second only to lung cancer, colorectal cancer and gastric cancer.[3] With the extension of life expectancy associated with economic development, the popularisation of cancer screening, improvements in diagnostic capabilities, unhealthy lifestyles and late childbearing,[4] the incidence and mortality of BC are increasing year by year, posing a serious threat to women's lives and health.[5] At the same time, insomnia, depression, anxiety and other psychological symptoms often accompany the diagnosis of BC, seriously affecting patients' quality of life.[6] As an important method of treating malignant tumours, chemotherapy includes adjuvant and neoadjuvant therapy, rescue therapy and other stages in the management of BC. Chemotherapeutic drugs for BC often include anthracyclines (such as doxorubicin and epirubicin), vinca alkaloids, platinum compounds, alkylating agents and other types of chemotherapeutic drugs, and their effects have been verified in a number of large clinical trials. Although the survival time and quality of life of patients with BC have greatly improved, the threat of adverse reactions caused by BC chemotherapy to patients cannot be ignored. The side effects of different chemotherapeutic drugs vary, with cardiotoxicity accounting for the highest proportion. According to research, cardiovascular disease (CVD) is the second leading cause of morbidity and mortality in long-term survivors of cancer,[7,8] with an approximately threefold increased risk compared with the general population.[9]

Clinically, the detection methods for chemotherapy-induced cardiotoxicity mainly include electrocardiogram (ECG), echocardiography, myocardial enzymes, myocardial injury markers, endomyocardial biopsy (EMB) and brain natriuretic peptide (BNP). Detection methods such as myocardial injury markers and myocardial enzymes are currently routine clinical tests for CVDs such as acute myocardial injury, acute coronary syndrome and myocarditis. Their diagnostic value has been confirmed by large-scale clinical trials, but in the context of cardiotoxicity detection, there is still a lack of reliable clinical evidence. Previous single-centre studies have suggested that cardiac troponin I (cTnI) is not specific for detecting chemotherapy-induced cardiotoxicity, and its diagnostic effectiveness remains to be further confirmed.[10] Left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) are commonly used indicators for evaluating cardiac function. They can help identify high-risk groups for adverse cardiac events and have an important clinical effect in preventing acute cardiac insufficiency. However, LVEF is not sensitive in detecting cardiotoxic damage caused by chemotherapeutic drugs and may considerably underestimate the extent of cardiac injury.[11] Once a patient with a tumour shows a marked reduction in LVEF, it often indicates severe cardiotoxicity, and the optimal time window for treatment may have already passed. Studies both in China and internationally have confirmed that diastolic dysfunction may be an early manifestation of anthracycline-induced cardiac insufficiency, whereas systolic function, as measured by LVEF, can remain compensated in the early stages of cardiotoxicity.[12] Sawaya et al also report that the decrease in LVEF greatly lags behind the onset of chemotherapy-related cardiotoxicity.[13] Endomyocardial biopsy is an invasive examination method for the diagnosis of cardiotoxicity. The specificity and sensitivity of EMB in diagnosing cardiotoxicity are high. However, EMB is difficult to implement and carries a high risk of complications. It is challenging to apply in clinical practice and is not easily accepted by the general patient population.

The molecular mechanisms underlying chemotherapy-induced cardiotoxicity include oxidative stress, mitochondrial dysfunction and DNA damage. Anthracyclines such as doxorubicin primarily cause cardiotoxicity through the production of reactive oxygen species and inhibition of topoisomerase II, whereas trastuzumab disrupts ErbB2 signalling, which is essential for cardiomyocyte survival and function.[14,15] Recent studies have shown that cardioprotective strategies, including ACE inhibitors, beta-blockers and dexrazoxane, can reduce the risk of cardiotoxicity when used prophylactically or early after the detection of subclinical cardiac dysfunction.[16]

At present, there is no effective method to monitor early cardiotoxicity in clinical practice. Identifying high-risk patients for chemotherapy-induced cardiotoxicity and exploring sensitive early detection methods have become

a research focus in the interdisciplinary field of cardiovascular and oncology. In this retrospective study of 415 patients with early BC (EBC) followed up for 5 years after chemotherapy, we evaluate the occurrence of cardiotoxicity following anti-tumour therapy and analyse potential risk factors, aiming to provide more effective tools for clinicians to assess the risk of cardiotoxicity in patients with BC after chemotherapy.

Research Participants and Methods

Research Participants

Patient data were retrospectively collected from the electronic medical record system. A total of 415 patients with BC who had undergone a complete chemotherapy cycle between January 2016 and January 2019 in the department of gland surgery of our hospital were identified, and follow-up data were collected for 5 years from the beginning of chemotherapy. The inclusion criteria were as follows: (1) female patients; (2) pathological diagnosis of BC confirmed by surgery or biopsy; (3) first-time recipients of radiotherapy, chemotherapy or endocrine therapy; (4) complete chemotherapy cycle performed at our hospital. The exclusion criteria were as follows: (1) incomplete physical examination; (2) severe heart failure (LVEF <50%) confirmed before chemotherapy, as this indicated pre-existing considerable cardiac dysfunction that could confound the assessment of chemotherapy-induced cardiotoxicity; (3) history of other malignant tumours, as prior cancer treatments might have affected cardiac function; (4) aged >70 years, due to the higher prevalence of age-related cardiovascular comorbidities that could confound the assessment of chemotherapy-specific effects; (5) presence of allergic rhinitis, nasal septal deviation or other structural abnormalities of the nasal cavity that could independently induce cardiovascular complications. Early BC was defined as stage I–III BC according to the AJCC 8th edition staging criteria.

This study was approved by the hospital's ethics committee (2024-KY-046-01). All participants provided written informed consent.

Research Methods

Chemotherapy Regimens

All patients with EBC received adjuvant or neoadjuvant treatment at our hospital: trastuzumab 8 mg/kg as a loading dose, followed by 6 mg/kg every 21 days; epirubicin 75 mg/m² (or pirarubicin 50 mg/m²); docetaxel 75 mg/m² (or paclitaxel 175 mg/m²); and cyclophosphamide 1000 mg/m², with each cycle lasting 21 days.

Definition of Cardiotoxicity

The definition of cardiotoxicity was based on the criteria established by the American Heart Function Assessment Committee for chemotherapy-related cardiotoxicity: a reduction in LVEF ≥10% (absolute value ≤55%) with associated heart failure symptoms or an asymptomatic reduction in ejection fraction ≥15% (absolute value ≤50%).[17–19] Late-onset (>5 years) events were reported but peaked within the first 60 months; hence, a 5-year window captured the majority of clinically relevant cases.

Grouping Method

In the study of cardiotoxicity across different treatment regimens, the cases were divided into a targeted therapy group (211 cases) and a conventional chemotherapy group (204 cases). This division was based on the primary research question of whether the addition of trastuzumab substantially increased cardiotoxicity compared with conventional chemotherapy alone. The targeted therapy group received trastuzumab, whereas the conventional chemotherapy group did not. In the analysis of cardiotoxicity related to anthracyclines and trastuzumab, patients were categorised into a control group (68 cases), a single-drug group (204 cases) and a combined group (143 cases). The control group received neither anthracyclines nor trastuzumab, the single-drug group received only one of the two agents and the combined group received both anthracyclines and trastuzumab. In the study of risk factors for cardiotoxicity, patients were divided into a negative group (340 cases) and a positive group (75 cases) according to the presence or absence of cardiotoxicity.

Data Collection

The main patient-related factors collected included: age; body mass index (BMI); oestrogen receptor (ER) status; progesterone receptor (PR) status; history of hypertension (blood pressure >140/90 mmHg, including patients using antihypertensive drugs); history of coronary atherosclerotic heart disease; history of diabetes (random blood glucose >126 mg/dl, 2-hour serum glucose >200 mg/dl or use of hypoglycaemic drugs); tumour location; clinical tumour stage (AJCC cancer staging); type of chemotherapy; ECG abnormalities; LVEF; myocardial enzyme spectrum abnormalities (including creatine kinase [CK], CK isoenzyme, lactate dehydrogenase and aspartate aminotransferase – the presence of one or more abnormalities was considered indicative of enzyme spectrum abnormality); and TnI abnormalities. Before chemotherapy (T0), at the end of 2 cycles (T1), 4 cycles (T2), 6 cycles (T3) and 8 cycles of chemotherapy (T4), the following parameters were collected and analysed: ECG abnormalities; LVEF; LVFS; pulse Doppler mitral early diastolic peak velocity/late diastolic peak velocity ratio (E/A); Tei index (isovolumic contraction time + isovolumic relaxation time / ejection time, reflecting global ventricular function); CK; CK-MB; high-sensitivity cTnI (hs-cTnI); and BNP.

Statistical Analysis

Power analysis suggested that a sample size of n = 356 would achieve 80% power ($\alpha = 0.05$) to detect a 10% difference in cardiotoxicity; the final cohort (n = 415) exceeded this requirement. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Normality was tested using the Kolmogorov–Smirnov method. Measurement data that conformed to a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$). The independent sample *t*-test was used for comparisons between groups, and the paired *t*-test was used for within-group comparisons. Data that did not follow a normal distribution were expressed as median (Q1, Q3), and the Mann–Whitney *U*-test was used for group comparisons. Categorical data were expressed as frequency (n) or percentage (%). The chi-squared (χ^2) test was used where applicable; otherwise, Fisher's exact test was applied. Logistic regression was used to analyse potential risk factors. The predictive value of each factor was assessed using receiver operating characteristic curves. A two-sided $P < 0.05$ was considered statistically significant.

Results

General Information

The targeted therapy group included 211 patients with a mean age of 51.1 ± 8.7 years. The conventional chemotherapy group included 204 patients, with a mean age of 50.2 ± 7.6 years. Statistically significant differences were observed between the two groups in the proportion of ER positivity, PR positivity, the number of anthracycline cycles and the number of paclitaxel cycles ($P < 0.05$), as shown in Table 1.

Comparison of the Incidence of Cardiotoxicity in Different Chemotherapy Regimens

Among all enrolled patients, a total of 75 (18.1%) experienced cardiotoxicity events meeting the diagnostic criteria. The incidence of cardiotoxic events in patients with EBC receiving trastuzumab-targeted therapy was 23% (49 cases), which was significantly higher than the 12.7% (26 cases) observed in the conventional chemotherapy group ($P = 0.006$).

A Kaplan–Meier (KM) curve was plotted to show the cumulative incidence of cardiotoxicity events within the first 5 years following conventional chemotherapy combined with trastuzumab treatment, as shown in Figure 1 (**$P < 0.001$). The KM curve showed a steeper and earlier decline in the trastuzumab group, indicating a higher and faster accumulating risk of cardiotoxicity within the observation period. The incidence of cardiotoxicity in patients receiving combination therapy increased year by year, and events occurred earlier compared with those in the conventional chemotherapy group ($P < 0.001$).

Another KM curve was plotted to analyse the cumulative incidence of cardiotoxicity within 5 years following anthracycline-based chemotherapy combined with trastuzumab, as shown in Figure 2 (**$P < 0.001$). Use of either anthracyclines or trastuzumab significantly increased the risk of cardiotoxicity. When both drugs were used in combination, the risk was markedly elevated, indicating a strong synergistic effect ($P < 0.001$).

Table 1 Case Characteristics of Enrolled Patients

Variable	Targeted Therapy Group (n=211)	Conventional Chemotherapy Group (n=204)	*P* value
Age (year, $\bar{x} \pm s$)	51.1±8.7	50.2±7.6	0.244
BMI[kg/m^2, M (Q1, Q3)]	24.8 (22.6, 27.4)	24.2 (22, 26.1)	0.154
Estrogen receptor			<0.001
Negative	122	77	
Positive	89	127	
Progesterone receptor			<0.001
Negative	143	100	
Positive	68	104	
Hypertension(number)	37	49	0.103
Coronary heart disease(number)	14	21	0.180
Diabetes(number)	9	12	0.452
Tumor location(number)			0.300
Left	102	109	
Right	109	95	
Neoplasm staging(number)			0.792
I	54	52	
II	113	104	
III	44	48	
Chemotherapy mode(number)			0.433
New adjuvant	63	54	
Adjuvant	148	150	
Exposure cycle of anthracycline drugs(number)			<0.001
0	44	69	
1-4	105	61	
>4	62	74	
Taxol drug exposure cycle(number)			<0.001
0	29	14	
1-4	49	81	
>4	133	109	
Cyclophosphamide drug exposure cycle(number)			0.135
0	111	89	
1-4	77	83	
>4	23	32	
Radiotherapy(number)	92	102	0.192

Univariate and Multivariate Logistic Regression Analysis of Influencing Factors of Cardiotoxicity

To investigate the risk factors associated with cardiotoxicity within five years after chemotherapy, patients were divided into a cardiotoxicity-positive group (75 cases) and a cardiotoxicity-negative group (340 cases). Univariate logistic regression analysis identified several significant risk factors for cardiotoxicity. These included an anthracycline exposure cycle greater than four (odds ratio [OR] = 2.51, 95% confidence interval [CI]: 1.25–5.06, P = 0.01), receipt of radiotherapy (OR = 2.05, 95% CI: 1.23–3.43, P = 0.01), use of trastuzumab (OR = 3.83, 95% CI: 2.16–6.77, P < 0.001), abnormal myocardial zymogram results (OR = 2.41, 95% CI: 1.35–4.30, P = 0.003), and elevated troponin I levels (OR = 7.00, 95% CI: 3.96–12.40, P < 0.001). Subsequent multivariate logistic regression analysis confirmed that these factors remained statistically significant predictors of cardiotoxicity. Specifically, anthracycline exposure cycle >4 (OR = 2.76, 95% CI: 1.26–6.04, P = 0.01), radiotherapy (OR = 3.25, 95% CI: 1.75–6.05, P < 0.001), use of trastuzumab (OR = 4.69, 95% CI: 2.41–9.11, P < 0.001), abnormal myocardial zymogram (OR = 2.87, 95% CI: 2.34–4.12, P < 0.001), and abnormal troponin I levels (OR = 7.96, 95% CI: 3.98–15.92, P < 0.001) were independently associated with increased cardiotoxicity risk. These findings are detailed in Table 2.

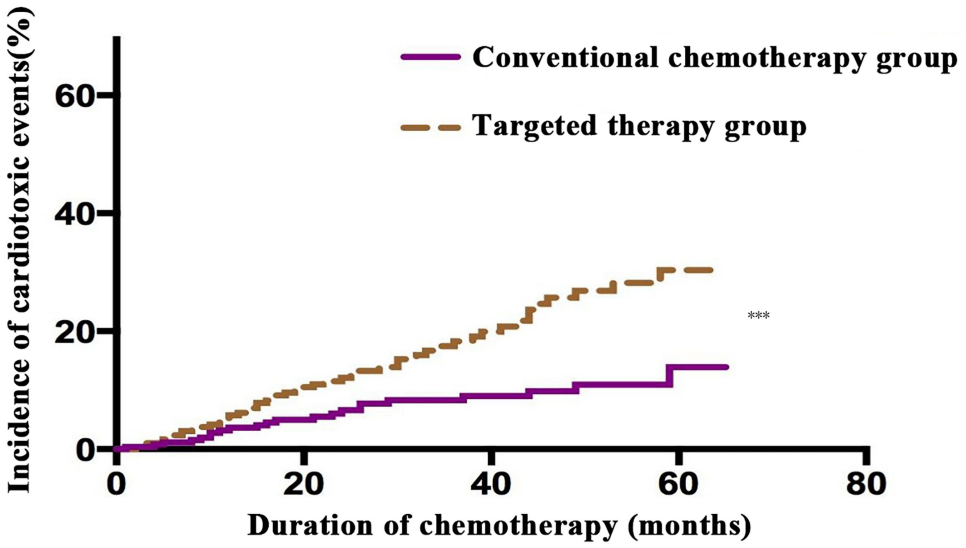

Figure 1 Comparison of cardiotoxicity events between Targeted therapy group and Conventional chemotherapy group (***P < 0.001).

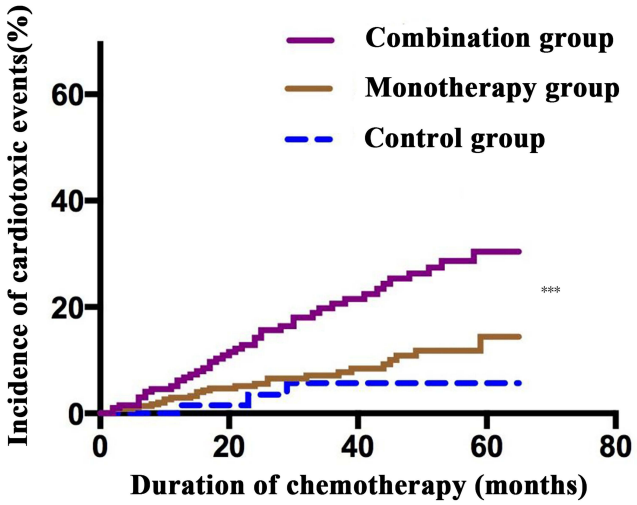

Figure 2 Comparison of cardiac toxicity events after anthracyclines combined with or without trastuzumab treatment (***P < 0.001).

Predictive Value of Various Factors on Cardiotoxicity

The results showed that each index had a certain predictive value for cardiotoxicity. The area under the curve (AUC) of the anthracycline exposure period >4 was 0.845, and the 95% CI was 0.812–0.914. The AUC of radiotherapy was 0.634 (95% CI: 0.543–0.689). The AUC of trastuzumab was 0.821, and the 95% CI was 0.783–0.872. The AUC of abnormal myocardial enzymes was 0.876 (95% CI: 0.830–0.922). The AUC of abnormal TnI level was 0.871, and the 95% CI was 0.826–0.915. See Table 3.

Comparison of the Abnormal Rate of Electrocardiogram at Each Time Point in Patients with Cardiotoxicity

Electrocardiogram (ECG) abnormalities were evaluated at five time points (T0 to T4) in patients who developed cardiotoxicity. At baseline (T0), no abnormalities were observed. At the T1 time point, one patient (1.3%) exhibited ECG abnormalities. At T2 and T3, the number of abnormal cases increased to two (2.7%) and three (4.0%) respectively, while at T4, five patients (6.7%) showed abnormal ECG findings. However, statistical analysis indicated that none of the

Table 2 Univariate and Multivariate Logistic Regression Analysis of Influencing Factors of Cardiotoxicity

Variable	Single Factor Analysis			Multiple-Factor Analysis		
	P value	*OR value*	95% CI	*P* value	*OR value*	95% CI
Older age	0.79	0.99	0.97~1.02			
BMI	0.11	1.08	0.98~1.18			
Estrogen receptorPositive	0.44	1.22	0.74~2.01			
Progesterone receptorPositive	0.29	0.75	0.44~1.27			
With hypertension	0.60	1.18	0.64~2.15			
With coronary heart disease	0.90	0.94	0.37~2.37			
With diabetes	0.89	1.08	0.34~3.33			
The tumor is on the right side.	0.99	0.99	0.60~1.65			
Neoplasm staging						
I	~	Reference	Reference			
II	0.82	1.07	0.58~1.96			
III	0.52	0.77	0.36~1.66			
Chemotherapy mode(number)						
New adjuvant	~	Reference	Reference			
Adjuvant	0.78	0.92	0.53~1.61			
Exposure cycle of anthracycline drugs						
0	~	Reference	Reference	~	Reference	Reference
1~4	0.48	1.29	0.63~2.64			
>4	0.01	2.51	1.25~5.06	0.01	2.76	1.26~6.04
Taxol drug exposure cycle						
0	~	Reference	Reference			
1~4	0.97	1.01	0.41~2.50			
>4	0.73	0.86	0.37~2.02			
Cyclophosphamide drug exposure cycle						
0	~	Reference	Reference			
1~4	0.13	1.54	0.87~2.73			
>4	0.16	1.73	0.79~3.77			
Conducting Radiotherapy	0.01	2.05	1.23~3.43	<0.001	3.25	1.75~6.05
Use trastuzumab	<0.001	3.83	2.16~6.77	<0.001	4.69	2.41~9.11
Abnormal electrocardiogram	0.47	1.27	0.66~2.44			
Abnormal myocardial zymogram	0.003	2.41	1.35~4.30	<0.001	2.87	2.34~4.12
Abnormal level of troponin I	<0.001	7.00	3.96~12.40	<0.001	7.96	3.98~15.92

Table 3 Predictive Value of Each Index on Cardiotoxicity

Variable	Sensitivity (%)	Specificity (%)	AUC value	95% CI
Exposure cycle of anthracycline drugs>4	86.7	88.5	0.845	0.812~0.914
Conducting Radiotherapy	71.2	61.5	0.634	0.543~0.689
Use trastuzumab	87.3	72.1	0.821	0.783~0.872
Abnormal myocardial zymogram	96.4	84.8	0.876	0.830~0.922
Abnormal level of troponin I	93.3	82.1	0.871	0.826~0.915

time points showed a significant difference in ECG abnormality rates when compared to T0 ($P > 0.05$ for all comparisons). These results suggest a trend toward increased ECG abnormalities over time, although the differences were not statistically significant. Full details are provided in Table 4.

https://doi.org/10.2147/DDDT.S516457

Table 4 Comparison of Abnormal Rate of Electrocardiogram at Different Time Points in Patients with Cardiotoxicity

Time	Abnormal Number of Cases	Abnormality Rates (%)	*P* value*
T0	0	0	Reference
T1	1	1.3	1.000
T2	2	2.7	0.497
T3	3	4.0	0.245
T4	5	6.7	0.058

Note:*Compared with T0, the difference was statistically significant.

Comparison of Echocardiography at Each Time Point in Patients with Cardiotoxicity

The results showed that there was no significant difference in LVEF (F = 1.976, P = 0.098), LVFS (F = 0.784, P = 0.536) and E/A (F = 1.115, P = 0.349) at the five time points in patients with cardiotoxicity. The Tei index (isovolumic contraction time + isovolumic relaxation time/ejection time, reflecting global ventricular function) increased over time (F = 53.359, P < 0.001). Further comparison showed that the Tei index of the patients was statistically significant at T2 compared with that at T0 (0.41 ± 0.03 vs 0.36 ± 0.04, P < 0.05), as shown in Table 5.

Comparison of Biochemical Indexes at Different Time Points in Patients with Cardiotoxicity

The results showed that there was no significant difference in the levels of CK (F = 0.621, P = 0.648) and CK-MB (F = 2.360, P = 0.053) at the five time points in patients with cardiotoxicity. The levels of hs-cTnI and BNP increased over time. Further comparison showed that the levels of hs-cTnI (0.050 ± 0.002 vs 0.019 ± 0.002, P < 0.05) and BNP (52.66 ± 5.32 vs 33.48 ± 3.72, P < 0.05) were significantly different between T4 and T0, as shown in Table 6.

Table 5 Comparison of Echocardiography at Each Time Point in Patients with Cardiotoxicity

Time	LVEF (%)	LVFS (%)	E/A	Tei Index
T0	66.87±2.19	36.30±1.43	1.22±0.30	0.36±0.04
T1	66.36±2.16	36.08±1.23	1.15±0.39	0.36±0.03
T2	66.45±1.86	36.08±1.37	1.19±0.28	0.41±0.03*
T3	66.31±1.73	36.05±1.14	1.25±0.28	0.41±0.04*
T4	65.98±1.79	35.94±1.04	1.17±0.32	0.42±0.02*
F value	1.976	0.784	1.115	53.359
P value	0.098	0.536	0.349	<0.001

Note:*Compared with T0, the difference was statistically significant.

Table 6 Comparison of Biochemical Indexes at Different Time Points in Patients with Cardiotoxicity

Time	CK (U/L)	CK-MB (U/L)	hs-CTnI (ng/mL)	BNP (pg/mL)
T0	41.46±4.37	11.33±1.14	0.019±0.002	33.48±3.72
T1	41.18±4.51	11.30±0.85	0.019±0.003	32.86±3.62
T2	40.99±4.82	11.38±1.10	0.020±0.005	35.22±4.03
T3	41.89±4.95	11.63±1.21	0.021±0.004	36.24±3.41
T4	40.93±4.98	11.51±1.29	0.050±0.002*	52.66±5.32*
F value	0.621	2.360	1166.401	307.267
P value	0.648	0.053	<0.001	<0.001

Note:*Compared with T0, the difference was statistically significant.

The Predictive Value of the Tei Index for Early Cardiotoxicity

The results showed that the Tei index had a certain predictive value for cardiotoxicity. The AUC was 0.867, and the 95% CI was 0.833–0.903.

Discussion

Among the 415 patients with EBC enrolled, approximately 18.1% experienced cardiotoxicity events meeting the diagnostic criteria, with this rate increasing to 23% among those receiving sequential trastuzumab-targeted therapy. This represents an approximate 10% absolute increase in cardiotoxicity risk associated with trastuzumab exposure. A key finding of our study is the early and progressive elevation of the Tei index, a sensitive marker of global ventricular function, which was observed to significantly increase as early as after four chemotherapy cycles—earlier than measurable changes in LVEF or the onset of clinical symptoms. This highlights the Tei index as a promising predictor of subclinical cardiac dysfunction. Additionally, our longitudinal data showed that serum biomarkers such as hs-cTnI and BNP rose significantly over time, with statistically significant differences between T4 and baseline (T0), demonstrating a temporal relationship between biomarker elevation and subsequent cardiotoxicity. These results support the use of Tei index and cardiac biomarkers in combination for early detection and dynamic monitoring of chemotherapy-induced cardiac injury. Many studies have shown that anti-tumour chemotherapy increases the incidence of cardiotoxicity, though the reported rates vary considerably depending on the specific regimen and patient population.[20,21] Because of their design, clinical trials often exclude patients with cardiovascular risk factors, which may lead to an underestimation of cardiotoxic events in real-world settings. In actual practice, clinicians tailor chemotherapy plans based on a patient's age and comorbid conditions. Our findings suggest that even mild, asymptomatic reductions in LVEF should not be overlooked, as previous studies have shown that such changes are predictive of future heart failure.[22] Therefore, cardiotoxic effects from chemotherapy warrant close monitoring and long-term follow-up.

Studies have shown that when anthracyclines are used, high BMI, blood pressure and age may be risk factors for chemotherapy drug-related cardiotoxicity.[23,24] This study shows that a previous history of coronary heart disease, the use of anthracyclines and combined adjuvant radiotherapy may increase the risk of cardiotoxicity from chemotherapeutic drugs. It is worth noting that the results of this study showed that the use of anthracyclines within 4 cycles did not increase the risk of cardiotoxicity in patients with EBC. However, the exposure dose of high-dose anthracyclines (more than 4 cycles) substantially increased the risk of subsequent adverse cardiac events. In this study, we used the number of anthracycline cycles (>4) as a surrogate marker for cumulative exposure rather than calculating exact cumulative dosages. This approach was chosen because the cycle number has been validated in previous literature as a reliable clinical indicator of anthracycline exposure and was consistently documented in our medical records.[23] Although precise cumulative dose calculations might provide additional granularity, the cycle-based threshold approach offers a clinically practical metric that can be readily applied in routine patient assessment to identify those at higher risk. Future studies with more detailed pharmacokinetic monitoring could further refine the relationship between anthracycline cumulative dosage and cardiotoxicity risk. Previous studies have shown that the use of trastuzumab combined with anthracycline drugs leads to a considerable increase in the risk of cardiotoxicity.[25] To avoid or reduce cardiotoxic injury, clinicians may avoid combining anthracycline drugs with trastuzumab and instead opt for paclitaxel as an alternative. The results of the population analysis of patients with EBC enrolled in this study also confirmed these conclusions. The cardiotoxicity of anthracyclines has long been recognised, and the occurrence of cardiotoxicity is correlated with the cumulative dose of anthracyclines.[26] Therefore, low-dose use of anthracyclines is a safe and effective choice for cardiac protection while ensuring their anti-tumour effect. Similarly, radiotherapy, as an effective anti-tumour treatment for patients with EBC, may have a certain synergistic effect with the combined application of trastuzumab, resulting in enhanced toxic damage to the heart. Previous animal experiments have shown evidence of synergy between radiotherapy and trastuzumab. Radiotherapy-induced cardiotoxic injury requires a median latency of 3–20 years from the start to the onset of obvious clinical symptoms.[27] Currently, the follow-up time of the study is mostly within 5 years, so the cardiac safety issue after the combined application of the two is far from being concluded. The cardiotoxic injury caused by sequential

trastuzumab combined with radiotherapy in conventional chemotherapy may be more complicated and requires further follow-up observation.

Studies have shown that myocardial enzymes have some predictive value for cardiac function in patients undergoing chemotherapy.[28] However, in 2016, the ESC recommended the use of cTn and biomarkers such as BNP or NT-proBNP to screen for and detect the risk of chemotherapy-related CVD and clarified that serum myocardial enzymes are not specific, less sensitive than Tn and do not provide value in the evaluation of chemotherapy-related cardiotoxicity.[29] Emerging markers such as soluble ST2 and galectin-3 are under investigation and may further refine risk stratification in the future.

Cardiac TnI is one of the subunits of cTn, which is composed of cTnT and cTnC; cTn is an important component of cardiac muscle contraction.[30] When myocardial cell damage leads to cell membrane rupture, a large amount of cTnI can quickly enter the peripheral blood, with a considerable increase occurring in the early stage of cardiotoxicity.[31] Myocardial injury and apoptosis can be monitored by cTnI when myocardial damage occurs.[32] Studies have shown that[33] the serum level of hs-cTnI in patients with tumours treated with anthracycline chemotherapy was substantially higher than that in those treated without anthracycline chemotherapy. It is concluded that hs-cTnI has important value in the early evaluation of cardiotoxicity. The monitoring role of cTnI in anti-tumour drug-related cardiotoxicity has been unanimously endorsed by the US Food and Drug Administration expert committee as a cardiotoxicity test indicator recommended by the ESMO clinical practice guidelines.[34] In our study, hs-cTnI and BNP levels showed a progressive upward trend during chemotherapy, with significant increases observed at later time points (T4 vs T0). This temporal association suggests that biomarker monitoring may offer early warning before overt cardiac dysfunction becomes apparent. The results of this study also show that cTnI has good predictive value for the early detection of cardiotoxicity caused by BC chemotherapy and has promising application prospects in clinical practice.

Clinical strategies to mitigate trastuzumab-anthracycline cardiotoxicity include (i) sequential rather than concurrent administration, (ii) prophylactic ACE inhibitors or β-blockers and (iii) dose-capped anthracycline regimens, all of which have shown cardioprotective benefits in recent trials.[35–37] The Tei index, also known as the MPI, is a new index for evaluating cardiac function by ultrasound, which can comprehensively assess cardiac function.[38] However, it cannot specifically evaluate whether systolic or diastolic dysfunction is present. Some scholars have suggested that the Tei index has a higher correlation with cardiotoxicity than the indicators measured by cardiac catheterisation.[39] Additionally, some researchers measured the left ventricular Tei index by tissue Doppler imaging in 51 patients who underwent anthracycline chemotherapy after BC surgery, exploring its sensitivity to early myocardial toxicity compared with conventional echocardiography. They found that, compared with before chemotherapy, the Tei index increased considerably after chemotherapy, whereas LVEF did not notably change. This suggests that subclinical myocardial damage caused by anthracycline chemotherapy can be detected earlier and more accurately by the tissue Doppler Tei index.[40] The results of this study showed that the Tei index changed the earliest during chemotherapy (at the end of the 4th cycle), whereas the change in LVEF was not obvious, remaining within the normal range, with no significant statistical difference. This indicates that the Tei index is more sensitive to early myocardial damage caused by chemotherapy drugs.

This study also has some limitations. First, although the case data and records of all enrolled patients were carefully reviewed, they were still subject to the inherent limitations of retrospective study design, including the lack of random case selection. Potential biases in data collection due to the retrospective nature of the study may have influenced the results. Second, this is a single-centre study with a relatively small sample size, which considerably limits the validity and robustness of the statistical findings. Finally, the study used 2D echocardiography to evaluate LVEF, and relying on changes in LVEF as the sole indicator of cardiotoxicity lacks both reliability and accuracy. High-throughput CRISPR screens and patient-derived xenograft models could further elucidate the molecular determinants of chemotherapy-induced cardiotoxicity and validate the clinical predictors identified in this study.[41]

Conclusion

In patients with EBC, cumulative anthracycline exposure of more than 4 cycles, trastuzumab use and radiotherapy independently increased 5-year cardiotoxicity risk (adjusted OR >3), whereas a Tei index > 0.40 predicted early

subclinical injury with an AUC of 0.867. The cardiotoxicity associated with targeted therapies such as trastuzumab is mostly characterised by asymptomatic LVEF reduction, which has a synergistic effect when combined with anthracyclines. Long-term anthracycline exposure, radiotherapy, trastuzumab use, abnormal myocardial enzymes and elevated TnI levels are all risk factors for cardiotoxicity, and these indicators have predictive value. During chemotherapy, the Tei index, hs-cTnI and BNP are sensitive markers for the early assessment of cardiotoxicity, with the Tei index showing higher accuracy in evaluating myocardial injury.[38]

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Jingjiang People's Hospital Affiliated to Yangzhou University (2024-KY-046-01). Written informed consent was obtained from all participants.

Consent for Publication

The manuscript is not submitted for publication or consideration elsewhere.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research did not receive any funding support.

Disclosure

The authors declare that they have no competing interests in this work.

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