Original Article

Development of a multivariable clinical prediction model for liposomal doxorubicin-induced cardiotoxicity in adult breast cancer patients: a retrospective multicenter study

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Background: The clinical use of anthracyclines is limited by the risk of cardiotoxicity. So, we aim to develop a clinical prediction model for liposomal doxorubicin-induced cardiotoxicity in adult breast cancer patients.

Methods: We designed a multicenter retrospective cohort study. A total of 257 hospitalized breast cancer patients treated with doxorubicin liposomes were finally enrolled in the study, including 58 patients from Beijing Friendship Hospital and 199 from Beijing Cancer Hospital. In all, 32 cases developed cardiotoxicity, including 4 at the Beijing Friendship Hospital and 28 at the Beijing Cancer Hospital. The study involved breast cancer patients with no pre-existing heart disease, whose clinical data were collected from their medical records. All patients underwent electrocardiogram (ECG) and/or left ventricular ejection fraction (LVEF) measurements prior to treatment with doxorubicin liposomes. Patients were clinically assessed after each cycle of treatment, and ECG and/or LVEF measurements were performed at least once after treatment. Liposomal doxorubicin-induced cardiotoxicity was defined when one of the following three conditions was met: (I) a reduction in LVEF of at least 5% from the baseline and the absolute value was less than 55%, accompanied by congestive heart failure (CHF) symptoms or signs; (II) a reduction in LVEF of at least 10% to an absolute value of less than 55%, without CHF symptoms or signs; (III) the definite diagnosis of CHF. Variables associated with cardiotoxicity were identified by univariate and multivariate logistic regression, and the consistency and differentiation of the final model were evaluated.

Results: In our final model, age [odds ratio (OR): 5.626, 95% confidence interval (CI): 2.321 to 13.639], cancer metastasis (OR: 3.873, 95% CI: 1.220 to 12.299), paclitaxel (OR: 3.601, 95% CI: 1.010 to 12.843), and hypertension (OR: 2.435, 95% CI: 1.046 to 5.671) were significantly associated with cardiotoxicity. The final model was tested for Hosmer-Lemeshow goodness-of-fit, the χ^2 was 2.696 and the P value was 0.747, and the resultant predictive model had an area under the receiver operating characteristic (ROC; AUC) curve of 0.781.

Conclusions: This study established a risk prediction model for liposomal doxorubicin-induced cardiotoxicity in breast cancer patients and performed a stratified risk scores

Keywords: Breast cancer; liposomal doxorubicin; cardiotoxicity; prediction model; risk score

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Introduction

The clinical use of anthracyclines is influenced by the risk of cardiotoxicity (1,2), and anthracycline-based chemotherapeutic regimens can cause clinical heart failure (HF) and reduced asymptomatic left ventricular ejection fraction (LVEF) (3,4). Liposomal doxorubicin is encapsulated in polyethylene glycol liposomes, which increases the lipophilicity of the drug, changes the tissue distribution and pharmacokinetic properties of the free drug, prolongs the drug circulation time in the blood, and may reduce cardiotoxicity and other side effects at the same time (5). Clinical factors associated with cardiotoxicity include cumulative anthracycline dose (6), age (6-8), body mass index (BMI) (9), cancer metastasis (10), hypertension (7), dyslipidemia (9), diabetes (6), and other cardiotoxic drugs in combination (9-11), among others.

A study (12) published in 2019 by Upshaw *et al.* showed the development of a risk prediction model for anthracycline cardiotoxicity in 967 patients with human epidermal growth factor receptor 2 (HER2)-negative breast cancer. In this study, they started by including four routinely available predictors—age, hypertension, BMI, and baseline LVEF. In multivariate analysis, only age [odds ratio (OR), 1.04; P=0.0119], BMI (OR, 1.06; P=0.0010), and baseline LVEF (OR, 0.93; P=0.0044) were included in the final model. The risk model discrimination based on the c-statistic was 0.701 [95% confidence interval (CI): 0.627 to 0.774]. Bootstrap internal validation yielded an optimism-corrected c-statistic of 0.68 [95% prediction interval (PI): 0.62 to 0.75]. In general, a prediction model with a c-statistic greater than 0.70 can be considered that it has an adequate power of discrimination. So, both in the establishment and verification of this model, the c-statistic didn't show a good predictive performance. And although their study considered clinically influential factors, some important cardiac risk factors such as diabetes, smoking, and previous diagnosis of heart disease, the inclusion of which might have improved the model's performance, were not collected.

In another study published in 2020 (13), Chaix *et al.* performed exome sequencing in 289 childhood cancer survivors who had been exposed to anthracycline for at least three years. Their final model included five clinical factors and 31 genes that were significantly associated, and the final model had an area under the curve (AUC) of 0.72 (95% CI: 0.63 to 0.80). The AUC of their model showed it has a comparatively adequate power of discrimination, but they didn't have an external validation. Meanwhile, their study was limited to pediatric late cancer survivors; patients' early cardiotoxicity was not explored, and it cannot be extrapolated to adult patients. Their study only provided information for the establishment of a predictive model of anthracycline cardiotoxicity. The effect of each factor was not assigned, so it was impossible to calculate according to the formula to obtain reference results in clinical application. Moreover, although the inclusion of rare genes in modeling is very comprehensive, it is currently difficult to sequence the genes of every patient in clinical practice.

Through a comprehensive search of PubMed databases, we found that although there have been many studies (6-13) on the various risk factors for cardiotoxicity caused by anthracyclines, most of the clinical studies (6-11) conducted both within and outside of China have been confined to univariate analysis and multivariate analysis. To date, no effective risk prediction model of cardiotoxicity risk factors has been established in addition to the two studies mention above (12,13). Therefore, it is necessary to develop a prognostic model in which patients with cancer received doxorubicin liposomes as the core of chemotherapy, to guide clinical stratification according to the risk factors and further achieve safe and rational drug use. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1935/rc).

Methods

Study design and data source

We conducted a multicenter, retrospective study of hospitalized patients by collecting electronic medical records from Beijing Friendship Hospital and Beijing Cancer Hospital. The study included breast cancer patients who were treated with doxorubicin liposomes during hospitalization from January 2018 to July 2021 from Beijing Cancer Hospital and Beijing Friendship Hospital, Capital Medical University. The liposome dosage form of doxorubicin alters the tissue distribution and pharmacokinetic characteristics of the free drug (5), which may result in a reduced likelihood of cardiotoxicity, thus the results of the analysis may be unreasonable if patients treated with both liposome and non-liposome dosage forms were included in the study.

The inclusion criteria were as follows: (I) ≥18 years old; (II) definite diagnosis of breast cancer; (III) the therapy was chemotherapy with doxorubicin liposome as the core; (IV) electrocardiogram (ECG) or LVEF were recorded before treatment, and these two indicators were normal; and (V) clinical evaluation was performed after each treatment cycle, and an ECG and/or LVEF measurements were performed at least once after treatment. The exclusion criteria were as follows: (I) pre-existing cardiac disease; (II) symptoms of cardiac insufficiency such as edema, palpitations, or pleural effusion before treatment; and (III) the basic state of the body is too weak.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Beijing Friendship Hospital (No. 2021-P2-123-01) and the Ethics Committee of Beijing Cancer Hospital (No. 2017YJZ1208). Individual consent for this retrospective analysis was waived.

Outcomes

Our outcome was cardiotoxicity. The occurrence of a cardiotoxic event in this study was defined as a compound outcome by reference to the definition of cardiotoxicity in published studies (4,7,9,10,12,14-18) and the data available to us in this study: (I) a reduction in LVEF of at least5% from the baseline and the absolute value was less than 55%, accompanied by congestive heart failure (CHF) symptoms (dyspnea, edema, etc.) or signs; or (II) a reduction in LVEF of at least 10% to an absolute value of less than 55%, without CHF symptoms or signs (third heart sound gallop, tachycardia, etc.); or (III) definite clinical diagnosis of CHF was recorded. To ensure the objectivity of outcome evaluation, cardiotoxicity evaluation was conducted uniformly after data extraction of 257 patients, which effectively avoided the influence of risk factor information of each patient.

Predictor variables

We extracted data on demographic factors (age, weight, BMI), clinical diagnoses (hypertension, diabetes, dyslipidemia, cancer metastasis), imaging examination (ECG, echocardiography), and treatment protocols (chemotherapy cycle, drug combination, and the cumulative dose of doxorubicin liposomes) from the hospital's electronic database records. Drug combinations were defined as drugs that were used simultaneously during the treatment cycle included in the study, including docetaxel, rituximab, cyclophosphamide, carboplatin, paclitaxel, dexrazoxane, and trastuzumab. The formula: weight (kg)/height^2 (m^2) was used to calculate BMI. The chemotherapy cycle was defined as: (I) if cardiotoxicity occurred, the cycle in which the outcome occurred is recorded; (II) if no cardiotoxicity occurred, the total number of cycles of chemotherapy was recorded. Cumulative dose is the sum of doxorubicin liposomes doses used during the chemotherapy cycle. All predictive variables were independently and clearly recorded and were based on the most recent information in the pre-study database.

Missing data

There was no missing data for all predictors and outcome.

Statistical analysis

The continuous variables conforming to normal distribution were expressed as the mean ± standard deviation (SD), and the independent *t*-test was used for inter-group comparison. Non-normally distributed continuous variables were presented as the median (interquartile range), and groups were compared using the Mann-Whitney U test. Categorical variables were expressed as number (percentage) and analyzed using the χ^2 test.

The statistical model we used was the logistic regression model. We selected the initial predictors based on our reading of the reported literature and the data available to us. Variables that were significant at P<0.1 in the univariate analyses were entered in the stepwise multivariable logistic regression model, removing terms with P<0.1 and adding those with P<0.05. The risk model was constructed using the variables retained in the final multivariate logistic regression model, and a points system was created to score the cardiotoxicity risk according to the logistic regression coefficient.

To evaluate the discriminability of the risk model, the receiver operating characteristic (ROC) curves were constructed, and the AUC was calculated. Hosmer-Lemeshow test and calibration plot were used to evaluate the calibration effect of the risk model. All data analyses were performed using the software SPSS 25.0 (IBM Corp., Armonk, NY, USA). A two-sided P<0.05 was considered statistically significant.

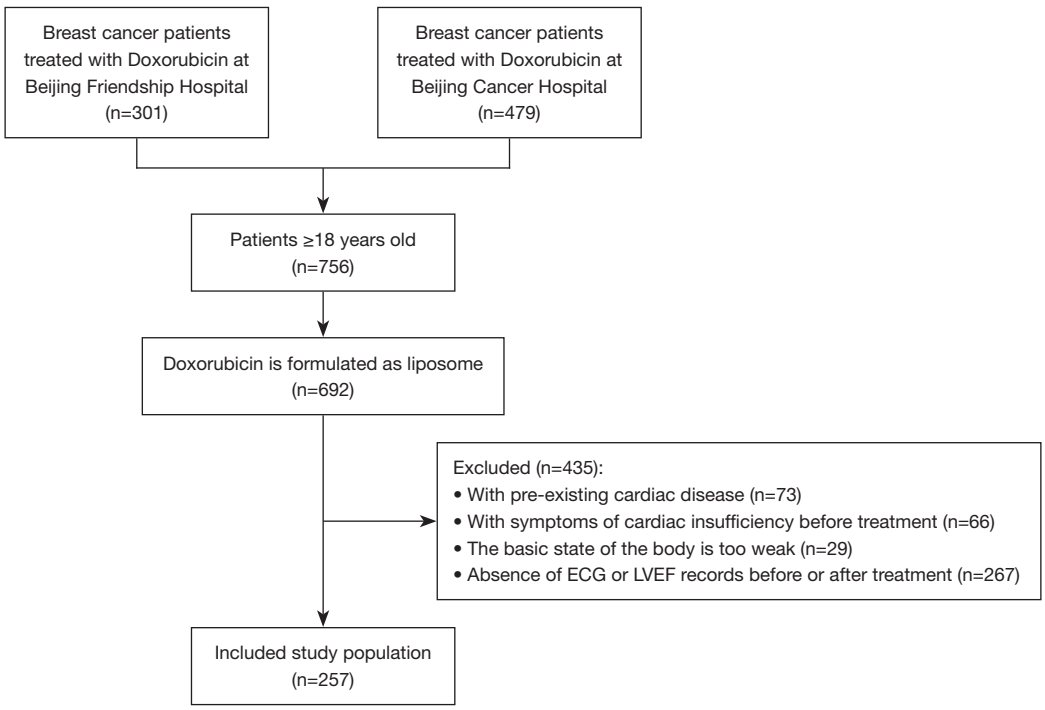

Figure 1 Flowchart of patients included in this study. ECG, electrocardiogram; LVEF, left ventricular ejection fraction.

Results

Study population

We collected all the electronic medical records of breast cancer patients who received liposomal doxorubicin treatment in both Beijing Cancer Hospital and Beijing Friendship Hospital from January 2018 to July 2021. As shown in *Figure 1*, a total of 257 breast cancer patients who met the eligibility criteria were finally enrolled in the study for the development of the model. In all, 32 cases developed cardiotoxicity, including 4 from Beijing Friendship Hospital and 28 from Beijing Cancer Hospital.

Univariate analysis

Five variables were significant (P<0.1) in the univariate analyses (*Table 1*) and finally entered multivariable logistic regression analysis: age, hypertension, diabetes, cancer metastasis, and combination use of paclitaxel. There was no missing data for predictors or the outcomes.

Multivariable logistic regression model

Multiple logistic regression analysis (*Table 2*) revealed that age (OR: 5.626, 95% CI: 2.321 to 13.639), cancer metastasis (OR: 3.873, 95% CI: 1.220 to 12.299), paclitaxel (OR: 3.601, 95% CI: 1.010 to 12.843), and hypertension (OR: 2.435, 95% CI: 1.046 to 5.671) were risk factors for cardiotoxicity. Based on the multiple logistic regression model, the cardiotoxicity risk prediction model of breast cancer patients was constructed:

$$Logit(P) = -4.012 + 0.890 \times hypertension + 1.727 \times age + 1.354 \times cancer\ metastasis + 1.281 \times paclitaxel \quad [1]$$

where hypertension, yes =1, no =0; age, <65 =1 and ≥65 =2; cancer metastasis, yes =1, no =0; combination use of paclitaxel, yes =1, no =0.

Discrimination and calibration

The risk model had good discriminative power (*Figure 2*), with an AUC of 0.781 (95% CI: 0.693 to 0.869). According to its sensitivity (0.719) and specificity (0.742), the highest Youden index was 0.461 and the best cut-off point was 0.090. The model was also well-calibrated with the Hosmer-Lemeshow χ^2 statistic of 2.696 (P=0.747; *Figure 3*).

Table 1 Association of characteristics and cardiotoxicity (univariate analysis, P<0.1)

Characteristics	Cardiotoxicity (n=32)	No-cardiotoxicity (n=225)	P value
Demographic characteristics			
Age, years [n (%)]			0.000
<65	17 (53.1)	200 (88.9)	
≥65	15 (46.9)	25 (11.1)	
Weight, kg	62.5 (55.0, 71.0)	60 (55.0, 67.0)	0.640
BMI, kg/m^2 [n (%)]			0.113
<24	13 (40.6)	125 (55.6)	
≥24	19 (59.4)	100 (44.4)	
Clinical diagnoses [n (%)]			
Hypertension	16 (50.0)	53 (23.6)	0.002
Diabetes	13 (40.6)	56 (24.9)	0.060
Dyslipidemia	3 (9.4)	13 (5.8)	0.431
Metastasis	27 (84.4)	152 (67.6)	0.053
Drug combination [n (%)]			
Docetaxel	1 (3.1)	9 (4.0)	0.811
Rituximab	0 (0.0)	2 (0.9)	0.592
Cyclophosphamide	9 (28.1)	95 (42.2)	0.128
Carboplatin	0 (0.0)	4 (1.8)	0.447
Paclitaxel	6 (18.8)	14 (6.2)	0.013
Dexrazoxane	0 (0.0)	2 (0.9)	0.592
Trastuzumab	1 (3.1)	5 (2.2)	0.752
Accumulated dose, mg			
Liposome doxorubicin [n (%)]			0.552
<200	19 (59.4)	121 (53.8)	
≥200	13 (40.6)	104 (59.4)	

Values are n (%), median (interquartile range). BMI, body mass index.

Risk score development

To facilitate the clinical application, each risk factor was assigned a risk score according to the cardiotoxicity risk assessment model (*Table 3*). The scoring rules were based on the methodology in previous report (19). In this study, the reference value of the variable with the smallest regression coefficient (hypertension) was set as 1 point; the relative multiple of the regression coefficient was calculated respectively, and the scores were assigned accordingly.

The total risk score included 0, 2–9, and 12, with corresponding predicted probabilities of cardiotoxicity ranging from 1.84 to 80.99% (0, 1.84%; 2, 4.55%; 3, 7.18%; 4, 10.28%; 5, 16.15%; 6, 21.43%; 7, 30.59%; 8, 38.08%; 9, 52.33%, and 12, 80.99%).

Risk scoring was categorized into four levels to improve the clinical application of the risk score model: low risk (score 0 and 2), medium–low risk (score 3–5), medium–high risk (score 6–7), and high risk (score 8–9 and 12). The actual incidence and predicted probability of cardiotoxicity according to the four risk classes was shown in Figure S1, and the trend of higher risk level linking to a higher incidence of cardiotoxicity was apparent.

Discussion

In our study, we found that hypertension, cancer metastasis, paclitaxel, and advanced age (≥65) were risk factors for cardiotoxicity, and a risk prediction model for adult breast cancer patients was developed. Our results showed that when other variables remain unchanged, the risk of cardiotoxicity increases 1.435 times in patients with hypertension, 2.601 times in patients with paclitaxel, 2.873 times in patients with cancer metastasis, and 4.626 times in patients over 65 years old. Although the individual risk factors for doxorubicin cardiotoxicity were known, to the best of our knowledge, no risk prediction model of cardiotoxicity in patients exposed to doxorubicin liposome had been established.

Age and cardiotoxicity risk

In our study, when the value of the Youden index was 0.358, the corresponding age was 64.5, so age was divided into two groups (<65 and ≥65 years) according to the best discriminator values defined by ROC analysis. As an independent risk factor for cardiotoxicity, age has been reported in many studies (6,7,20,21). Most clinical cancer studies set a cut-off age of 60 or 65 years for younger and elderly patients (8,15,18). The American Society of Clinical Oncology (ASCO) guidelines indicated that patients over 65 years of age were a high-risk group for chemotherapy-induced cardiotoxicity (18). Although the age cut-off values in all reported studies were different (10,12,15-17,22), the results all indicated that older patients were at higher risk of cardiotoxicity after chemotherapy, which is consistent with our findings using 65 years as the cut-off age value.

Table 2 Multivariable analysis of risk factors for cardiotoxicity

Factors	β	SE	Wald χ^2	P value	OR	95% CI
Hypertension	0.890	0.431	4.257	0.039	2.435	1.046–5.671
Paclitaxel	1.281	0.649	3.900	0.048	3.601	1.010–12.843
Metastasis	1.354	0.590	5.275	0.022	3.873	1.220–12.299
Age	1.727	0.452	14.620	0.000	5.626	2.321–13.639

SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval.

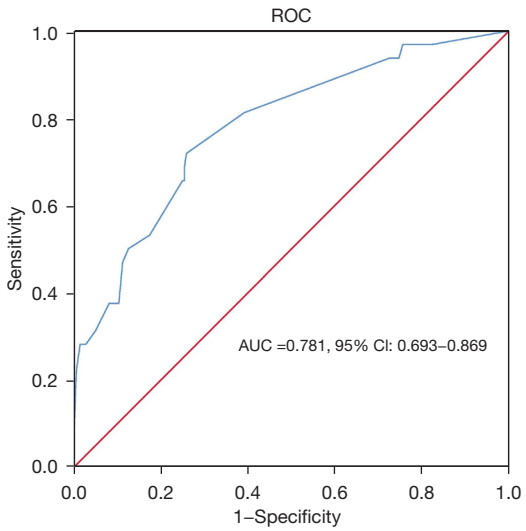

Figure 2 ROC curve for the liposomal doxorubicin-induced cardiotoxicity risk model. ROC, receiver operating characteristic; AUC, area under the curve; 95% CI, 95% confidence interval.

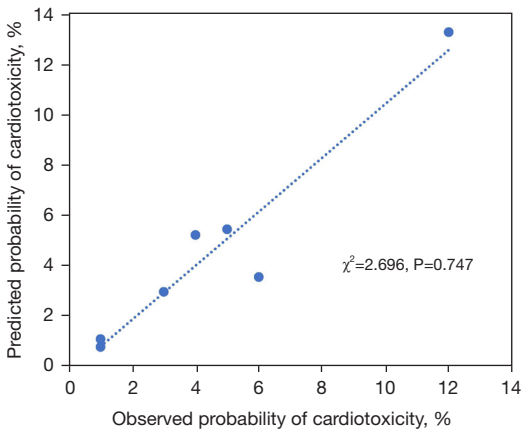

Figure 3 Calibration chart of Hosmer-Lemeshow goodness of fit test.

Paclitaxel and cardiotoxicity

In a pharmacologic investigation of the possible interference between doxorubicin and paclitaxel, it was shown that paclitaxel caused nonlinear distribution and elimination of the anthracycline (23). In the meantime, doxorubicin and paclitaxel were consistent with competition for excretion as they both had a predominant biliary elimination route. Bile canaliculi express P-glycoproteins (P-gp) from the mdr gene family that contribute to xenobiotics excretion, and both paclitaxel and doxorubicin are well-characterized substrates for mdr-1 P-gp. Thus, the most likely cause of pharmacokinetic interaction is the inhibitory effects exerted by paclitaxel on P-gp-mediated biliary excretion (24), which increased plasma concentration and reduced the clearance of doxorubicin, leading to an increasing risk of cardiotoxicity.

Other articles have pointed out that arrhythmias and ischemia are the most common cardiotoxic side effects in patients receiving paclitaxel, which may be related to accelerated release of calcium (2). Paclitaxel can increase NCS-1 levels in cardiomyocytes which may lead to increased InsP3R-dependent calcium release from intracellular stores of calcium. In other words, paclitaxel enhances their interaction to increase calcium signaling and calcium oscillations in cardiomyocytes, which might be the basis of paclitaxel-induced cardiac arrhythmia (25).

In the existing studies, no results have shown that paclitaxel was a significant factor influencing cardiotoxicity in univariate or multivariate analyses. Only one study (9) included paclitaxel as an initial factor. In our study, a total of 20 patients with combined chemotherapy using paclitaxel were recorded in electronic medical records, including 6 of 32 patients in the cardiotoxic group (18.8%). After univariate and multivariate analyses, paclitaxel (OR: 3.60, 95% CI: 1.01 to 12.84) was identified as an independent predictor of cardiotoxicity for the first time and was included in the final prediction model formula.

Many other studies have investigated the effect

Table 3 Risk scores for all predictors

Risk factors	Score
Hypertension	
No	0
Yes	2
Cancer metastasis	
No	0
Yes	3
Use paclitaxel in combination	
No	0
Yes	3
Age, years	
<65	0
≥65	4

of many other drugs [rituximab (15), carboplatin (6), dexrazoxane (15), and trastuzumab (9-11) on cardiotoxicity. These drugs were also set as the initial factor in our study, but because the sample size of our patients applying these drugs was limited, it was not clear whether there was a statistical difference in the results. Therefore, the association between these drugs and cardiotoxicity was absent in our cohort.

Hypertension, diabetes, dyslipidemia, and cardiotoxicity risk

Cardiotoxicity is associated with cardiovascular risk factors (8,9), therefore, hypertension, diabetes, and dyslipidemia are often included as initial factors in various studies. In previous studies of doxorubicin-induced cardiotoxicity, hypertension has never been shown to be associated with cardiotoxicity in a multivariate analysis. In the studies that included hypertension as a covariate, univariate analysis of two studies (7,18) showed that hypertension was a significant factor, but their multivariate analysis was not performed. Two other studies (12,16) performed a multivariate analysis that included hypertension, but no significant association was found between hypertension and cardiotoxicity. Therefore, our study was the first to identify hypertension as a significant factor in the multivariate analysis and include it in the final model. Our study defined hypertension as follows: (I) patients who had a history of hypertension, (II) patients who were currently taking antihypertensive medications, or (III) when patients' blood pressure was measured 3 times on different days during the study period, the systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

Our results showed that diabetes was a significant factor in univariate analysis (P=0.060), but was not significantly associated with cardiotoxicity in multivariate analysis (P=0.468). This result is consistent with a study published in 2020 (6) that conducted only a univariate analysis. As for other studies (7-11), diabetes was not a significant factor in either univariate or multivariate analysis.

In a multicenter prospective study (9) of 26 French cancer centers, dyslipidemia was shown to have a significant effect on cardiotoxicity in a univariate analysis. In our univariate analysis, dyslipidemia showed no significant association with cardiotoxicity (P=0.431), which was consistent with other reports (10,16,18). This is possibly due to the low prevalence of dyslipidemia comorbidity recorded in the electronic medical records we extracted.

Cancer metastasis and cardiotoxicity

Only one study (10) has shown that metastasis [adjusted hazard ratio (aHR) =2.66; 95% CI: 1.36 to 5.20; P<0.01) was associated with cardiotoxicity within 2 years of doxorubicin administration. Our results showed that cancer metastasis increased cardiotoxicity 2.87-fold. However, in our study, cardiotoxicity was recorded during or within a few weeks after the treatment cycle included in the study, which was classified as acute cardiotoxicity, so that was not comparable to chronic cardiotoxicity at a 2-year follow-up in the previous study.

Influence of cumulative doxorubicin liposomes dose on cardiotoxicity risk

The cumulative dose of doxorubicin was considered as the major cause of doxorubicin-induced cardiotoxicity (18). A guideline (26) pointed out that the risk for doxorubicin-related cancer therapeutics-related cardiac dysfunction (CTRCD) is a continuum that spans from 0.2% to 100%, for cumulative doses of 150 to 850 mg/m^2, respectively. The recommended lifetime cumulative maximum dose of doxorubicin is up to 450 mg/sqm (18), and the induced cardiotoxicity should be monitored from the cumulative dose of 240 mg/m^2.

Many studies (6,16,22) have reported that cumulative

dose of doxorubicin significantly affects the occurrence of cardiotoxicity. However, in our study it was not a predictor of induced cardiotoxicity. The AUC value of accumulated dose was 0.414, so it was meaningless to use the ROC curve to find the cut-off point. Considering the accumulated dose range was from 20 to 480 mg, an approximate median dose of 200 mg was selected as the cut-off point. As for why it has not become a predictor affecting cardiotoxicity, one reason may be that the patients included in our study were treated with liposome-encapsulated doxorubicin. The liposomal doxorubicin may prolong the plasma half-life and may enhance tumor localization of the drug while reducing the cardiotoxicity in patients (5). Another reason may be that as a well-known risk factor for induced cardiotoxicity, the cumulative dose has been considered in the stage of clinical administration. Among the patients enrolled in our study, the highest cumulative dose of liposomal doxorubicin was 480 mg, so low-dose administration limited cardiotoxicity to some extent.

Radiotherapy, BMI, and cardiotoxicity risk

As a retrospective study, the time, dose, and location of radiotherapy received by patients were not clearly recorded in some electronic medical records, so radiotherapy could not be included as a variable in our study.

We divided BMI into two groups (<24 and ≥24 kg/m^2) according to whether patients were overweight or not. Although a frequently mentioned risk factor in other reports (9,17), BMI was not screened out to be the factor in our study. This may be due to the small sample size of this study, resulting in no significant statistical difference in BMI between the cardiotoxic and non-toxic groups.

Limitations

Our study had several limitations. Firstly, this study was conducted retrospectively, and some initial factors (baseline cardiac risk factors, drug combination, smoking status, radiotherapy status, etc.) that were intended to be included in the design stage of the study could not be included due to incomplete information records in electronic medical records. In addition, the outcomes in our study were all cardiac toxicity that occurred during the chemotherapy cycle included in the study (acute cardiotoxicity). Therefore, prospective studies with large sample sizes and long-term follow-up should be conducted to screen for more comprehensive risk factors and to assess the occurrence of late chronic cardiotoxic events in breast cancer patients treated with doxorubicin liposomes. This information is essential to further refine clinical prediction models of cardiotoxicity and to provide breast cancer patients with personalized information on the risks and benefits of cancer treatment. Finally, all patients included in the study were in China, so there was a lack of data from international patients for verification. Thus, additional studies of external validation are needed prior to implementation of this cardiotoxicity prediction model in routine clinical practice.

Conclusions

This study established a multivariable risk prediction model of liposomal doxorubicin-induced cardiotoxicity in breast cancer patients, which includes four predictors: age, hypertension, metastasis, and combination use of paclitaxel. The risk scores were divided into four levels to evaluate the risk of cardiotoxicity, providing a relatively practical tool for clinicians to identify patients at risk of cardiotoxicity.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1935/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1935/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1935/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Beijing Friendship Hospital (No. 2021-

P2-123-01) and the Ethics Committee of Beijing Cancer Hospital (No. 2017YJZ1208). Individual consent for this retrospective analysis was waived.

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