# Correlation of UGT2B7 Polymorphism with Cardiotoxicity in Breast Cancer Patients Undergoing Epirubicin/Cyclophosphamide-Docetaxel Adjuvant Chemotherapy

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**Purpose:** The present study aimed to investigate correlations between uridine glucuronosyltransferase 2B7 (UGT2B7) -161 single nucleotide polymorphism C to T (C>T) and the occurrence of cardiotoxicity in Chinese breast cancer (BC) patients undergoing epirubicin/cyclophosphamide-docetaxel (EC-D) adjuvant chemotherapy.

**Materials and Methods:** 427 BC patients who had underwent surgery were consecutively enrolled in this prospective cohort study. All patients were scheduled to receive EC-D adjuvant chemotherapy regimen, and they were divided into UGT2B7 -161 CC (n=141), UGT2B7 -161 CT (n=196), and UGT2B7 -161 TT (n=90) groups according to their genotypes. Polymerase chain reaction was performed for determination of UGT2B7 -161 genotypes. Cardiotoxicity was defined as an absolute decline in left ventricular ejection fraction (LVEF) of at least 10% points from baseline to a value less than 53%, heart failure, acute coronary artery syndrome, or fatal arrhythmia.

**Results:** LVEF values were lower at cycle (C) 4, C8, 3 months after chemotherapy (M3), M6, M9, and M12 compared to C0 (all $p<0.001$), in BC patients undergoing EC-D adjuvant chemotherapy. Cardiotoxicity was recorded for 4.2% of the overall population and was lowest in the UGT2B7 -161 TT group (1.1%), compared to UGT2B7 -161 CT (3.1%) and UGT2B7 -161 CC (7.8%) group ($p=0.026$). Multivariate logistic regression revealed that UGT2B7 -161 T allele could independently predict a low occurrence of cardiotoxicity in BC patients undergoing EC-D adjuvant chemotherapy ($p=0.004$).

**Conclusion:** A UGT2B7 -161 T allele serves as a potential biomarker for predicting a low occurrence of cardiotoxicity in BC patients undergoing EC-D adjuvant chemotherapy.

**Key Words:** UGT2B7, polymorphism, chemotherapy, cardiotoxicity, breast cancer

## INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer in females, accounting for 25% of all cancer cases and 15% of all cancer deaths in women worldwide. Its incidence and mortality in Asia have been increasing in recent decades.[1] Currently, adjuvant chemotherapy for BC is considered to reduce tumor recurrence and to prolong patient survival, with the development of new drugs and various chemotherapy regimens.[2] Adjuvant chemotherapy using epirubicin and cyclophosphamide, followed by docetaxel (adjuvant EC-D), is the most recommended adjuvant chemotherapy regimen for eradicating residual

tumors and eliminating post-surgical hematogenous metastasis; however it has been frequently reported to be associated with an increased risk of cardiotoxicity in BC patients.[3-6] Therefore, it is necessary to explore novel biomarkers that predict the occurrence of cardiotoxicity in BC patients undergoing EC-D adjuvant chemotherapy to reduce cardiovascular morbidity and to improve quality of life.

Uridine glucuronosyltransferase 2B7 (UGT2B7), a polymorphic protein-coding gene, mediates glucuronidation to eliminate metabolites of antineoplastic drugs.[7] Accumulating evidence has demonstrated that UGT2B7 gene polymorphisms regulate drugs metabolism and toxicity, thereby affecting treatment outcomes. UGT2B7 -161 (rs7668258; Genebank Ref mRNA NM_001074) single nucleotide polymorphism (SNP) C to T (C>T) has been shown to be correlated with epirubicin metabolism, toxicity, and efficacy when treating early-stage BC patients.[8] However, studies of UGT2B7 -161 C>T in relation to cardiotoxicity in BC patients are lacking, particularly in Chinese patients undergoing EC-D adjuvant chemotherapy. Therefore, this prospective cohort study aimed to explore the associations of UGT2B7 polymorphism with the occurrence of cardiotoxicity in Chinese BC patients undergoing EC-D adjuvant chemotherapy.

## MATERIALS AND METHODS

### Participants
Between January 2013 and December 2015, 427 BC patients who had undergone surgery at The Central Hospital of Wuhan were consecutively recruited in this prospective cohort study. The inclusion criteria consisted of 1) diagnosis with primary BC with confirmed TNM stage I–III according to clinical, imaging and pathological findings; 2) age above 18 years; 3) Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.0; 4) having undergone surgical treatment for BC; 5) normal left ventricular ejection fraction (LVEF) examined by echocardiogram, defined as LVEF ≥55%; 6) absence of chemotherapy contraindications; 7) scheduled to receive EC-D adjuvant chemotherapy; and 8) able to be followed up regularly. The exclusion criteria were as follows: 1) histologically confirmed metastatic disease (Stage IV) or bilateral BC; 2) received neoadjuvant therapy before surgery; 3) any previous systemic therapy (including chemotherapy, immunotherapy, human epidermal growth factor receptor-2 (HER2) targeted agents, and antitumor vaccines) or radiation therapy for other disease; 4) inadequate bone marrow function (absolute neutrophil count less than $1.2×10^9$/L, platelet count less than $100×10^9$/L or haemoglobin below 10 g/dL) and severe renal or liver dysfunction; 5) history or evidence of cardiovascular conditions, such as congestive heart failure, cardiomyopathy, arrhythmia, myocardial infarction, etc.; 6) severe or uncontrolled systemic disease; 7) poorly controlled diabetes or evidence of clinically

significant diabetic vascular complications; 8) history of severe infection, other solid tumors, or hematologic malignancy; and 9) pregnant or breast-feeding women.

### Ethics
This study protocol was approved by the Ethics Committees of The Central Hospital of Wuhan (approval number ChiCTR-COC-17008261) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

### Date collection
Baseline characteristics were collected from all patients after enrollment, which included age, body mass index (BMI), smoking status, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, chromic kidney disease, ECOG performance, TNM stage and levels of cardiac troponin I (cTnI) (reference range: 0–0.1 ng/mL) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (reference range: 0–0.1 ng/mL). Both cTnI and NT-proBNP were measured by a QMT8000 immunoassay analyzer (Wuhan Easy Diagnosis Biomedicine Co., Ltd, Wuhan, China) using rapid test kits.

### Determination of UGT2B7 -161 genotype
QIAamp DNA Mini Kits (Qiagen, Hilden, Germany) were used to extract genomic DNA from the leukocyte portion of whole blood collected from all patients prior to adjuvant chemotherapy. Then, polymerase chain reaction (PCR) was performed for the amplification of UGT2B7 -161 (rs7668258; Genebank Ref mRNA NM_001074). The PCR reactions were carried out on a Gene Amp PCR System 9700 (Applied Biosystems, Foster City, CA, USA) with an initial denaturation step at 95°C for 5 min, followed by 50 cycles of 95°C for 15 sec, 60°C for 30 sec, 72°C for 30 sec, a final extension step at 72°C for 5 min, and incubation at 4°C. After that, UGT2B7 -161 was genotyped by pyrosequencing on the PSQ™96MA System (Qiagen) according to the manufacturer's instructions.

### Treatment
After surgery, patients underwent laboratory testing and physical examination to confirm indications for chemotherapy before initiating adjuvant chemotherapy. Then, according to disease condition and patient willingness, patients received an EC-D adjuvant chemotherapy regimen, which was administrated as follows: epirubicin (E) at a dose of 100 mg/m² via intravenous (IV) infusion on day 1 and cyclophosphamide (C) at a dose of 600 mg/m² via IV infusion on day 1. Both E and C were repeated every 21 days for four cycles, followed by docetaxel (D) 75–100 mg/m² via IV infusion on day 1 every 21 days for four cycles. Patients who were HER2 positive were administrated trastuzumab at a dose of 4 mg/kg in the first week concurrently with docetaxel, followed by a dose of 2 mg/kg weekly for the next 11 weeks and a dose of 6 mg/kg every 21 days thereafter

until completing 1 year of trastuzumab therapy.

## Evaluation of cardiotoxicity

Cardiotoxicity was defined as an absolute decline in LVEF of at least 10 percentage points from baseline to a value less than 53% on an echocardiogram,[9] heart failure, acute coronary artery syndrome, or fatal arrhythmia.[10] LVEF was evaluated before adjuvant chemotherapy (Cycle 0, C0), at the completion of four cycles of EC chemotherapy (C4), at the end of four cycles of docetaxel treatment (C8), and at 3, 6, 9, and 12 months (M3, M6, M9, and M12) after adjuvant chemotherapy, according to the American Society of Echocardiography recommendations.[11]

## Statistics analysis

Statistical analysis was carried out with the use of SPSS 22.0 software (IBM Corp., Armonk, NY, USA) and GraphPad Prism 6.01 software (GraphPad Software Inc., La Jolla, CA, USA). Count data are expressed as percentages or rates and were compared using the chi-square test among groups. Measurement data are presented as a mean±standard deviation or median (interquartile range). For normal distributed data, comparison among three groups was determined by one-way ANOVA. As for the skewed distributed continuous data, comparison among three groups was determined by Kruskal-Wallis H rank sum test, and comparison at paired time point was performed using Wilcoxon signed-rank sum test. To evaluate the effect of UGT2B7 -161 T allele on cardiotoxicity, an addictive model was employed in the logistic regression model analysis of factors affecting cardiotoxicity occurrence. $p$ values <0.05 were considered statistically significant.

# RESULTS

## Study flow

In this study, 640 BC patients who underwent surgery were initially invited to participate; 46 were excluded (31 patients missed the invitation date and 15 patients refused to attend the pre-screening procedure). Then, 594 BC patients were screened for eligibility, and of these, 167 patients were excluded (144 patients did not meet the inclusion criteria and 23 patients were not willing to provide informed consent). Eventually, 427 BC patients were included in the analysis with their UGT2B7 -161 genotypes determined before adjuvant chemotherapy, and the patients were assigned to CC (n=141), CT (n= 196), and TT (n=90) groups according to their UGT2B7 -161 genotypes (Fig. 1).

## Correlation of UGT2B7 -161 C>T genotypes with clinical characteristics

The mean age of the 427 BC patients was 45.3±6.0 years, and the median values of LVEF, cTnI, and NT-proBNP were 67.0% (64.0–71.0), 0.022 (0.010–0.056) ng/mL, and 0.076 (0.059–0.102) ng/mL, respectively. There were 141 (33.0%), 196 (45.9%), and
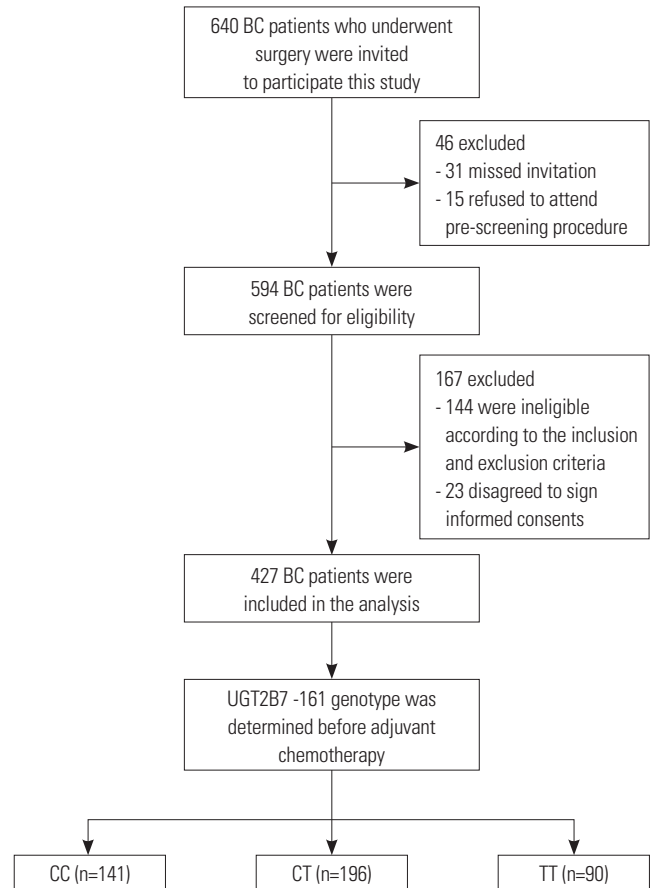


**Fig. 1.** Study flow. BC, breast cancer; UGT2B7, uridine glucuronosyltransferase 2B7.

90 (21.1%) patients who presented with UGT2B7 -161 CC, CT, and TT genotypes, respectively. No differences were observed in age, BMI, overweight, smoke, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, chromic kidney disease, molecular subtype, ECOG performance, TNM stage, cardiac function, cumulative dose of epirubicin, or administration of trastuzumab among BC patients with UGT2B7 -161 CC, CT, and TT genotypes (all $p$>0.05) (Table 1).

## LVEF during and after adjuvant chemotherapy in BC patients

Median values of LVEF in BC patients at C0, C4, C8 (M0), M3, M6, M9, and M12 were 67.0% (64.0–71.0), 64.0% (60.0–69.0), 63.0% (58.0–67.0), 63.0% (58.0–68.0), 65.0% (60.0–69.0), 64.0% (60.0–70.0), and 64.0% (59.0–71.0), respectively (Fig. 2). Compared to C0, median values of LVEF were lower at C4, C8 (M0), M3, M6, M9, and M12 in BC patients undergoing EC-D adjuvant chemotherapy (all $p$<0.001).

## Cardiotoxicity after adjuvant chemotherapy in BC patients

The percentages of cases presenting with heart failure, acute coronary syndrome, life-threatening arrhythmias, and decrease

**Table 1.** Correlation of UGT2B7 -161 Genotype with Clinical Characteristics of Patients

| Clinical characteristics | UGT2B7 rs7668258 genotype | | | | |
|---|---|---|---|---|---|
| | Total patients (n=427) | CC (n=141) | CT (n=196) | TT (n=90) | *p* value |
| Age (yr) | 45.3±6.0 | 45.6±6.4 | 45.0±6.1 | 45.4±5.2 | 0.669 |
| BMI (kg/m²) | 23.3±2.1 | 23.3±2.1 | 23.4±2.0 | 23.0±2.1 | 0.370 |
| Overweight (BMI >25 kg/m²) | 82 (19.2) | 23 (16.3) | 46 (23.5) | 13 (14.4) | 0.112 |
| Smoke | 104 (24.4) | 35 (24.8) | 43 (21.9) | 26 (28.9) | 0.440 |
| Hypertension | 91 (21.3) | 32 (22.7) | 38 (19.4) | 21 (23.3) | 0.666 |
| Diabetes mellitus | 19 (4.4) | 6 (4.3) | 10 (5.1) | 3 (3.3) | 0.790 |
| Dyslipidemia | 80 (18.7) | 23 (16.3) | 41 (20.9) | 16 (17.8) | 0.546 |
| Hyperuricemia | 83 (19.4) | 27 (19.1) | 42 (21.4) | 14 (15.6) | 0.504 |
| Chromic kidney disease | 15 (3.5) | 3 (2.1) | 7 (3.6) | 5 (5.6) | 0.385 |
| Molecular subtype | | | | | 0.374 |
| Luminal A | 30 (7.0) | 9 (6.4) | 14 (7.1) | 7 (7.8) | |
| Luminal B | 82 (19.2) | 35 (24.8) | 31 (15.8) | 16 (17.8) | |
| ERBB2⁺ | 113 (26.5) | 32 (22.7) | 60 (30.7) | 21 (23.3) | |
| Basal-like | 202 (47.3) | 65 (46.1) | 91 (46.4) | 46 (51.1) | |
| ECOG performance | | | | | 0.346 |
| 0 | 338 (79.1) | 106 (75.2) | 158 (80.6) | 74 (82.2) | |
| 1 | 84 (19.7) | 34 (24.1) | 34 (17.4) | 16 (17.8) | |
| 2 | 5 (1.2) | 1 (0.7) | 4 (2.0) | 0 (0.0) | |
| TNM stage | | | | | 0.786 |
| I | 49 (11.5) | 16 (11.3) | 20 (10.2) | 13 (14.4) | |
| II | 268 (62.8) | 91 (64.5) | 125 (63.8) | 52 (57.8) | |
| III | 110 (25.8) | 34 (24.1) | 51 (26.0) | 25 (27.8) | |
| Cardiac function | | | | | |
| LVEF (%) | 67.0 (64.0–71.0) | 67.0 (63.5–70.0) | 67.0 (64.0–71.0) | 67.5 (64.0–70.3) | 0.747 |
| cTnI (ng/mL) | 0.022 (0.010–0.056) | 0.022 (0.010–0.058) | 0.023 (0.011–0.059) | 0.017 (0.008–0.045) | 0.137 |
| NT-proBNP (ng/mL) | 0.076 (0.059–0.102) | 0.079 (0.059–0.119) | 0.073 (0.057–0.095) | 0.077 (0.061–0.101) | 0.076 |
| Cumulative dose of epirubicin (mg/m²) | 302.0 (281.0–321.0) | 301.0 (282.5–320.0) | 301.0 (276.0–322.5) | 304.0 (286.0–323.2) | 0.425 |
| Administration of trastuzumab | 102 (23.9) | 32 (22.7) | 44 (22.4) | 26 (28.9) | 0.456 |

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; UGT2B7, uridine glucuronosyltransferase 2B7.
Data are presented as a mean±standard deviation, median (interquartile range), or count (%). Comparison was determined by one-way ANOVA, Kruskal-Wallis H rank sum test, or chi-square test. *p* value <0.05 was considered significant.

in LVEF ≥10% to absolute <53% were 0.5, 0.0, 0.2, and 4.0%, respectively (two patients presented with both heart failure and LVEF decreased ≥10% to absolute <53%). The total occurrence of cardiotoxicity was 4.2% (Fig. 3A). The occurrence rate of cardiotoxicity was reduced as more patients carried UGT2B7 -161 (*p*=0.026) (Fig. 3B).

### Factors affecting cardiotoxicity occurrence by univariate logistic regression model analysis in the addictive model
Univariate logistic regression revealed that UGT2B7 -161 T allele was correlated with a low occurrence of cardiotoxicity (*p*=0.013), whereas high cTnI concentration (>0.022 ng/mL) (*p*=0.003), high NT-proBNP concentration (>0.076 ng/mL) (*p*=0.023), and adminstration of trastuzumab (*p*=0.044) were correlated with increased occurrence of cardiotoxicity in BC patients undergoing EC-D chemotherapy after surgery (Table 2).

### Factors affecting cardiotoxicity occurrence by multivariate logistic regression model analysis in the addictive model
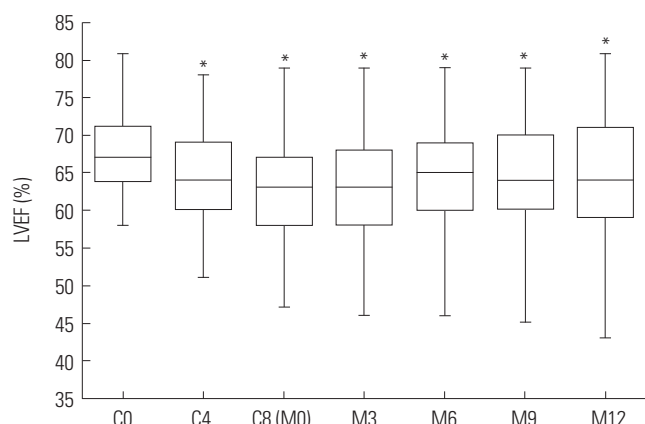Multivariate logistic regression indicated that a UGT2B7 -161 T allele could independently predict a low occurrence of cardiotoxicity in BC patients undergoing EC-D chemotherapy (*p*=0.004). However, high cTnI concentration (>0.022 ng/mL) (*p*=0.002), high NT-proBNP concentration (>0.076 ng/mL) (*p*=0.035), high cumulative dose of epirubicin (>302 mg/m²) (*p*=0.048), and administration of trastuzumab (*p*=0.032) were independent risk factors for cardiotoxicity in BC patients undergoing EC-D chemotherapy (Table 3).
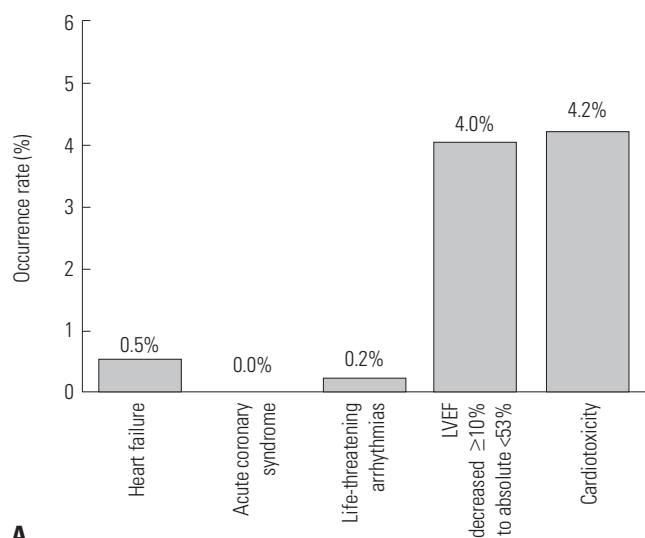
## DISCUSSION

In this prospective study, we observed that 1) LVEF is reduced

in BC patients during and after EC-D adjuvant chemotherapy and that the occurrence rate of cardiotoxicity is 4.2%. 2) A UGT2B7 -161 T allele independently predicts a low occurrence of cardiotoxicity in Chinese BC patients undergoing EC-D adjuvant chemotherapy.

Cardiotoxicity is one of the most common adverse effects in BC patients receiving anthracycline-based adjuvant therapies, which has been widely investigated in various studies. For example, a retrospective cohort study demonstrated that risk of heart failure is increased in BC patients receiving anthracycline-based adjuvant chemotherapy, compared to non-che-



**Fig. 2.** LVEF during and after adjuvant chemotherapy in BC patients. LVEF values were lower at C4, C8 (M0), M3, M6, M9, and M12, compared to C0 in BC patients undergoing EC-D adjuvant chemotherapy. Comparison between paired time points was performed using Wilcoxon signed-rank sum test. *$p<0.001$ compared with C0. LVEF, left ventricular ejection fraction; C4/C8, 4th/8th cycle of adjuvant chemotherapy; M3/M6/M9/M12, 3/6/9/12 months after adjuvant chemotherapy; BC, breast cancer.
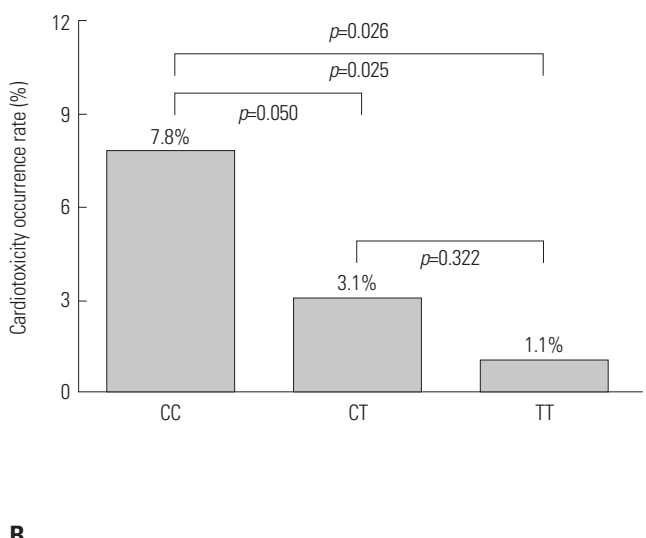
motherapy group.[12] Also, a low dose of epirubicin in adjuvant chemotherapy was found to result in less decline in LVEF and to lower the risk of cardiac damage in BC patients.[13] Another study revealed that the risk of cardiotoxicity is higher in HER2-possitive BC patients undergoing doxorubicin and cyclophosphamide, followed by docetaxel plus trastuzumab, compared with that in patients receiving non-anthracycline-combined trastuzumab adjuvant therapy.[14] Accordingly, this evidence suggests that anthracyclines-based adjuvant chemotherapy may cause an increased risk of cardiotoxicity in BC patients. In line with these previous studies, our study observed that LVEF was decreased during and after adjuvant chemotherapy, and the occurrence of cardiotoxicity was 4.2% in 427 BC patients receiving EC-D adjuvant chemotherapy. This might be because drugs or metabolites of anthracyclines, such as epirubicin, in an EC-D regimen are toxic to cardiac cells, which lead to impairment of cardiac cell function, thereby decreasing LVEF and increasing the risk of cardiotoxicity in BC patients receiving EC-D adjuvant chemotherapy. Epirubicin is a derivative of doxorubicin, which is the most commonly reported anthracycline leading to cardiotoxicity, and studies comparing epirubicin and doxorubicin-induced cardiotoxicity in BC patients have revealed a difference when doses are high.[15,16] Nevertheless, our data on the cardiotoxicity of epirubicin cannot be extrapolated to doxorubicin, although these two drugs have similar mechanisms in the treatment of BC.

UGT2B7 is a hepatic enzyme that plays an important role in mediating glucuronidation to eliminate antineoplastic drugs, as well as their active metabolites, and its polymorphism has been reported to alter glucuronidation ability and to affect metabolism and toxicity of drugs used for BC adjuvant therapy.[17]



**Fig. 3.** Occurrence of cardiotoxicity after adjuvant chemotherapy in BC patients. (A) The total occurrence of cardiotoxicity was 4.2% in 427 BC patients, and the percentage of cases presenting with heart failure, acute coronary syndrome, life-threatening arrhythmias, and LVEF decreased ≥10% to absolute <53% were 0.5, 0.0, 0.2, and 4.0%, respectively (Two patients presented with both heart failure and LVEF decreased ≥10% to absolute <53%). (B) The occurrence rate of cardiotoxicity in patients with UGT2B7 -161 TT genotype was 1.1%, which was lower than that in patients with UGT2B7 -161 CT (3.1%) and UGT2B7 -161 CC (7.8%) genotypes. Comparison among three groups was conducted using chi-square test, and $p<0.05$ was considered significant. BC, breast cancer; LVEF, left ventricular ejection fraction; UGT2B7, uridine glucuronosyltransferase 2B7.

An interesting study on Thai BC patients with impaired CYP3D6 discovered that UGT2B7 802 C>T polymorphism reduces the metabolism of tamoxifen as adjuvant hormonal therapy, as well as the active metabolite endoxifen, by decreasing glucuronidation.[18] As to the association of UGT2B7 polymorphism with epirubicin metabolism, a recent study disclosed that UGT2B7 802 C>T leads to lowered UGT glucuronidation capacity and delays the elimination of adjuvant epirubicin, as

**Table 2.** Factors Affecting Cardiotoxicity Occurrence in Univariate Logistic Regression Model Analysis (Addictive Model)

| Parameters | Univariate logistic regression | | | |
|---|---|---|---|---|
| | p value | OR | 95% CI | |
| | | | Lower | Higher |
| UGT2B7 -161 T allele (addictive model: CC-0, CT-1, TT-2) | 0.013 | 0.369 | 0.168 | 0.808 |
| Age (>45 yr) | 0.541 | 1.345 | 0.520 | 3.477 |
| Overweight (BMI >25 kg/m$^2$) | 0.350 | 1.658 | 0.574 | 4.790 |
| Smoke | 0.368 | 1.587 | 0.580 | 4.339 |
| Hypertension | 0.923 | 1.057 | 0.340 | 3.294 |
| Diabetes mellitus | 0.817 | 1.278 | 0.161 | 10.140 |
| Dyslipidemia | 0.320 | 1.713 | 0.593 | 4.951 |
| Hyperuricemia | 0.365 | 1.632 | 0.565 | 4.713 |
| Chromic kidney disease | 0.634 | 1.660 | 0.206 | 13.365 |
| Higher ECOG performance | 0.984 | 1.011 | 0.349 | 2.932 |
| Higher TNM stage | 0.325 | 1.498 | 0.669 | 3.355 |
| LVEF high (>67.0%) | 0.203 | 0.523 | 0.192 | 1.419 |
| cTnI high (>0.022 ng/mL) | 0.003 | 9.221 | 2.093 | 40.620 |
| NT-proBNP high (>0.076 ng/mL) | 0.023 | 3.693 | 1.196 | 11.411 |
| Cumulative dose of epirubicin high (>302 mg/m$^2$) | 0.110 | 2.260 | 0.832 | 6.139 |
| Administration of trastuzumab | 0.044 | 2.681 | 1.029 | 6.986 |

UGT2B7, uridine glucuronosyltransferase 2B7; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio; CI, confidence interval.
Data are presented as a p value or OR and 95% CI. UGT2B7 -161 genotype was analyzed using an addictive model, which was scored as CC-0, CT-1, and TT-2. All continuous variables were stratified by medians respectively. p value <0.05 was considered significant.

**Table 3.** Factors Affecting Cardiotoxicity Occurrence in Multivariate Logistic Regression Model Analysis (Addictive Model)

| Parameters | Multivariate logistic regression | | | |
|---|---|---|---|---|
| | p value | OR | 95% CI | |
| | | | Lower | Higher |
| UGT2B7 -161 T allele (addictive model: CC-0, CT-1, TT-2) | 0.004 | 0.259 | 0.103 | 0.651 |
| Age (>45 yr) | 0.675 | 1.267 | 0.419 | 3.826 |
| Overweight (BMI >25 kg/m$^2$) | 0.262 | 2.130 | 0.569 | 7.970 |
| Smoke | 0.085 | 3.468 | 0.843 | 14.266 |
| Hypertension | 0.199 | 0.375 | 0.084 | 1.675 |
| Diabetes mellitus | 0.662 | 1.755 | 0.141 | 21.781 |
| Dyslipidemia | 0.639 | 1.380 | 0.359 | 5.299 |
| Hyperuricemia | 0.550 | 1.533 | 0.377 | 6.233 |
| Chromic kidney disease | 0.142 | 9.087 | 0.479 | 172.445 |
| Higher ECOG performance | 0.703 | 0.774 | 0.207 | 2.890 |
| Higher TNM stage | 0.235 | 1.779 | 0.687 | 4.608 |
| LVEF high (>67.0%) | 0.764 | 1.217 | 0.338 | 4.385 |
| cTnI high (>0.022 ng/mL) | 0.002 | 16.124 | 2.691 | 96.614 |
| NT-proBNP high (>0.076 ng/mL) | 0.035 | 4.156 | 1.108 | 15.592 |
| Cumulative dose of epirubicin high (>302 mg/m$^2$) | 0.048 | 3.324 | 1.009 | 10.950 |
| Administration of trastuzumab | 0.032 | 3.612 | 1.113 | 11.715 |

UGT2B7: uridine glucuronosyltransferase 2B7, BMI: body mass index; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio; CI, confidence interval.
Data are presented as a p value or OR and 95% CI. UGT2B7 -161 genotype was analyzed using an addictive model, which was scored as CC-0, CT-1, or TT-2. All continuous variables were stratified by medians respectively. p value <0.05 was considered significant.

well as its active metabolites, in BC patients.[7] Also, UGT2B7 -161 C>T has been shown to be located on promoter region, and UGT2B7 -161 TT homozygote presents with higher UGT glucuronidation ability than UGT2B7 -161 CT heterozygote or UGT2B7 -161 CC homozygote. UGT2B7 -161 TT homozygote appears to increase the clearance of epirubicin and decrease the risk of myelosuppression, compared to UGT2B7 -161 CC homozygotes, in BC patients.[8,19] Therefore, these previous studies imply that UGT2B7 polymorphisms alter the glucuronidation ability of UGT enzyme to affect drug metabolism, including epirubicin. Few clinical studies, however, have investigated the correlation of UGT2B7 polymorphisms with drug adverse effects in BC patients undergoing EC-D chemotherapy. Considering that UGT2B7 -161 C>T was located on the promoter region of UGT2B7 and that UGT glucuronidation is the main inactivation pathway of epirubicin, we assumed that UGT2B7 -161 C>T may influence the occurrence of cardiotoxicity in BC patients receiving EC-D adjuvant chemotherapy. In this study, we discovered that UGT2B7 -161 TT homozygote carriers expereience lower rates of cardiotoxicity than CT heterozygote and CC homozygote carriers. Interestingly, UGT2B7 -161 T allele appeared to independently predict a low occurrence of cardiotoxicity in BC patients undergoing EC-D chemotherapy. The possible explanation may be that UGT2B7 -161 C>T is located on the promoter region and activates the transcription of UGT2B7 protein to increase UGT enzyme activity, as well as the glucuronidation of epirubicin in EC-D adjuvant chemotherapy, protecting cardiac cells from epirubicin and its toxic metabolites, thereby reducing the risk of cardiotoxicity in BC patients. However, the underlying mechanism of UGT emzymatic activation and glucuronidation by UGT2B7 -161 C>T needs further validation.

There were several limitations in our study. 1) All patients in this study were Chinese and from a single center: UGT2B7 -161 SNP is also seen in other Asian population, as well as European and Sub-Saharan African.[20] Therefore, our study was subject to selection bias. 2) The smple size in this study was relatively small, which reduced the statistical power. 3) The follow-up peroid for cardiotoxicity in BC patients after EC-D adjuvant chemotherapy was only 12 months, and the correlation of UGT2B7 -161 C>T with long-term cardiotoxicity was not investigated.

In conclusion, we found a UGT2B7 -161 T allele to serve as a potential biomarker for predicting low occurrence of cardiotoxicity in BC patients undergoing EC-D adjuvant chemotherapy.

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