Anthracycline therapy for breast cancer-induced arrhythmias: a meta-analysis of a single-arm trial

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Abstract

Introduction: As of 2020, breast cancer has become the leading cause of cancer incidence worldwide, and chemotherapy based on anthracycline is an important component of breast cancer treatment. Anthracycline-based drugs are known to cause cardiac toxicity and arrhythmia in breast cancer treatment. This is the first clinical quantitative analysis to accurately assess the incidences of arrhythmia and arrhythmia subtypes and abnormal electrocardiogram (ECG) changes, providing data to support clinical drug use and drug monitoring.

Methods: We systematically searched CNKI, VIP, Wanfang and other Chinese databases, PubMed, Embase, Web of Science, Cochrane Library and other English databases. The random effect model or fixed effect model was used to calculate the incidence of combined arrhythmias in breast cancer patients and the associated heterogeneity. STATA16 was used for statistical analysis.

Results: A total of 37 articles were included in this study, including 5705 breast cancer patients treated with anthracyclines, of whom 2257 developed arrhythmias. Meta-analysis showed that the incidence of anthracycline-associated arrhythmias in breast cancer patients was 0.41 (0.37, 0.44). Subgroup analysis showed that the incidence of QT-QTC interphase change was 0.08 (0.05, 0.11), that of P wave change was 0.10 (0.05, 0.15), that of ST-T segment change was 0.19 (0.15, 0.23), and that of QT-QTC interphase change was 0.08 (0.05, 0.11). The incidence of low voltage abnormalities was 0.05 (0.03, 0.08). In addition, according to the subgroup analysis of arrhythmia subtypes, the incidence of conduction block was 0.04 (0.02, 0.05), the incidence of heart rate changes was 0.12 (0.10, 0.15), the incidence of premature beats was 0.09 (0.07, 0.11), and the incidence of atrial fibrillation was 0.41 (0.00, 0.12).

Conclusion: The overall incidence of anthracycline-associated arrhythmias in breast cancer treatment was 0.41. ST-T segment was the most common ECG change. The results of this study are of great significance for guiding postoperative chemotherapy for and monitoring of breast cancer patients.

Trial registration: The study has been registered in the international prospective register of systematic reviews (PROSPERO). Registration No.: CRD42022321213.

Background

By 2020, breast cancer had surpassed lung cancer to become the main cause of cancer incidence worldwide and the fifth leading cause of cancer death worldwide(1). According to relevant literature reports, from the 1990s to the early 21st century, 1.15 million people were diagnosed with breast cancer every year on average, and 410,000 people died from breast cancer every year(2). The treatment of breast cancer is systemic comprehensive treatment mainly based on surgery. Relevant studies have shown that adjuvant chemotherapy can reduce the 10-year recurrence risk of breast cancer by 23.5% and the 10-year death risk by 15%, indicating that adjuvant chemotherapy can prolong the survival time of breast cancer patients and reduce recurrence(3). Therefore, except for in a few patients with a low risk of recurrence and intolerance to chemotherapy, most adenocarcinoma patients require adjuvant chemotherapy after surgery, and chemotherapy regimens containing anthracyclines play are important for breast cancer therapy (4). Anthracyclines are landmark drugs in the development of medical oncology. They mainly include daunorubicin (DNR) and adriamycin (ADM), doxorubicin, pirarubicin, mitoxantrone (MIT), and carubicin. Carubicin is widely used in the treatment of hematological malignancies and solid tumors, including acute leukemia, lymphoma, breast cancer, ovarian cancer, gastric cancer and soft tissue sarcoma(5). Although anthracyclines have powerful anticancer effects, their clinical toxicity limits their use. Studies have shown that anthracyclines can cause alopecia, bone marrow suppression, cardiotoxicity and other toxic side effects, among which cardiotoxicity is the most serious (6). Cardiotoxicity induced by anthracyclines can be divided into acute, chronic and delayed cardiotoxicity, which can manifest as arrhythmia, intracardiac conduction disorder, pericarditis, heart failure, cardiomyopathy, etc. A study by Ma Jun et al. showed that using anthracyclines to treat breast cancer patients can cause conduction block, palpitations, QT prolongation, ventricular arrhythmias, supraventricular arrhythmias and other types of electrocardiogram (ECG) changes and arrhythmias(6-8). Anthracycline-induced arrhythmias occur in a dose-dependent manner. Taking adriamycin as an example, studies have shown that when the cumulative dose of adriamycin reaches 300 mg/m², the incidence of arrhythmia is 0.34, while an incidence of arrhythmia of 0.53 was found for a cumulative doxorubicin dose of 450 mg/m²(9). Since the cardiotoxicity of anthracycline was first reported by Lefrak in 1973, the incidence and clinical characteristics of anthracycline cardiotoxicity in breast cancer patients have been reported in a number of studies, but the sample size of each independent study is relatively small, and there are large differences among the results of each study(10-13). Second, there are few reviews on the toxicity and side effects of anthracyclines in the treatment of breast cancer-induced arrhythmias, and quantitative analysis is lacking(14, 15). To increase the accuracy of the statistics and the credibility of the results, this quantitative analysis was performed to accurately assess the incidences of arrhythmia overall and specific subtypes of arrhythmia and electrocardiogram (ECG) changes to better define the side effects of anthracycline-based drugs and provide supporting data for clinical drug use and drug monitoring.

Materials And Methods

We conducted a meta-analysis based on the Meta-analyses of Observational Studies in Epidemiological (MOOSE) guidelines.

Literature retrieval strategy

Three Chinese databases, CNKI, VIP and Wanfang, and four English databases, PubMed, Embase, Web of Science and Cochrane Library, were comprehensively searched. The search terms used for the Chinese databases included (breast cancer, milk rock, breast cancer, breast tumor) and (doxorubicin, epirubicin, pirubicin, daunorubicin, arubcin, idalbicin, anthracycline) and (safety, adverse reactions, cardiotoxicity, arrhythmia, electrocardiogram, etc.); the search terms used for the English databases included (Breast Neoplasm, Breast Tumor, Breast Cancer, Mammary Cancer, Malignant Neoplasm of Breast, and Breast Malignant Neoplasm, Malignant Tumor of Breast, Breast Malignant Tumor, Cancer of the Breast, Human Mammary, Carcinoma, and Human Mammary Neoplasm, Breast Carcinoma) AND (Anthracyclines, Aclarubicin, Daunorubicin, Carubicin, Doxorubicin, Idarubicin, Nogalamycin, Plicamycin, Adriamycin AND
Inclusion and exclusion criteria

Included in the standard

Only clinical studies with a sample size of ≥20 and meeting the following criteria were included in the analysis without limiting the type of study.

(1) Studies that included patients who had breast cancer diagnosed by histopathology

(2) Studies that included patients who had received anthracyclines (including daunorubicin, doxorubicin/epirubicin/, mitoxantrone and carubicin) alone or anthracycline-based chemotherapy

(3) Studies that reported the incidence of reported arrhythmia events and indicators of ECG abnormalities.

(4) Studies including a control group and that studied cardioprotective drugs

Exclusion criteria

1. Reviews, case reports, conference papers, and animal or in vitro studies

2. The latest research results were taken for identical or duplicate studies.

3. Unavailable full-text

4. Studies lacking dose or duration data

5. Studies not specifying the number of arrhythmias

Literature collection bias control

Two individuals performed the literature retrieval. A retrieval strategy was used to arrange and screen studies and eliminate duplicate documents. For the rest of the studies, the title and abstract were read. If the study did not meet the inclusion criteria, the study went into preliminary screening. If the study still did not meet the inclusion criteria, the study's full-text was read again. Ultimately, the studies that met the inclusion criteria were included in the study. If there was disagreement during the process, a third reviewer searched relevant explanatory literature or explored the methods to decide whether the study should be included or collective discussion with experts and scholars in the field was employed.

Risk assessment of literature bias

The quality evaluation of each study was carried out by adopting the methodological evaluation indices of nonrandomized controlled experiments proposed by Slim et al. in 2007. There were 12 evaluation indices, and each index was scored with 0-2 points. For the first 8 studies without a control group, the maximum score was 16. The last four and first eight studies included a control group, and the highest score was 24 points. A score of 0 indicated no reporting, a score of 1 indicated reporting of insufficient information; 2 indicated reporting of sufficient information; < 12 indicated low-quality literature; and ≥12 indicated high-quality literature.

Data extraction

Two evaluators independently extracted and processed the data of the included literature and uploaded the data according to their own preferred forms. After completion, they cross-checked the data. In case of any inconsistency, a third evaluator was included, and the final results were determined through collective discussion. The data extracted included first author's name, year of publication, study type, number of patients, patient age, treatment regimen, treatment dose, administration mode, treatment duration, number of patients lost to follow-up, incidence of arrhythmia, and abnormal ECG changes.

Statistical analysis

STATA16 software was used for statistical analysis, and the incidence of arrhythmia was the main effect index. Given the number of patients and extreme differences in proportions in some studies, a 95% confidence interval (CI) was calculated using the Wilson score. Since the incidence data were not normally distributed, the incidence rates reported in all studies were calculated by logit transformation after combination. Cochrane's Q-test and I² statistical data were used to evaluate the heterogeneity between studies. With P>0.1 and I²<50%, a fixed-effect model was used. Otherwise, a random effects model was used. The factors assessed included study publication year (before 2014 vs. after 2014), study sample size (<100, 100-200, >200), anthracycline dose (< 200, 200-399, ≥400 mg/m²), medication cycle (< 4, 4, 6, > 6 cycles), arrhythmia type (conduction abnormality, heart rate change, premature beat, atrial fibrillation), and ECG change (QT-QTc interphase change, PR interphase change, P wave change, ST-T segment change, low voltage abnormality). Funnel plots and Egger's and Begg's tests were used to evaluate publication bias. A P value less than 0.05 was considered statistically significant.
Results

Literature retrieval results

According to the retrieval strategy, a total of 11,272 articles were retrieved, including 328 from PubMed, 324 from the Cochrane Library, 300 from Embase, 7855 from Web of Science, 1396 from CNKI, and 1019 from Wanfang, VIP obtained 50 articles: 2465 articles in Chinese and 8807 articles in English. Preliminary retrieval results: After 7008 review articles and 1143 articles that could not be accessed were screened out, the remaining articles were imported into the ENDNOTE literature management tool, and 1199 duplicate articles were automatically identified and removed. For the remaining 1,922 studies, the titles and abstracts were preliminarily screened, and 1,726 studies with obvious similarity and irrelevant abstract data were excluded. For the remaining 196 papers, the full-text was downloaded and read carefully according to the inclusion and exclusion standards for secondary screening, resulting in 146 studies being eliminated. For the remaining 50 articles, after strict quality evaluation, we ruled out low-quality studies and checked references from 13 studies, resulting in 37 studies derived from references, including 32 studies in Chinese and 5 studies in English. The document selection flow chart is shown in Figure 1.

Basic characteristics of the included studies

A total of 37 studies published between 2000 and 2022 were included, including 11 published before 2014 and 26 published after 2014. The total sample size was 5706, including 1 patient who was lost to follow-up, so the actual sample size was 5705. Of the 5705 patients, the youngest was 22 years, and the oldest was 77 years, with a median number of patients included was 70 (range 20-436). Since the 12 studies had divided the patients into multiple study groups based on different factors (drug, dose, duration, etc.), we ultimately reviewed 46 treatment groups. Of the 46 treatment groups, 13 were treated with an anthracycline alone, the most commonly used anthracycline being doxorubicin, and 33 were treated with combination chemotherapy, such as CAF, TA or TE, the most common being CAF. Eleven of the 46 studies assessed agents protecting against chemotherapy-associated arrhythmias, for which only control data (placebo rather than a cardioprotective agent) were used. Anthracycline was administered at doses of 75-800 mg/m². 22 treatment groups received intravenous infusion, 2 treatment groups received oral administration, and the remaining 21 treatment groups did not have specific reports of administration route. The basic characteristics of the included studies are shown in Table 1.
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<td>40</td>
<td>R-wave low voltage(9)T wave change(14)ST segment change(20)QT interval change(5) Sinus tachycardia/Sinus bradycardia(7) RBBB(5) PAC(7) PVC(5) AVB(3)</td>
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<td>R-wave low voltage(29)T wave change(9)ST segment elevation(36)ST segment depression(19)QT interval change(25) Atrioventricular block(9) RBBB(3) Sinus tachycardia(16) Sinus bradycardia(18) Premature beat(9)</td>
<td>AC-T 3</td>
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<tr>
<td>Wu QD</td>
<td>2016</td>
<td>Chinese</td>
<td>70</td>
<td>QRS low voltage(4)ST-T segment change(6) Sinus bradycardia(4) Sinus tachycardia(8) Atrial premature contraction(4) Ventricular premature contraction(3) Supraventricular tachycardia(1) Bundle branch block(3) Atrioventricular block(2)</td>
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<td>2016</td>
<td>Chinese</td>
<td>70</td>
<td>QRS low voltage(2)ST-T segment change(4) Sinus bradycardia(3) Sinus tachycardia(5) Atrial premature contraction(3) Ventricular premature contraction(2) Bundle branch block(3) Atrioventricular block(1)</td>
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<tr>
<td>Liu B</td>
<td>2018</td>
<td>English</td>
<td>409</td>
<td>ST-T segment change(45)QRS low voltage(14) Sinus tachycardia(37) Sinus arrhythmia(8) Sinus bradycardia(4) Ventricular premature contraction(3) Atrial premature contraction(2) RBBB(2) Atrial flutter and borderline premature beat(1)</td>
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<td>Hu G.</td>
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<td>English</td>
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<td>ST-T segment change(2)OT-QTc change(3)QRS low voltage(3) Atrial premature beat(6) Ventricular premature beat(4) Sinus tachycardia(4) Sinus bradycardia(4) Ventricular block(2)</td>
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<td>Hu G.</td>
<td>2022</td>
<td>English</td>
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<td>ST-T segment change(3)QT-QTc change(3)QRS low voltage(2) Atrial premature beat(7) Ventricular premature beat(5) Supraventricular tachycardia(2) Sinus tachycardia(7) Sinus bradycardia(4) Ventricular block(2)</td>
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<td>Huang ZQ</td>
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<td>English</td>
<td>250</td>
<td>Limb lead low voltage(12)T wave change(29)T wave change(12)ST segment depression(18)QT interval change(28) Sinus tachycardia(8)</td>
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<td>Ando M</td>
<td>2000</td>
<td>English</td>
<td>39</td>
<td>ST-T segment change(2) Atrial arrhythmia(3) Ventricular arrhythmia(2) Atrioventricular block(4)</td>
<td>ADR 6</td>
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</table>

Results of the meta-analysis

Incidence of anthracycline-associated arrhythmias
A total of 2,257 anthracycline-associated arrhythmia events were reported in the 37 studies (n=5705), with a wide incidence range from 20% to 71%. Due to significant heterogeneity between studies ($I^2=84.6\%, P <0.001$), a random effects model was used for analysis, and Figure 2 shows a forest map of the incidences of anthracycline-induced arrhythmias in breast cancer. A pooled analysis of the 37 studies showed that the incidence of cardiotoxicity in breast cancer patients receiving anthracycline chemotherapy was approximately 0.41 (0.37, 0.44).

**Subgroup analysis**

Subgroup analysis was performed according to publication year, sample size, and dose and duration of administration.

To explore the source of heterogeneity, subgroup analysis was performed based on year of publication, sample size, and dose and duration of anthracycline administration. As shown in Table 2, treatment cycle may be one of the sources of heterogeneity in this study.

The results (shown by year of publication in Table 2) showed that the incidence of anthracycline-associated arrhythmias was 0.39 (0.32, 0.46) in 11 treatment groups of 11 studies published before 2014 and 0.41 (0.37, 0.46) in 35 treatment groups of 26 studies published in 2014 and after. The heterogeneity between groups was $p=0.604$.

For the analysis based on sample size (Table 2), we defined subgroups: sample size < 100 was considered a small sample size, sample size = 100-200 was considered a medium sample size, and sample size > 200 was considered a large sample size. Subgroup analysis showed that the incidence of anthracycline-associated arrhythmias was 0.44 (0.39, 0.49) in 27 treatment groups of 20 studies with small sample sizes. The incidence of anthracycline-associated arrhythmias was 0.37 (0.31, 0.42) in six treatment groups of five studies with moderate sample sizes. The incidence of anthracycline-associated arrhythmias was 0.39 (0.32, 0.45) in 12 treatment groups in 12 studies with large sample sizes. The intergroup heterogeneity was $p=0.158$.

A subgroup analysis according to dose of anthracycline was also performed (Table 2). To explore the effect of different doses of anthracyclines on the incidence of arrhythmia, we divided the study into Group A (cumulative dose < 200 mg/m$^2$), Group B (cumulative dose 200-399 mg/m$^2$), and Group C (cumulative dose $\geq$400 mg/m$^2$) according to the cumulative dose of anthracycline. The treatment dose was clearly not reported for 12 treatment groups in 11 studies, including the studies of He, F and others, so these studies were not included in the subgroup analysis. The results of the subgroup analysis of the remaining studies showed that the number of studies in Group A was less than or equal to 3, which was too low for STATA and MetaProp to be used for the subgroup analysis (the number of study groups needs to be $>3$). Therefore, subgroup analysis could not be performed. There were 16 studies in Group B and 19 in the treatment group, and the combined analysis showed that the cumulative dose of anthracycline ranged from 200 mg/m$^2$ to 399 mg/m$^2$. The incidence of arrhythmia was 0.41 (0.35, 0.47). There were 10 studies in Group C and 12 in the treatment group. The combined analysis results showed that the cumulative dose of anthracycline was $\geq$400 mg/m$^2$. The incidence of arrhythmia was 0.46 (0.39, 0.54). The intergroup heterogeneity was $p=0.304$.

A subgroup analysis based on anthracycline cycle was also performed (Table 2), and studies in which patients received less than four cycles of chemotherapy were included in Group A. Studies in which patients received four cycles of chemotherapy were included in Group B. Studies in which patients received six cycles of chemotherapy were included in Group C, and studies in which patients received more than six cycles of chemotherapy were included in Group D. The study of Feng YY and 8 other studies (including 9 treatment groups) were not included in the subgroup analysis due to their unclear report of anthracycline cycle. Subgroup analysis of the remaining studies showed that group A included 3 studies and 5 treatment groups. Combined analysis showed that the incidence of arrhythmias was 0.34 (0.27, 0.41) with no more than 3 cycles of anthracycline therapy. A total of 8 studies and 8 treatment groups were included in Group B, and the combined analysis showed that the incidence of arrhythmia was 0.50 (0.41, 0.58). A total of 14 studies and 18 treatment groups were included in Group C, and the combined analysis results showed that the incidence of arrhythmia was 0.43 (0.38, 0.49). There were 6 studies and 6 treatment groups in Group D, and the combined analysis showed that the incidence of arrhythmia was 0.39 (0.31, 0.47). The intergroup heterogeneity was $p=0.04 (<0.05)$, so chemotherapy cycle may be one of the sources of heterogeneity in this study.

Table 2

Subgroup analysis based on publication year, sample size, and dose and duration of administration
Datasets | Total | Event | Proportion (95% CI) | $p$ | $\phi$ | heterogeneity between groups($P$)
--- | --- | --- | --- | --- | --- | ---
Year of publication
Before 2014 | 11 | 1499 | 594 | 0.39 (0.32, 0.46) | $\leq 0.001$ | 84.34% | 0.604
After 2014 | 35 | 4206 | 1638 | 0.41 (0.37, 0.46) | $\leq 0.001$ | 85.08%
Sample size
100 | 28 | 1434 | 618 | 0.44 (0.39, 0.49) | $\leq 0.001$ | 71.76% | 0.158
100-200 | 6 | 884 | 322 | 0.37 (0.31, 0.42) | 0.01 | 67.57%
200 | 12 | 3171 | 1220 | 0.39 (0.32, 0.45) | $\leq 0.001$ | 94.32%
Dosage
$\geq 200mg/m^2$ | 3 | 330 | 132 | / | / | / | 0.304
200-399mg/m$^2$ | 19 | 2342 | 928 | 0.41 (0.35, 0.47) | $\leq 0.001$ | 87.25%
$\geq 400mg/m^2$ | 12 | 963 | 403 | 0.46 (0.39, 0.54) | $\leq 0.001$ | 77.56%
Cycle
4 cycle | 5 | 463 | 151 | 0.34 (0.27, 0.41) | 0.05 | 57.06% | 0.04
4 cycle | 8 | 955 | 457 | 0.50 (0.41, 0.58) | $\leq 0.001$ | 82.63%
6 cycle | 18 | 1801 | 750 | 0.43 (0.38, 0.49) | $\leq 0.001$ | 79.14%
6 cycle | 6 | 760 | 315 | 0.39 (0.31, 0.47) | $\leq 0.001$ | 74.55%

Subgroup analysis based on type of ECG change

Subgroup analysis based on type of ECG change, including QT-QTc interphase change, PR interphase change, P wave change, ST-T segment change, and low voltage abnormality, was also performed. (Table 3)

QT-QTc interphase change

Zhang KK et al. reported prolongation of the QT-QTc interval induced by anthracycline chemotherapy in 20 treatment groups in 16 studies. In a total of 2291 patients, 255 patients developed QT-QTc prolongation, with an incidence of 0.03-0.28. Analysis of the combined results showed that the incidence was 0.08 (0.05, 0.11) (Table 3).

PR interphase change

The study by Yang M was the only study to report a short PR interval induced by anthracycline chemotherapy, with an incidence of 0.01. A study conducted by Chen MC explored the influence of treatment cycle on the incidence of short PR interval. The incidence was 0.55 with 4 cycles of chemotherapy and increased to 0.65 with 6 cycles, showing a certain dose-related relationship.

P wave change

Two studies by Ding SQ et al. and three treatment groups reported anthracycline-related P wave changes, including 18 patients with P wave changes (14 of them with P wave broadening) in a total of 175 patients, with an incidence of 0.03-0.11. The combined analysis showed an incidence of 0.10 (0.05, 0.15) (Table 3).

ST-T period change

ST-T changes were the most common ECG changes in anthracycline-associated arrhythmias, reported in 45 treatment groups in 37 studies and in 1011 of 5514 patients, for an incidence of 0.03-0.70. The combined analysis showed that the incidence of ST-T segment change associated with anthracycline was 0.19 (0.15, 0.23).

Wang F et al. reported 7 studies and 9 treatment groups of patients with only ST segment changes. Among 1337 patients, 197 patients showed ST segment changes (including ST segment elevation in 37 patients and ST segment decline in 44 patients), with an incidence of 0.05-0.40. The combined analysis showed an incidence of 0.17 (0.09, 0.27).

Yang M et al., in 10 studies and 12 treatment groups, reported only T-segment changes in 289 of 1880 patients (including 14 patients with T-wave decrease and 12 patients with T-wave inversion), and the combined analysis showed a 0.15 (0.12, 0.19) incidence of T-wave changes associated with anthracycline chemotherapy (Table 3).

Low voltage abnormalities
Low-voltage abnormalities induced by anthracycline therapy in breast cancer was described in 18 studies, 24 treatment groups, and 161 of 2920 patients, for an incidence ranging from 0.01 to 0.23, and the pooled analysis showed an incidence of 0.05 (0.03, 0.08).

Among the studies, the study by Yi SY et al., 11 studies and 15 treatment groups reported anthracycline-associated QRS low voltage, and 82 of 1714 patients developed QRS low voltage, for an incidence of 0.01-0.13. The combined analysis showed an incidence of 0.04 (0.03, 0.06). The incidence of low R-wave voltage was reported in two studies and four treatment groups, for a combined incidence of 0.16 (0.09, 0.24). Other low voltage abnormalities were limb lead low voltage (0.03, 23/884) and chest lead low voltage (0.03, 7/279) (Table 3).

Subgroup analysis based on arrhythmia.

Finally, subgroup analysis based on arrhythmia subtype, including conduction block, heart rate changes, premature beats, and other arrhythmias, was performed. (Table 3)

Conduction block

Anthracycline-induced block was reported in 29 treatment groups in 26 studies and 127 of 3859 patients, for an incidence ranging from 0.01 to 0.20, and the pooled analysis showed an incidence of 0.04 (0.02, 0.05).

Yang M et al. reported the incidence of bundle branch block in 9 studies and 14 treatment groups, and 47 of 1798 patients developed bundle branch block, for an incidence ranging from 0.01 to 0.11. The combined analysis showed that the incidence was 0.03 (0.02, 0.04). Among the studies, 5 studies including HeF and 7 treatment groups reported the incidence of complete right bundle branch block in detail: 19 of 977 patients developed complete right bundle branch block. The combined analysis showed that the incidence was 0.03 (0.01, 0.05). In addition, He F reported two cases of incomplete right bundle branch block and one case of left anterior bundle branch block in a study of 213 people.

Pan Y et al. reported the incidence of anthracycline-related atrioventricular block in 17 studies and 21 treatment groups. A total of 57 patients developed atrioventricular block in 2724 patients, including 13 cases of first-degree atrioventricular block, 2 cases of second-degree atrioventricular block, and 1 case of third-degree atrioventricular block. The incidence of atrioventricular block ranged from 0.01 to 0.10, and the incidence in the pooled analysis was 0.02 (0.01, 0.03). In addition, a study with a sample size of 101 conducted by Hu and G showed 4 cases of ventricular block (Table 3).

Heart rate change

Changes in heart rate associated with anthracycline use were reported in 42 treatment groups in 34 studies and in 576 of 4977 patients, for an incidence ranging from 0.01 to 0.54. The incidence in the pooled analysis was 0.12 (0.10, 0.15).

Yi SY et al. reported the occurrence of anthracycline-related tachycardia in 25 studies and 30 treatment groups. A total of 285 cases of tachycardia occurred in 4003 patients, for an incidence of 0.03-0.29. The combined analysis showed that the incidence was 0.07 (0.06, 0.09).

Meng KX et al. reported anthracycline-related bradycardia in 14 studies and 18 treatment groups, and 130 of 2866 patients developed bradycardia, for an incidence of 0.01-0.13. The combined analysis showed an incidence of 0.05 (0.03, 0.06).

Three studies by Feng YY et al. and four treatment groups reported anthracycline-related supraventricular tachycardia, and 6 of 493 patients developed supraventricular tachycardia, for an incidence of 0.01-0.03. The combined analysis showed an incidence of 0.01 (0.00, 0.02). In addition, Wu QD et al. reported one case of ventricular tachycardia induced by anthracycline chemotherapy, and Chen MC et al. reported 47 cases of shortwave ventricular tachycardia induced by anthracycline chemotherapy (Table 3).

Premature beat

Premature beat induced by anthracycline therapy in breast cancer was described in 31 studies in 38 treatment groups, with 399 cases occurring in 4716 patients, for an incidence ranging from 0.01 to 0.34. The incidence in the pooled analysis was 0.09 (0.07, 0.11).

The study of Zhang KK et al., 21 studies and 27 treatment groups reported anthracycline-related atrial premature beats, and 179 of 3487 patients had atrial premature beats, for an incidence of 0.01-0.29. The combined analysis showed an incidence of 0.05 (0.04, 0.07).

He, F et al. reported anthracycline-related premature ventricular contractions in 23 studies and 29 treatment groups, and 163 of 3972 patients developed premature ventricular contractions, for an incidence ranging from 0.01 to 0.15. The combined analysis showed an incidence of 0.04 (0.02, 0.05).

In addition, Cheng Y and Liu BL reported one case of premature beat, while Chen MC et al. reported 26 cases of frequent premature ventricular beat and 27 cases of paired premature ventricular beat in their study (n=80). (Table 3)

Other ECG changes

Xu GQ et al. reported 17 cases of atrial fibrillation induced by anthracyclines in 3 studies (n=546), and the combined results showed that the incidence was 0.04 (0.00, 0.12) (Table 3). A study by Liu BL (n=409) reported a case of anthracycline-associated atrial flutter. A study by Dong XJ (n=279) reported 3 patients with clockwise and 7 patients with counterclockwise flutter, a study by Qi CC (n=123) reported 8 patients with electroaxial flutter, and a study by Dong XJ (n=279) reported 2 patients with left ventricular hypervoltage.
Table 3
Subgroup analysis based on type of ECG change and arrhythmia

<table>
<thead>
<tr>
<th>ECG changes</th>
<th>Datasets</th>
<th>Total</th>
<th>Event</th>
<th>Proportion (95%CI)</th>
<th>p</th>
<th>χ²</th>
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<tr>
<td>QT-QTc interval</td>
<td>QT-QTc interval change</td>
<td>20</td>
<td>2291</td>
<td>255</td>
<td>0.08 (0.05,0.11)</td>
<td>0.001</td>
</tr>
<tr>
<td>P wave</td>
<td>P wave change</td>
<td>3</td>
<td>175</td>
<td>18</td>
<td>0.10(0.05,0.15)</td>
<td>0.53</td>
</tr>
<tr>
<td>ST-T segment</td>
<td>ST-T segment change</td>
<td>45</td>
<td>5144</td>
<td>1011</td>
<td>0.19(0.15,0.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low voltage</td>
<td>Low voltage</td>
<td>24</td>
<td>2920</td>
<td>161</td>
<td>0.05(0.03,0.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Conduction block</td>
<td>29</td>
<td>3859</td>
<td>127</td>
<td>0.04(0.02,0.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Conduction block</td>
<td>Branch bundle block</td>
<td>14</td>
<td>1798</td>
<td>47</td>
<td>0.03(0.02,0.04)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Heart rate change</td>
<td>42</td>
<td>4977</td>
<td>576</td>
<td>0.12(0.10,0.15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Heart rate change</td>
<td>30</td>
<td>4003</td>
<td>285</td>
<td>0.07(0.06,0.09)</td>
<td>0.001</td>
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<tr>
<td>Atrioventricular tachycardia</td>
<td>Tachycardia</td>
<td>18</td>
<td>2866</td>
<td>130</td>
<td>0.05(0.03,0.06)</td>
<td>0.001</td>
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<tr>
<td>Premature beat</td>
<td>Premature beat</td>
<td>38</td>
<td>4716</td>
<td>399</td>
<td>0.09(0.07,0.11)</td>
<td>0.001</td>
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<tr>
<td>Atrial fibrillation</td>
<td>atrial fibrillation</td>
<td>3</td>
<td>546</td>
<td>17</td>
<td>0.04(0.00,0.12)</td>
<td>0.001</td>
</tr>
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</table>

**Publication bias**

Funnel plots and Begg's and Egger's tests were used to evaluate publication bias. The funnel plot is shown in Figure 3. The included study scatter points were basically symmetrically distributed along the midline. The funnel plot was complete and symmetrical, suggesting that there was no publication bias. Publication bias is defined as P<0.05 in Begg's and Egger's tests. The results of Begg's test (P =0.103) and Egger's test (P =0.083) are shown in Fig. 4 and Fig. 5, and there was no evidence of publication bias in this assessment of the incidence of anthracycline-related cardiotoxicity. Since there was no obvious publication bias in the included literature in this study, it was not necessary to evaluate the impact of publication bias on the results by sequentially removing each study and reanalyzing the data.

**Discussion**

Although chemotherapy based on anthracyclines can improve the quality of life and survival time of breast cancer patients, unfortunately, a large number of patients develop different types of arrhythmias during or after chemotherapy with anthracyclines, which not only seriously affects the quality of life of
patients but also endangers their lives. Therefore, accurate assessment of the incidence of anthracycline-related arrhythmias in breast cancer patients is essential to guide the safe use of anthracyclines. To raise awareness of the dangers of anthracycline-associated arrhythmias and guide drug safety, we assessed the incidence of arrhythmias and ECG abnormalities in breast cancer patients receiving anthracycline chemotherapy.

We used an extensive search strategy to capture all relevant literature and excluded studies that did not clearly report the details of anthracycline therapy to accurately assess the impact of each influencing factor on the incidence. Although we had to exclude approximately half of the articles from the meta-analysis because they lacked details about the treatment regimen, the findings of the excluded articles were generally consistent with the pooled quantitative results, and there was no evidence of publication bias. Ultimately, a meta-analysis of 37 studies addressing the specific research questions was conducted. We found that the incidence of arrhythmias was approximately 41% among breast cancer patients receiving chemotherapy with anthracyclines, and subgroup analysis showed that treatment cycle was a factor affecting incidence. Yang XL's study described the detection rate of anthracycline-associated arrhythmias of both 12-lead electrocardiogram and dynamic electrocardiogram, and the results showed that the detection rate of dynamic electrocardiogram (0.41, 182/436) was higher than that of 12-lead electrocardiogram (0.36, 155/436) (16).

Analyses of the abnormal ECG findings of this study found that anthracycline-based chemotherapy drugs could cause QT, PR interval period and interphase, ST segment, T wave, and ST-T changes, abnormal Q wave, abnormal QRS wave, conduction abnormalities (including conduction block, complete right bundle branch block, incomplete right branch block), bundle branch block, left anterior branch block, room block, and first to fourth degree atrioventricular block), heart rate changes (including arrhythmia, tachycardia, bradycardia, ventricular tachycardia, short atrioventricular tachycardia and ventricular tachycardia), premature beat (including borderline premature beat, room premature beat, ventricular premature beat, frequent ventricular premature beat, and ventricular premature beat), low voltage abnormalities (including chest lead low voltage, limb and/or body lead low voltage, R wave low voltage, and QRS low voltage), electrical axis deflection, bell direction transposition, bell direction transposition, among which ST-T segment change was the most common variation. Studies have shown that drug administration should be stopped immediately when the QRS wave voltage decreases by 1/3 compared with the original voltage; otherwise, irreversible myocardial damage can be caused, leading to heart failure(17). However, QT prolongation is associated with syncope and sudden death as well as other rapid ventricular arrhythmias. An important ECG manifestation of anthracycline-induced ventricular arrhythmias is QT prolongation and the risk of progression to ventricular arrhythmias (18).

Regarding the pathogenesis of anthracycline-associated arrhythmias, Carmine Rocca et al. proposed that excessive reactive oxygen species (ROS) generation during anthracycline drug metabolism can inhibit the function of cardiac antioxidant enzymes (such as mitochondrial enzymes and NADPH oxidase). This results in damage to DNA, RNA, protein and lipid molecular membranes and typical redox modifications of macromolecules, including nitrotyrosine formation, lipid peroxidation, and protein carbonylation. In addition to the damage to cardiomyocytes themselves, oxidative stress also targets ion channels and affects ion membrane currents. This results in abnormal action potential propagation and arrhythmia (19). Nathan H Waldron et al. pointed out that anthracyclines lead to arrhythmias by affecting autonomic nervous function, and that autonomic nervous imbalance caused by increased sympathetic activity or decreased vagal activity may cause ventricular arrhythmias. This mechanism may involve shortening the effective refractory period of the myocardium, shortening the duration of the action potential, increasing the dispersion of the effective refractory period, increasing the heterogeneity of repolarization, and inducing the early and later depolarization state. These electrophysiological changes reduce the threshold of ventricular arrhythmias and may induce ventricular arrhythmias.(20). Christos Kontogiannis et al. found that anthracyclines selectively bind to endogenous cardiolipin in mitochondria, resulting in mitochondrial accumulation and disruption of the electron transport chain via inhibition of mitochondrial complexes I and II; these effects result in additional ROS production and cardiolipin peroxidation. Mitochondrial damage can mediate the increase in calcium load and ROS production induced by adrenaline signaling and can induce the phosphorylation of the ryanodine receptor, leading to sarcoplasmic reticulum Ca\(^{2+}\) leakage, which leads to arrhythmia(21). Additionally, anthracycline-based drugs can be mediated by reactive oxygen species groups, and free-state iron complex formation, and in the process, iron can generate ROS. Grain damage and iron metabolism disorders can interact, causing extension of action potential schedule, which increases the instability of the cell membrane potential and increases the probability of arrhythmia(22). Thavendiranathan P et al. showed that anthracyclines can directly inhibit the adenylate-activated protein kinase signaling pathway and neuromodulin/ErbB signaling pathway in myocardial tissue, deplete the cardiomyocyte transcription factor GATA-4 and cardiac anchor chain repeat protein, induce activation and release of a series of inflammatory factors, inhibit transient and delayed outward potassium currents, and affect Na\(^+-\)Ca\(^{2+}\) exchange, leading to myocardial ischemia and hypoxia and bundle branch conduction system block and ultimately arrhythmia (23, 24). Shao WW et al. believed that the occurrence of arrhythmia may be related to calcium overload, increased cell membrane permeability, increased internal Ca\(^{2+}\) flow, inhibited Na\(^+-\)K\(^+\)ATPase activity, decreased Na\(^+-\)K\(^+\) exchange, increased Na\(^+-\)Ca\(^{2+}\) exchange, accelerated internal Ca\(^{2+}\) flow, and activation of sarcoplasmic reticulum Ca\(^{2+}\) channels, increasing Ca\(^{2+}\) release (25). Other related theories include apoptosis theory and theories related to energy metabolism disorders(26).

Cumulative drug dose, age, sex, diet, genetic background, and past medical history are considered risk factors for cardiotoxicity of anthracyclines(25). Other relevant studies have shown that the combined use of anthracyclines with cyclophosphamide can increase the cardiotoxicity of anthracyclines, but the effect is not significant when a conventional does is used. This information is different from that reported by Von Hoff et al., and further studies are needed to clarify the exact relationships. The existing research suggests that the combination of anthracycline chemotherapy with cyclophosphamide might have an impact on our the results of our study(27, 28).

With regard to the cardiotoxicity of anthracycline-associated prophylaxis, the protective effect of dexrazoxane (DZR) on anthracycline-associated cardiotoxicity is now well established. A large amount of high-level evidence-based medical data indicate that dexrazoxane is the only drug that can effectively prevent cardiotoxicity induced by anthracyclines(29). Meanwhile, dose control, slow intravenous infusion and the use of anthracycline liposomes are considered to be effective measures to reduce the incidence of cardiotoxicity(30). Interestingly, exercise was also found to have a protective effect on anthracycline-related cardiotoxicity. Hornsby WE et al. found that aerobic training not only completely eliminated the harmful effects of chemotherapy but also
led to significant improvement in cardiopulmonary function during concurrent neoadjuvant therapy (31). Studies have shown that proprietary Chinese medicines such as ginkgo biloba extract, Wenxin granule and Shenmai injection also have protective effects on anthracycline-related cardiotoxicity (32, 33).

Some limitations in the literature and our meta-analysis are worth mentioning. (1) This study was not based on individual patient, and the vast majority of studies included in this meta-analysis were observational studies. These observational studies, unlike randomized controlled trials, may be more likely to exhibit inherent bias in research design, and those studies that lacked a control group may be at risk of measurement bias. (2) Because of study design flaws, it was often not clear whether the arrhythmia events were due to anthracyclines alone, preexisting cardiovascular disease, other treatments (radiotherapy or other nonanthracycline agents, such as paclitaxel drugs), or confounding factors. In this paper, only studies with complete original data records were integrated and analyzed, and risk factors and other information evaluated based on subjective judgment and related epidemiological data were not integrated and systematically analyzed, so the data and analysis were relatively limited. (3) Although it is difficult for any meta-analysis to completely exclude the possibility of publication bias and we did not detect evidence of publication bias, we cannot completely exclude the possibility of publication bias in this study because we found that the incidence of arrhythmias was higher in the studies with smaller sample sizes. In addition, most of the studies included in this study were Chinese studies, and thus, regional differences may have affected the results. (4) The present meta-analysis produced inconsistent incidence rates, and the software used for analysis varied. The specific operation steps and analysis methods, such as the publication bias analysis method and the method used to analyze differences, are not perfect, and the scarcity of literature may have affected the results. This meta-analysis provides strong supporting evidence that can lead to rapid improvements. (5) The literature covered in this study covers 22 years, from 2000 to 2022, during which significant advances have been made in the treatment of breast cancer and the detection of arrhythmias. However, our analysis found that earlier studies had similar incidence rates to newer studies.

Conclusion

Patients with breast cancer treated with anthracyclines have an approximately 41% chance of developing arrhythmias, with ST-T segment changes and heart rate changes as the main ECG findings. Our study is the first quantitative systematic review of anthracycline-associated arrhythmias in breast cancer patients, and its findings have important implications for guiding the treatment and monitoring of breast cancer patients.

Abbreviations

ECG: electrocardiogram
DNR: daunorubicin
ADM: adriamycin
MIT: mitoxantrone
CAF: Adriamycin + fluorouracil + cyclophosphamide
TA: Adriamycin + docetaxel
TE: Paclitaxel + epirubicin
ROS: reactive oxygen species

Declarations

Ethical Approval
Not applicable

Competing interests
The authors declare that they have no competing interests

Authors’ contributions
All authors attest they meet the ICMJE criteria for authorship. All authors were involved in the conception of the study. TR and JYC participated in the collection and generation of the study data. TR and MM performed the study. MZ guided TR to complete and revise the discussion part of the manuscript. All authors were involved in the analyses and interpretation of the data. All authors revised the manuscript critically for important intellectual content and the author(s) read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article [Table.1].

Consent for publication

Not applicable

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References


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forest map of the incidences of anthracycline-induced arrhythmias in breast cancer
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Supplementary Files
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- Table.1Thebasiccharacteristicsoftheincludedstudies.docx
- Table.2subgroupanalysiscbasedonessentialinformation.docx
- Table.3Subgroupanalysiscbasedonrhythmia.docx