Original Article

Neoadjuvant therapy with *vs*. without anthracyclines for HER2-positive breast cancer: a systematic review and meta-analysis

Jingjin Zhu[1,2#], Ningning Min[1,2#], Yizhu Chen[3], Xiru Li[2]

[1]School of Medicine, Nankai University, Tianjin, China; [2]Department of General Surgery, The First Medical Center of Chinese PLA General Hospital, Beijing, China; [3]Medical School of Chinese PLA, Beijing, China

Contributions: (I) Conception and design: X Li, J Zhu; (II) Administrative support: X Li; (III) Provision of study materials or patients: X Li; (IV) Collection and assembly of data: J Zhu, N Min; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xiru Li. Department of General Surgery, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, China. Email: 2468li@sina.com.

Background: Neoadjuvant therapy has become the standard treatment for early human epidermal growth factor receptor 2 (HER2)-positive breast cancer, with most regimens using a combination of anti-HER2-targeted drugs and chemotherapy. However, the combination of anthracyclines and trastuzumab has high cardiac toxicity, and the efficacy evaluation of targeted therapy with or without anthracyclines is not unified. The purpose of this meta-analysis was to evaluate the relative efficacy and safety of anti-HER2-targeted therapy combined with *vs*. without anthracyclines neoadjuvant treatment.

Methods: The following databases: PubMed, Medline, Embase, and Cochrane Library were systematically searched. Study inclusion was determined according to PICOS principles. PICOS: Patients, HER2-positive breast cancer; Intervention, anti-HER2-targeted therapy combined with anthracyclines; Control, without anthracyclines; Outcomes, the percentage of pathologic complete response (pCR), breast-conserving surgery (BCS), and grade 3 or worse adverse events according to CTCAE version 4.03; Studies, randomized controlled trials (RCTs) and retrospective studies. The meta-analysis was performed using RevMan5.3 software, and the odds ratio (OR) with 95% confidence intervals (CIs) was performed.

Results: In total, 11 articles involving 1,998 patients were included with 1,155 patients in the anthracycline-containing group and 843 patients in the anthracycline-free group. For efficacy, there was no statistically significant difference in the percentage of pCR (OR 0.95; 95% CI: 0.61–1.48; P=0.83) and BCS (OR 1.18; 95% CI: 0.93–1.49; P=0.17) on anthracycline-free regimens compared with anthracycline-containing regimens. For safety, the combined effect values showed a significantly lower incidence of left ventricular ejection fraction decreases with the anthracycline-free regimen than with the anthracycline-containing regimen (OR 0.50; 95% CI: 0.35–0.71; P=0.0001). Other adverse effects and survival events were generally not statistically different in incidence between the two groups. The subgroup analysis suggested that hormone receptor status might be the source of heterogeneity in this study.

Conclusions: Our study demonstrated that the targeted therapy combined with anthracyclines was associated with an increased risk of cardiac adverse events compared with the anthracycline-free group, with no significant difference in the percentage of pCR and BCS. Due to the high heterogeneity of this meta-analysis, more studies with longer follow-up are needed to validate the current findings and to further explore the removal and retention of anthracyclines.

Keywords: Breast neoplasms; neoadjuvant therapy; targeted therapy; trastuzumab; anthracyclines

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Introduction

Neoadjuvant therapy has become the standard treatment for high-risk, locally advanced breast cancer in an effort to gain access to surgery for inoperable breast cancer or improve the rates of breast-conserving surgery. Since the primary tumor is not affected by invasive operations in the treatment process, neoadjuvant treatment strategies can also be used to monitor tumor response to treatment and adjust treatment regimens in a timely manner. Several studies have shown that the pathologic complete response (pCR) rate of neoadjuvant treatment is an effective predictor of the improvement of event-free survival (EFS) and overall survival (OS) in patients with breast cancer, particularly in triple-negative and human epidermal growth factor receptor 2 (HER2) positive breast cancer (1-3). The pCR rate based on different treatment regimens emerged as an important reference for decision-making in breast cancer neoadjuvant treatment.

Although amplification or overexpression of HER2 is associated with poor prognosis in breast cancer patients (4), HER2-positive breast cancer is usually relatively sensitive to chemotherapy, exhibiting a particular sensitivity to anthracyclines. A pooled analysis of 8 randomized trials with 6,564 cases comparing anthracycline-containing and anthracycline-free regimens suggested that anthracycline-containing regimens improved OS (HR =0.73; 95% CI: 0.62–0.85; P<0.001) and disease-free survival (DFS) (HR =0.71; 95% CI: 0.61–0.83; P<0.001) significantly better than anthracycline-free regimens in the treatment of HER2-positive breast cancer (5). With the in-depth understanding of the physiological and pathological effects of HER2/neu, anti-HER2 target agents as represented by trastuzumab and pertuzumab have been introduced enabling effective improvement of survival outcomes of patients with metastatic HER2-positive diseases (6,7), and its application in neoadjuvant treatment has also brought significant survival benefits to patients with early HER2-positive breast cancer (8,9). However, the combination of anthracyclines and targeted agents such as trastuzumab is associated with higher cardiotoxicity. The majority of studies have confirmed that combining trastuzumab with anthracyclines is as effective as well-tolerated (10-12). In a pivotal phase III clinical trial of metastatic breast cancer, the combination resulted in an unacceptably high rate of cardiotoxicity (27%), and the incidence of grade III or IV cardiac dysfunction was as high as 16% (13). In NSABP B-31 and NCCTG N9831 clinical trials, 5.0% to 6.6% of women treated with anthracyclines were unable to receive trastuzumab (14,15).

With regard to cardiotoxicity concerns, anthracycline-free regimens have become a hot topic of research. The BCIRG 006 trial evaluated doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) with docetaxel, carboplatin, and trastuzumab (TCH) adjuvant regimens. There was no statistically significant difference in 5-year DFS (P=0.21) and OS (P=0.14) of HER2-positive breast cancer patients, and anthracycline-free regimens showed lower acute toxicity, cardiotoxicity and leukemia risk (16). Similar results were obtained from the TRAIN-2 trial (17,18). Interestingly, in the study of He *et al.* (19) and Bayraktar *et al.* (20), the neoadjuvant chemotherapy regimen of trastuzumab plus paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide (PH-FECH) showed higher pCR rate and progression-free survival (PFS) than TCH. There seems the clinical efficacy evaluation of anti-HER2 targeted therapy combined with anthracyclines or non-anthracyclines neoadjuvant therapy is not unified, and a systemic meta-analysis has yet to be reported to analyze the related studies.

Therefore, the purpose of this meta-analysis was to evaluate the relative efficacy and safety of anti-HER2 targeted therapy combined with *vs.* without anthracyclines

Highlight box

Key findings

- For neoadjuvant therapy, our study demonstrated no significant difference in the percentage of pathologic complete response and breast-conserving surgery in HER2-positive breast cancer patients treated with targeted therapy combined with anthracycline-containing or anthracycline-free regimens, but higher cardiotoxicity can result from the anthracycline-containing regimen.

What is known and what is new?

- Neoadjuvant therapy for HER2-positive breast cancer always uses a combination of anti-HER2-targeted drugs and chemotherapy.
- The combination of anthracycline and trastuzumab has high cardiac toxicity, and the efficacy evaluation of targeted therapy with *vs.* without anthracyclines is not clear.
- This meta-analysis evaluated the relative efficacy and safety of anti-HER2 targeted therapy combined with anthracycline vs. non-anthracycline drugs in neoadjuvant therapy.

What is the implication, and what should change now?

- Our study provided new evidence for the removal or retention of anthracyclines in the current neoadjuvant treatment of HER2-positive breast cancer.

in neoadjuvant therapy for HER2-positive breast cancer. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4030/rc).

Methods

Search strategy

This study has been registered in the International Prospective Register of Systematic Reviews 'PROSPERO' database (ID: CRD42022331040). The search strategy of this study was divided into three steps. First, the MeSH terms and free terms of breast neoplasms, neoadjuvant therapy, HER2-targeted therapy, and anthracycline were searched in the PubMed database, and corresponding search strategies were formulated according to the search methods of different databases. A full search strategy was detailed in the Table S1. Then, a comprehensive second search was conducted and the following databases: PubMed, Medline, Embase, and Cochrane Library were systematically searched for the articles published between January 1990 and April 2022 with no language restriction enforced. Finally, the retrieved studies were screened by 2 reviewers according to titles and abstracts and the full-text versions were reviewed to select relevant studies for follow-up research. The date when each source was last searched was 6th May 2022.

Eligibility criteria

Eligible studies were included based on PICOS (patients, intervention, comparison, outcomes, and study design) principles with the following criteria: (I) studies with subjects were HER2-positive primary breast cancer; (II) the treatment regimens studied were trastuzumab or other targeted drug therapy combined with anthracycline-free or anthracycline-containing drugs; (III) the primary endpoint was the percentage of pCR, defined as the absence of invasive tumor cells in the breast, regardless of axillary (ypT0/is ypN0 or ypT0/is); secondary endpoints were the percentage of patients who underwent breast-conserving surgery (BCS), the percentage of patients experiencing grade 3 or worse adverse events according to CTCAE version 4.03, EFS (time from randomization or the first dose of treatment to disease progression resulting in inoperability, recurrence, secondary primary malignant neoplasms, or death by any cause), and OS (time from randomization or the first dose of treatment to death from any cause); (IV) randomized controlled trials (RCTs) and prospective comparative cohort studies or retrospective studies were considered. Review articles, case reports, editorials or opinion pieces, conference abstracts, and articles without available full text were excluded.

Data extraction

Literature management was performed using the EndnoteX9 software with the duplicate studies deleted. Independent screening by two authors according to the title and abstract of the literature and excluding if it did not meet the inclusion criteria. Then, the full texts were read in detail to confirm the eligibility of each study, and finally, the included studies were confirmed. The two authors independently extracted information from the eligible studies using electronic tables: basic information, including the year of study publication, study design, regimen details, sample size, age, race, and time of follow-up; outcome information, including the percentage of pCR and secondary outcome measures. When there were discrepancies in the process of literature selection or any differences in interpreting the data, the third investigator reviewed and a consensus was reached at the end.

Quality assessment

Each included study was assessed for the risk of bias independently by two authors, and disagreements were resolved by consensus.

For RCTs, the risk of bias was assessed and graded according to the "GRADE" (Grading of Recommendations Assessment, Development, and Evaluation) classification system, with a judgment of either high, moderate, low, or very low quality.

For non-RCTs, the quality was assessed using the Newcastle-Ottawa scale (NOS), including selection, comparability, and outcome assessment. NOS scores of 7 or more points were considered to indicate high-quality studies and scores of 5–6 points were considered to indicate moderate quality.

Statistical analysis

The analyses were performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). The odds ratio (OR) were used to compare dichotomous variables and all results were reported with 95% confidence intervals

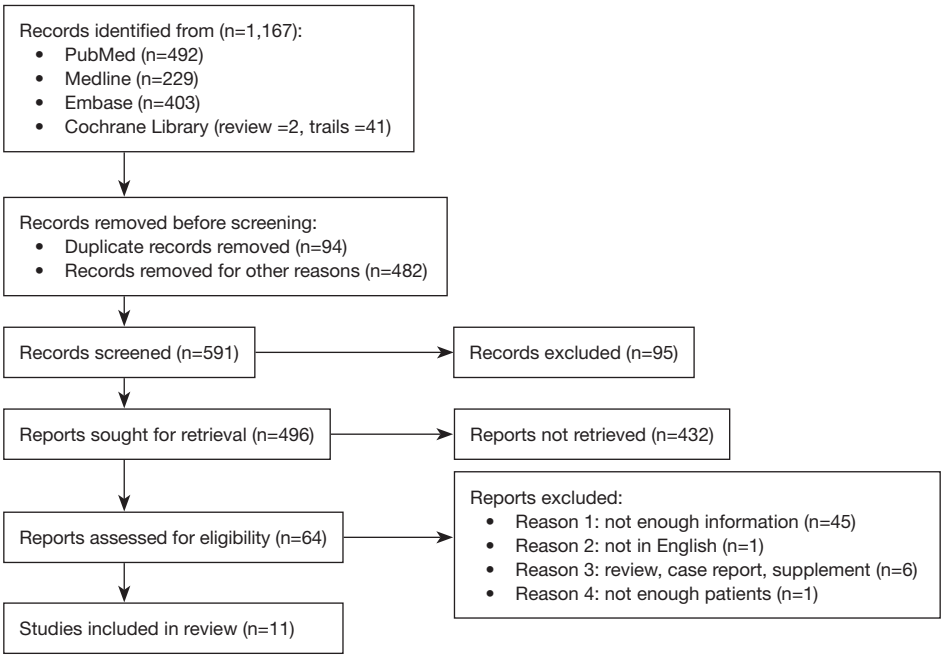

Figure 1 Article retrieval process.

(CIs). Probability values were two-sided, and P<0.05 was considered of statistical significance. A random effects model was utilized if significant heterogeneity was evident. Otherwise, the fixed-effects model was used. The I^2 test was used to measure statistical heterogeneity within comparison groups. The level of heterogeneity was defined as not (I^2<25%), low (I^2=25–50%), moderate (I^2=50–75%), high (I^2>75%).

Sensitivity analysis was carried out by deleting a study every time depending on the presence or absence of significant heterogeneity. Subgroup meta-analyses were planned based on age, race, type of study, and hormone receptor status for evaluating sources of heterogeneity, if appropriate. Funnel plots were used to evaluate publication bias.

Results

Literature search results

According to the established search strategy, 1,167 records were retrieved totally from PubMed, Medline, Embase, and Cochrane Library. After removing duplicates and irrelevant records, full-text reports were retrieved for 496 pieces of literature. Following an assessment according to inclusion and exclusion criteria, 11 studies were included for the meta-analysis (17,19-28). A PRISMA flow diagram summarizing the search procedure was presented in *Figure 1*.

Characteristics of the included studies

Of the 11 articles included in this study, 5 were RCTs and 6 were retrospective studies that included 1,998 patients from 2001 to 2019. The age of the patients ranged from 48 to 61 years. The main characteristics of these included studies are listed in *Table 1*.

The quality of the included studies was assessed and the results showed that the most of the included RCTs had a low risk of selection bias, detection bias, reporting bias, and other bias and non-RCTs that included had a quality score of 7 or higher were considered to have good quality (Figure S1, Table S2).

The rate of pCR and BCS

All included studies evaluated the correlation between anthracycline-free and anthracycline-containing regimens and the percentage of patients experiencing a pCR. Overall, there was no statistically significant difference in the percentage of pCR occurring in patients on anthracycline-free regimens compared with anthracycline-containing regimens (OR 0.95; 95% CI: 0.61–1.48; P=0.83). In

Table 1 Characteristics of the included studies

Study	Non-anthracycline group	Anthracycline group	Age, median years [range]/± SD	Disease stage	Hormone receptor status (–/+)	Time frame
van Ramshorst 2018 (17) (NCT01996267)	TCbHP (n=219) group received nine cycles of paclitaxel and carboplatin at the same dose and schedule as in the anthracycline group	FEC + HP-TCbHP group (n=219) received three cycles of 5-fluorouracil (500 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (500 mg/m^2) intravenously, once every 3 weeks, followed by six cycles of paclitaxel (80 mg/m^2 on days 1 and 8) and carboplatin (AUC 6 mg/mL per min on day 1 or optionally AUC 3 mg/mL per min on days 1 and 8, as per the preference within the hospital) intravenously, once every 3 weeks	48 [43–56]; 49 [43–55]	I 1; II 289; III 147; IV 1	–183, +255	Dec 9, 2013, and Jan 14, 2016 The median follow-up was 48.8 months (inter quartile range, 44.1–55.2 months)
Schneeweiss 2013 (26) (NCT00976989)	In TCbHP ×6 (n=77) group, carboplatin was administered at a dose of AUC 6 and docetaxel was given at 75 mg/m^2 (no dose escalation allowed)	In FEC + HP ×3-THP ×3 (n=73) group and FEC ×3-THP ×3 (n=75) group, the doses administered were 5-fluorouracil: 500 mg/m^2; epirubicin: 100 mg/m^2; cyclophosphamide: 600 mg/m^2; docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if no dose-limiting toxic effect occurred during cycle 4	50.0 [30–81]; 49.0 [27–77]; 49.0 [24–75]	–	–114, +111	December 2009 and January 2011 The median overall time on study including the post-treatment follow-up ranged from 20 to 21 months between arms
Huang 2015 (24) (NCT01428414)	In PTXCbH group (n=50), trastuzumab (4 mg/kg loading dose followed by 2 mg/kg) and paclitaxel (75 mg/m^2) weekly combined with carboplatin (AUC =2) weekly	In PTXEH group (n=50), trastuzumab (4 mg/kg loading dose followed by 2 mg/kg) and paclitaxel (75 mg/m^2) weekly combined with epirubicin (75 mg/m^2) every 3 weeks	48 [29–65]; 47.5 [30–63]	II 49; III 51	–	Aug, 2011 to May, 2012
Mukai 2020 (25) (UMIN000007074)	PTXT + T (n=100) group were treated with paclitaxel (80 mg/m^2) and trastuzumab (loading dose of 4 mg/kg followed by 2 mg/kg) for three doses, and continued on once-weekly paclitaxel and trastuzumab for a total of 12 additional doses	PTXT + T-ECT (n=55) group received initial treatment with paclitaxel (80 mg/m^2) and trastuzumab (loading dose of 4 mg/kg followed by 2 mg/kg) for three doses, and chemotherapy was switched to epirubicin (90 mg/m^2) plus cyclophosphamide (600 mg/m^2), administered every 3 weeks for three cycles, combined with once-weekly trastuzumab administered for a total of 12 doses	57.3 [25–75]	II 148; III 52	–91, +109	December 2011 and September 2015

Table 1 *(continued)*

Table 1 *(continued)*

Study	Non-anthracycline group	Anthracycline group	Age, median years [range]/± SD	Disease stage	Hormone receptor status (–/+)	Time frame
Gao 2021 (22) (NCT03140553)	TCbH (n=68) group were treated with docetaxel (75 mg/m^2) plus carboplatin (area under the curve, 6 mg/mL per min) administered every 3 weeks for six cycles concurrently with trastuzumab	EC-TH (n=67) group were administered four cycles of epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) intravenously, followed by four cycles of docetaxel (100 mg/m^2) and trastuzumab every 3 weeks	50.5 [23–68]; 50 [25–68]	II 88; III 47	–67, +68	May 2017 to November 2019
Ueno 2020 (27)	TCH ×6 (n=24) group were treated with docetaxel (75 mg/m^2, q3w) + cyclophosphamide (600 mg/m^2, q3w) + trastuzumab (2 mg/kg, weekly with loading 4 mg/kg, or 6 mg/kg, q3w with loading 8 mg/kg)	FEC-TCH (n=21) group were treated with four cycles of 5-fluorouraci (500 mg/m^2, q3w) + epirubicin (100 mg/m^2, q3w) + cyclophosphamide (500 mg/m^2, q3w) followed by four cycles of docetaxel (75 mg/m^2, q3w) + cyclophosphamide (600 mg/m^2, q3w) + trastuzumab (2 mg/kg, weekly with loading 4 mg/kg, or 6 mg/kg, q3w with loading 8 mg/kg) TCH-FEC (n=22) were treated with four cycles of TCH followed by four cycles of FEC	54.5 [33–67]; 55.5 [34–66]; 53 [38–70]; 52 [36–62]	–	–53, +74	September 2009 and September 2011 The median length of follow-up was 53 months
Horiguchi 2011 (23)	PTXH (n=20) group received four courses of 80 mg/m^2 paclitaxel weekly (days 1, 8, and 15) followed by a 1-week break and trastuzumab weekly (days 1, 8, 15, and 29)	PTXHE (n=21) group received four courses of 500 mg/m^2 5-fluorouracil, 100 mg/m^2 epirubicin, and 500 mg/m^2 cyclophosphamide every 3 weeks followed by concomitant 80 mg/m^2 paclitaxel and trastuzumab weekly for 12 weeks	49.5 [37–76]; 50 [29–71]	II 20; III 21	–	2004 and 2010 At a median follow-up of 32 months
Fujita 2022 (21)	In FEC omitted (n=40) group, the taxane regimen was composed of 12 cycles of paclitaxel (80 mg/m^2 every week) or 4 cycles of docetaxel (75 mg/m^2 every 3 weeks)	In FEC added (n=102) group, the anthracycline regimen was composed of 4 cycles of FEC (fluorouracil at 500 mg/m^2, epirubicin at 100 or 75 mg/m^2, and cyclophosphamide at 500 mg/m^2 every 3 weeks). All patients received trastuzumab (8 mg/kg as a loading dose and 6 mg/kg from the second dose onward every 3 weeks)	51 [28–73]; 51 [24–72]	I 43; II 98	–74, +68	September 2006 and July 2018 The median follow-up period was 61 months (range; 10–173)
He 2022 (19)	TCbH (n=65) group were treated with docetaxel (75 mg/m^2) plus carboplatin (area under the curve, 6 mg/mL/min), given every 3 weeks for 6 cycles concurrently with trastuzumab	PTXH-FECH (n=184) group were treated with 12 courses of weekly paclitaxel (80 mg/m^2) plus trastuzumab, followed by four 21-day cycles of 5-fluorouracil (500 mg/m^2), epirubicin (75 mg/m^2), and cyclophosphamide (500 mg/m^2) plus trastuzumab	48.63±10.7; 52.2±13.1	I+II 111; III 138	–	January 1, 2002 and June 30, 2018 The median follow-up duration for all patients was 109.0 months (range, 8.0–167.0 months)

Table 1 *(continued)*

Table 1 *(continued)*

Study	Non-anthracycline group	Anthracycline group	Age, median years [range]/± SD	Disease stage	Hormone receptor status (–/+)	Time frame
Bayraktar 2012 (20)	TCbH (n=65) included docetaxel 75 mg/m^2 IV on day 1, carboplatin at an AUC of 6 IV on day 1, and trastuzumab 8 mg/kg IV on day 1 followed by 6 mg/kg maintenance dose, administered at 3-week intervals for six cycles	PTXH-FECH (n=235) included paclitaxel 80 mg/m^2 intravenously (IV) weekly for 12 weeks or paclitaxel 225 mg/m^2 IV over 24 hours every 3 weeks, followed by 4 cycles of FEC (fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2) IV on day 1, every 3 weeks. A loading dose of 4 mg/kg IV trastuzumab was given on day 1 followed by 2 mg/kg weekly	53 [29–80]; 49 [21–81]	I 9; II 136; III 155	–	Between 2001 and 2009 Median follow-up of survivors was 26.8 months (range 5–99 months)
Watanuki 2019 (28)	The “no anthracycline” (n=49) cohort. In both cohorts, patients were planned to receive paclitaxel at dose of 80 mg/m^2 or docetaxel at a dose of 75 mg/m^2 with concurrent administration of trastuzumab (a loading dose of 4 mg/ kg on day 1, followed by 2 mg/kg weekly in combination with paclitaxel or a loading dose of 8 mg/kg on day 1, followed by 6 mg/kg triweekly in combination with docetaxel)	In the “anthracycline” (n=73) cohort, patients were planned to receive 5-fluorouracil at a dose of 500 mg/m^2; epirubicin, 100 mg/m^2; and cyclophosphamide, 500 mg/m^2	61.6±11.73; 53.8±9.82	I 74; II 127; III 16; NA 1	–	–

–, hormone receptor status negative; +, hormone receptor status positive. SD, standard deviation; AUC, area under the concentration-time curve; T, docetaxel; PTX, paclitaxel; Cb, carboplatin; C, cyclophosphamide; F, 5-fluorouracil; E, epirubicin; H, trastuzumab; P, pertuzumab.

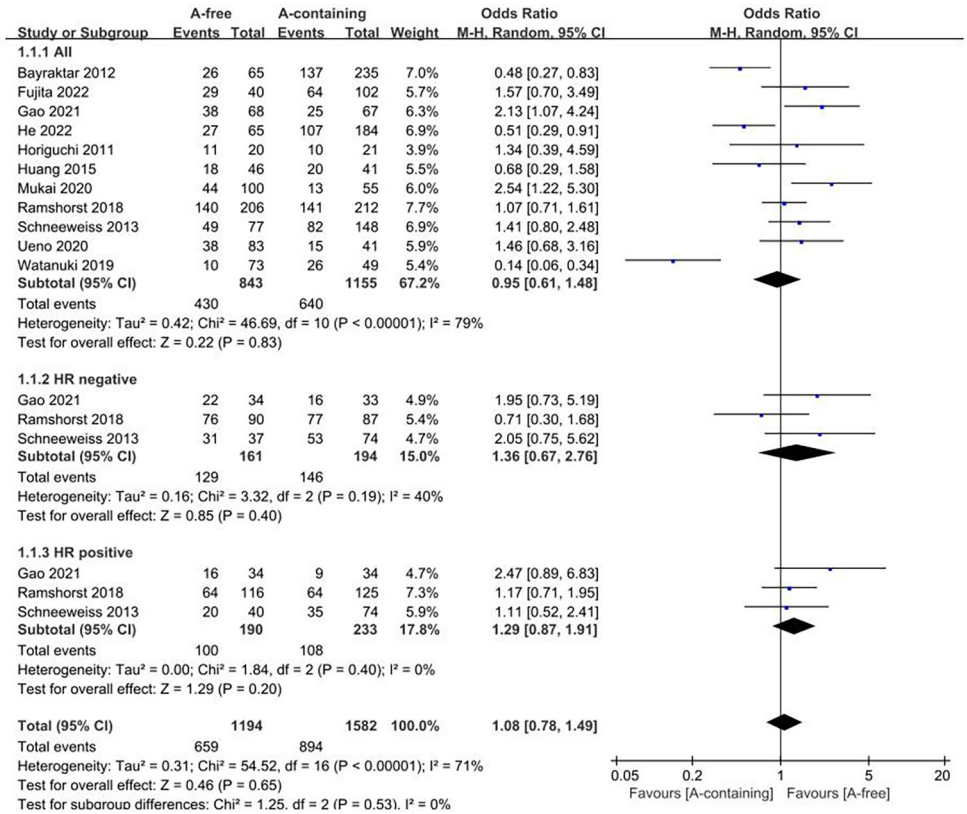

Figure 2 Forest plot showing the pooled odds ratios of the rate of pCR. pCR, pathologic complete response.

addition, three studies reported pCR rates for hormone receptor status and treatment regimens. The results showed that hormone receptor status was not associated with pCR rates (HR negative: OR 1.36, 95% CI: 0.67–2.76, P=0.40; HR positive: OR 1.29, 95% CI: 0.87–1.91, P=0.20) (*Figure 2*).

Breast surgery with axillary dissection or BCS is performed within 6 weeks after the last chemotherapy dose. BCS is a favorable option, but depends to some extent on the efficacy of neoadjuvant therapy. In the present study, eight studies reported BCS rates for both treatments. There was no difference in the proportions of patients undergoing BCS between the treatment groups (OR 1.18; 95% CI: 0.93–1.49; P=0.17) (*Figure 3*).

The rate of cardiac adverse events occurred during neoadjuvant treatment

Cardiotoxicity is a common side effect when trastuzumab and anthracyclines are combined, usually manifesting as a decrease in left ventricular ejection fraction (LVEF). A total of 4 studies reported LVEF decreases during neoadjuvant therapy with both regimens according to CTCAE version 4.03 (LVEF decline ≥10% or to <50%), and the combined effect values showed a significantly lower incidence of LVEF decreases with the anthracycline-free regimen than with the anthracycline-containing regimen (OR 0.50; 95% CI: 0.35–0.71; P=0.0001).

Another three studies reported LVEF incidence according to the commonly reported (non-CTCAE) definition of LVEF decline of 10% or more and LVEF below 50%. The result showed no statistically significant difference in the incidence of decreased LVEF between the two treatment groups (OR 0.69; 95% CI: 0.33–1.44; P=0.33) (*Figure 4*).

Symptomatic left ventricular systolic dysfunction occurred in 12 patients in the anthracycline-containing group and in 3 in the anthracycline-free group, although there was no statistical difference (OR 0.72; 95% CI: 0.23–2.29; P=0.58). In addition, 3 patients in the anthracycline-containing group suffered from heart failure and 1 patient died as a result.

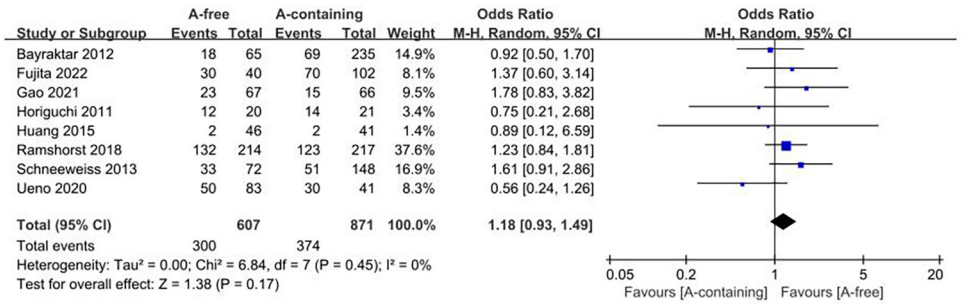

Figure 3 Forest plot showing the pooled odds ratios of the rate of BCS. BCS, breast-conserving surgery.

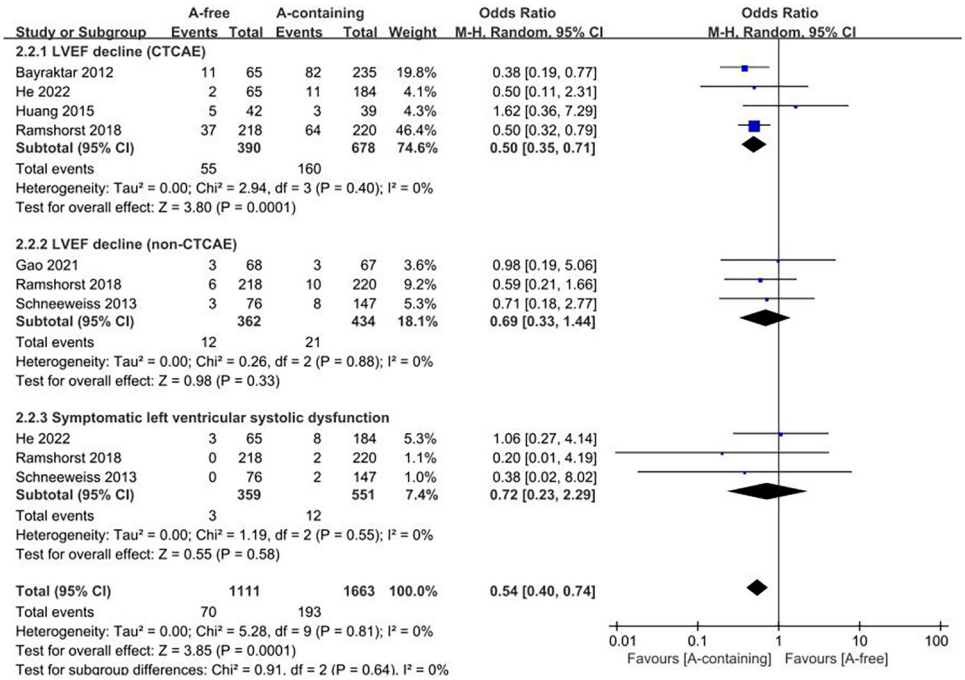

Figure 4 Forest plot showing the pooled odds ratios of the rate of cardiac adverse events occurred during neoadjuvant treatment. LVEF, left ventricular ejection fraction.

The rate of hematological adverse events and others occurred during neoadjuvant treatment

The incidence of neutropenia, febrile neutropenia and anemia was not statistically different between the two groups (neutropenia: OR 0.87, 95% CI: 0.67–1.14, P=0.32; febrile neutropenia: OR 0.54, 95% CI: 0.28–1.03, P=0.06; anemia: OR 2.67, 95% CI: 0.86–8.30, P=0.09). However, thrombocytopenia was more common in the anthracycline-free group (OR 4.21; 95% CI: 1.01–17.46; P=0.05) (Figure S2). Three patients treated with anthracyclines developed acute leukemia, all thought to be related to possibly treatment-related. There was no significant difference between the two treatment groups in the incidence of other toxic outcomes (Figure S3).

Survival benefits

A total of four studies reported in detail the events that occurred during follow-up, with a median follow-up time of 26.8-61.1 months. Because hazard ratios for survival were not presented, we used the number of events that occurred during follow-up as a substitute. An event occurred in 45 of 401 patients (11.2%) in the anthracycline-free group *vs.* 59

Table 2 Subgroup analyses

Subgroup	Included studies	Odds ratio, M-H, Random, 95% CI	I^2	P value of test for overall effect
Age				
Median years ≤50	Ramshorst 2018, Horiguchi 2011, Schneeweiss 2013, Huang 2015, Gao 2021	1.24 (0.90, 1.72)	21%	0.19
Median years >50	Mukai 2020, Fujita 2022, Ueno 2020, He 2022, Bayraktar 2012, Watanuki 2019	0.77 (0.36, 1.63)	86%	0.49
Race				
Asian	Huang 2015, Gao 2021, Horiguchi 2011, Mukai 2020, Ueno 2020, Fujita 2022, He 2022, Watanuki 2019	0.98 (0.51, 1.87)	82%	0.94
Non-Asian	Ramshorst 2018, Schneeweiss 2013, Bayraktar 2012	0.90 (0.50, 1.62)	75%	0.73
Type of study				
RCTs	Ramshorst 2018, Huang 2015, Schneeweiss 2013, Mukai 2020, Gao 2021	1.40 (0.94, 2.09)	52%	0.10
Non-RCTs	Ueno 2020, Fujita 2022, Horiguchi 2011, He 2022, Bayraktar 2012, Watanuki 2019	0.67 (0.34, 1.31)	79%	0.24

RCTs, randomized controlled trials; M-H, Mantel-Haenszel.

of 704 (8.4%) in the anthracycline-containing group. When comparing the EFS rate and OS rate between the two groups, the OR was 0.65 (95% CI: 0.35–1.22; P=0.18) and 0.71 (95% CI: 0.39–1.31; P=0.28), respectively (Figure S4).

Sensitivity analysis and publication bias

As part of the sensitivity analysis, excluding the study by Watanuki *et al.* (28), there was no statistical significance between the pCR rates between the two treatment groups (OR 1.12; 95% CI: 0.77–1.61; P=0.55), and excluding the study by Ueno *et al.* (27), there was no statistical significance in the BCS rates (OR 1.26; 95% CI: 0.99–1.61; P=0.06). The rest of the analysis showed no significant changes in outcomes.

In terms of the subgroup analysis, there was no significant change in the pooled OR with respect to the hormone receptor positive and hormone receptor negative subgroups in the pCR rate. However, heterogeneity I^2 decreased from 79% to 40% in the HR-negative group and 0% in the HR-positive group, suggesting that that there may be hormone receptor status differences in pCR benefits. Besides, subgroup analyses by age, race, and type of study showed that heterogeneity remained high (*Table 2*).

No obvious publication bias was observed in the funnel plots of the included studies in the group of pCR while the funnel plot regarding the BCS analysis was asymmetrical, suggesting the possibility of publication bias (Figure S5).

Discussion

In this systematic review and meta-analysis grounded on a total of 1,998 HER2-positive patients from 11 studies, we evaluated the correlation between the neoadjuvant regimens with or without anthracyclines in the context of the application of targeted therapy and the occurrence of pCR, BCS, toxic reactions, and long-term survival. It was demonstrated that the targeted therapy combined with anthracyclines was associated with an increased risk of cardiac adverse events compared with the control group who received anthracycline-free chemotherapy, with no significant difference in the percentage of pCR and BCS.

Various clinical guidelines for breast cancer mostly recommend TCbH(P), TH(P), or AC-TH(P) as neoadjuvant regimens for HER2-positive disease. Recently, several clinical trials have suggested that anthracycline-free may be non-inferior to anthracycline-containing regimens. Guiu *et al.* (29) first reported the long-term follow-up result, showing that the anthracycline-free trastuzumab-based therapy regimen combined either with docetaxel and/or carboplatin can achieve competitive results in terms of pCR, RFS, and OS. The phase II TRYPHAENA study compared 5-fluorouracil, epirubicin, cyclophosphamide (FEC) followed by docetaxel (T), with trastuzumab (H) and pertuzumab (P) given concurrently throughout with TCHP regimen. The results showed that the TCHP regimen

without anthracyclines achieved a pCR of 66%, higher than that of the FECHP-THP regimen with anthracyclines, and the findings were consistent regardless of HR positivity or negativity (26). The National Comprehensive Cancer Network guideline (version 4.2021) and the Chinese Society of Clinical Oncology guideline (version 2020) give priority to anthracycline-free TCbHP and THP regimens over anthracycline-containing AC-THP regimens.

However, the current opinion is not unanimous. In the 2021 St. Gallen/Vienna Consensus Conference, 54% of the panel would consider anthracyclines as needed in the treatment to HER2-positive breast cancer patients with lymph node metastases (30,31). To further compare the efficacy of different chemotherapy regimens in the neoadjuvant treatment of HER2-positive breast cancer, this meta-analysis combined clinical trials of targeted therapy combined with anthracycline-containing or anthracycline-free regimens. Three studies support the anthracycline-containing scheme can make patients achieve a higher rate of pCR, two studies support the anthracycline-free scheme, and six studies thought there was no difference in the two plans. The results were combined using random-effects models and no statistically significant difference in pCR rate and long-term survival rate between the two groups was observed. By further analysis of treatment regimens, we suggested that studies supporting one regimen may be due to longer cycles in that group.

Furthermore, the concurrent use of trastuzumab and anthracyclines has been proved with poor safety. In 2002, Seidman *et al.* (32) conducted a retrospective study to estimate cardiac dysfunction risk for patients receiving trastuzumab. The highest incidence (27%) occurred in patients receiving concomitant trastuzumab and an anthracyclines plus cyclophosphamide while significantly lower risk (13%) in patients receiving paclitaxel and trastuzumab. Bozovic-Spasojevic *et al.* (33) analyzed safety data from 1,765 patients from three clinical trials, 583 cases treated with concomitant trastuzumab and anthracyclines as neoadjuvant therapy, and concluded that the combination of the two drugs was associated with a significant increase in cardiotoxicity (OR 1.95, 95% CI: 1.16–3.29). A meta-analysis demonstrated that concomitant administration of anthracyclines with trastuzumab was moderately associated with an increased risk of cardiac-related adverse events (RR 1.97, 95% CI: 1.49–2.60, P<0.001) by fixed-effect model (34). Similar to theirs, the results of our meta-analysis also showed a significantly increased OR in anthracycline-containing group for LVEF. Therefore, our study supports that for neoadjuvant therapy of HER2-positive breast cancer, non-anthracycline regimens are less cardiotoxic and hematotoxic with equal efficacy and can be recommended as the preferred regimen.

It also should be recognized that tumors are heterogeneous diseases. HER2-negative tumor cells can be found in HER2-positive breast cancers. When the targeted therapy is emphasized and chemotherapy is subtracted, there may be insufficient treatment of HER2-negative tumor cells. Therefore, it is particularly crucial to clarify the indications for anthracycline therapy. An individual patient pooled analysis of patient cases from five adjuvant trials by Bartlett *et al.* (35) showed that patients whose tumors exhibited duplication of the Ch17 pericentromeric alpha satellite (CEP17) and topoisomerase 2-alpha (TOP2A) abnormalities had a 38% lower risk of recurrence when receiving anthracycline-containing chemotherapy compared to patients with normal CEP17 and TOP2A tumors, indicating that tumors with CEP17 duplications or TOP2A aberrations would benefit from anthracyclines. In addition, high expression of P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP), and ABC transporter protein breast cancer resistance protein (BCRP) can lead to anthracycline resistance, resulting in reduced chemotherapeutic efficacy (36-39). However, the biological effects of anthracyclines need to be more fully understood before this possibility can be translated into a real therapeutic strategy, especially in a disease as complex as breast cancer. On the other hand, in the neoadjuvant therapy setting without anthracycline, the combination of taxane, carboplatin, and anti-HER2 agents has been recommended as the standard regimen (40). However, its production of a high frequency of serious side effects such as diarrhea, neutropenia, anemia, and thrombocytopenia suggested that it would be poorly tolerated in patients (41,42). Fujita *et al.* (21) considered the protocols using carboplatin instead of anthracycline to not be de-escalation therapies for low-risk patients because of their high treatment intensity and rate of side effects. Several neoadjuvant chemotherapy regimens focusing on non-anthracyclines and non-platinum are being investigated, such as the DAPHNe trial (NCT03716180) (43) and Compass HER2 pCR trial (NCT04266249) (44). The efficacy and long-term follow-up outcomes of these studies will provide useful information for the omission of anthracyclines due to side effects or patient attitudes toward chemotherapy.

The main limitation of this meta-analysis was the heterogeneity of the included studies, except for the limited

number of included RCTs and the fact that neither of the two chemotherapy regimens and doses assessed is exactly the same in different studies. Besides, research into the survival analysis is limited, and relatively short follow-up time. Especially for hormone-receptor-positive breast cancer patients receiving adjuvant endocrine therapy, long-term follow-up remains important.

Conclusions

In conclusion, our study demonstrated no significant difference in pCR and BCS rates in HER2-positive breast cancer patients treated with targeted therapy combined with anthracycline-containing or anthracycline-free regimens, but higher cardiotoxicity can result from the anthracycline-containing regimen. This will provide new evidence for the removal or retention of anthracyclines in the current neoadjuvant treatment of HER2-positive breast cancer, and hopefully provide a reference for clinicians to choose treatment for patients. Given the limited number of RCTs included and the lack of reports on hormone receptor status, more studies with longer follow-up are needed to validate the current findings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4030/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4030/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.

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Supplementary

Table S1 Search strategies of this study in different databases

Search step	Search terms
PubMed	
#1	breast neoplasms: ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields])
#2	neoadjuvant therapy: ("neoadjuvant therapy"[MeSH Terms] OR ("neoadjuvant"[All Fields] AND "therapy"[All Fields]) OR "neoadjuvant therapy"[All Fields])
#3	Receptor, ErbB-2/ therapeutic use: (("receptor, erbb 2"[MeSH Terms] OR ("receptor"[All Fields] AND "erbb 2"[All Fields]) OR "erbb-2 receptor"[All Fields] OR "receptor erbb 2"[All Fields]) AND ("therapeutic use"[MeSH Subheading] OR "therapeutic"[All Fields] OR "therapeutic use"[All Fields] OR "therapeutic uses"[MeSH Terms] OR ("therapeutic"[All Fields] AND "uses"[All Fields]) OR "therapeutic uses"[All Fields] OR "therapeutic"[All Fields]))
#4	anthracycline: ("anthracyclin"[All Fields] OR "anthracyclines"[MeSH Terms] OR "anthracyclines"[All Fields] OR "anthracycline"[All Fields] OR "anthracyclins"[All Fields])
#5	#1 AND #2 AND #3 AND #4
Medline	
#1	breast neoplasms.af.
#2	neoadjuvant therapy.af.trastuzumab.af.
#3	Receptor, ErbB-2.af.
#4	anthracyclines.af.
#5	#1 AND #2 AND #3 AND #4
Embase	
#1	('human epidermal growth factor receptor 2 positive breast cancer'/exp OR 'human epidermal growth factor receptor 2 positive breast cancer')
#2	('neoadjuvant therapy'/exp OR 'neoadjuvant therapy')
#3	('anthracycline'/exp OR anthracycline)
#4	#1 AND #2 AND #3
Cochrane Library	
#1	"HER2-positive breast cancer" in All Text
#2	"neoadjuvant therapy" in All Text
#3	"anthracycline" in All Text
#4	#1 AND #2 AND #3

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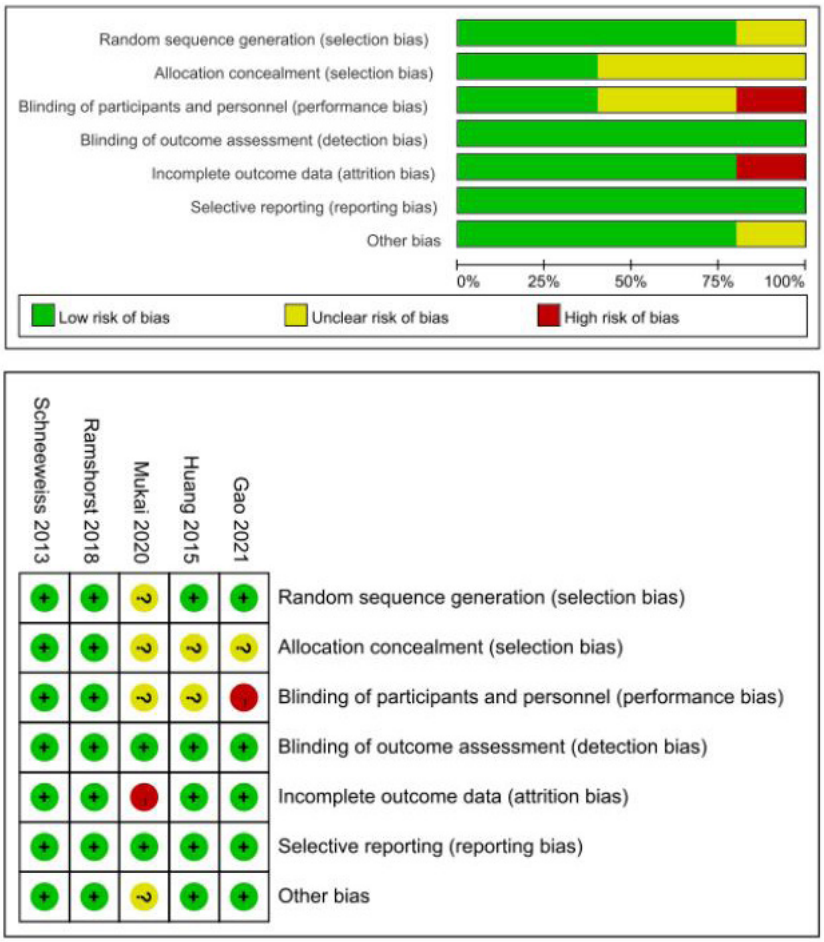

Figure S1 Risk of bias for the selected randomized controlled trials (RCTs).

Table S2 Newcastle-Ottawa scale for assessment of quality of included studies

Study, year (reference)	Selection				Comparability	Outcome			Quality score
	Representativeness of the exposed cohort (maximum:*)	Selection of the non-exposed cohort (maximum:*)	Ascertainment of exposure (maximum: *)	Demonstration that outcome of interest was not present at start of study (maximum:*)	Comparability of cohorts on the basis of the design or analysis (maximum:**)	Assessment of outcome (maximum:*)	Was follow up long enough for outcomes to occur (maximum:*)	Adequacy of follow up of cohorts (maximum:*)	
Horiguchi 2011 (23)	*	*	*	*	**	*		*	8
He 2022 (19)	*	*	*	*	**	*	*	*	9
Fujita 2022 (21)	*	*	*	*	*	*	*	*	8
Ueno 2020 (27)	*	*	*	*	**	*	*	*	9
Bayraktar 2012 (20)	*	*	*	*	*	*		*	7
Watanuki 2019 (28)	*	*	*	*	*		*	*	7

*, The asterisk (*) denotes the fulfillment of each criterion according to the Newcastle-Ottawa scale. * score as 1; ** score as 2.

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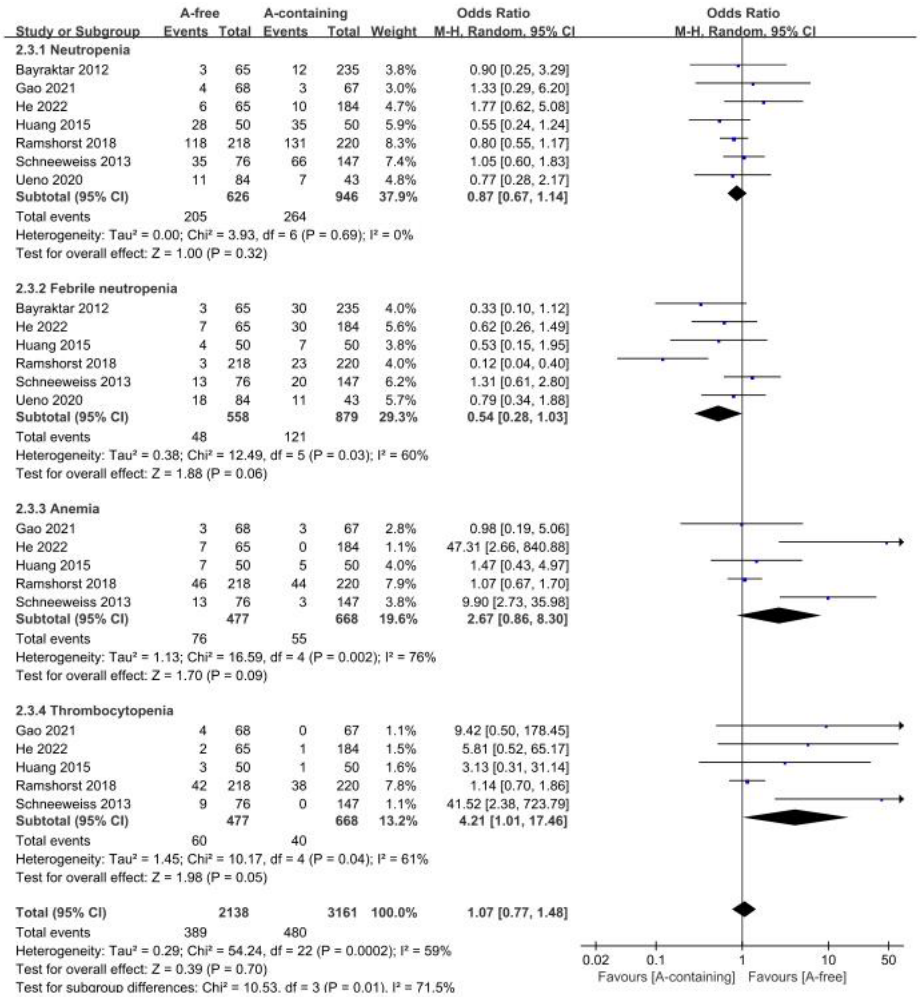

Figure S2 Forest plot showing the pooled odds ratios of the rate of hematological adverse events during neoadjuvant treatment.

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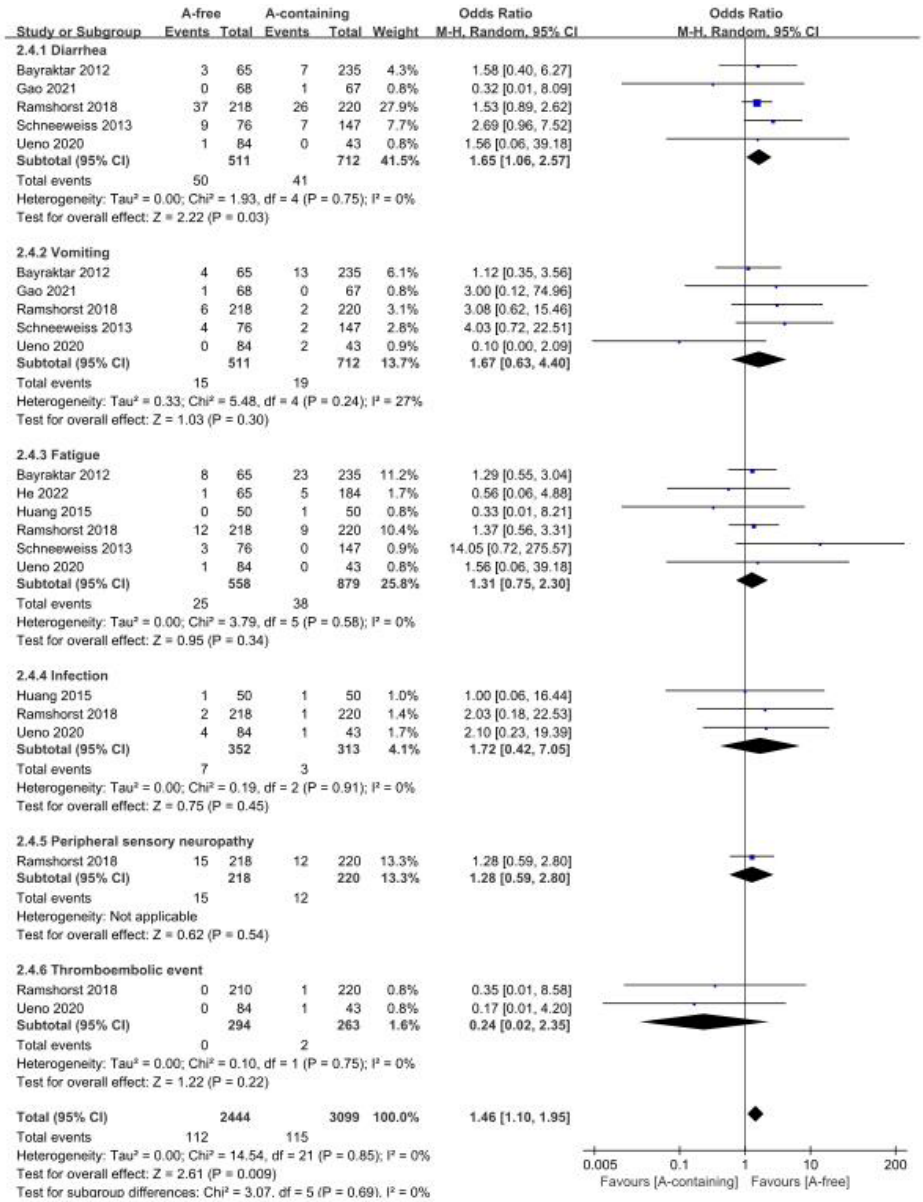

Figure S3 Forest plot showing the pooled odds ratios of the rate of other adverse events during neoadjuvant treatment.

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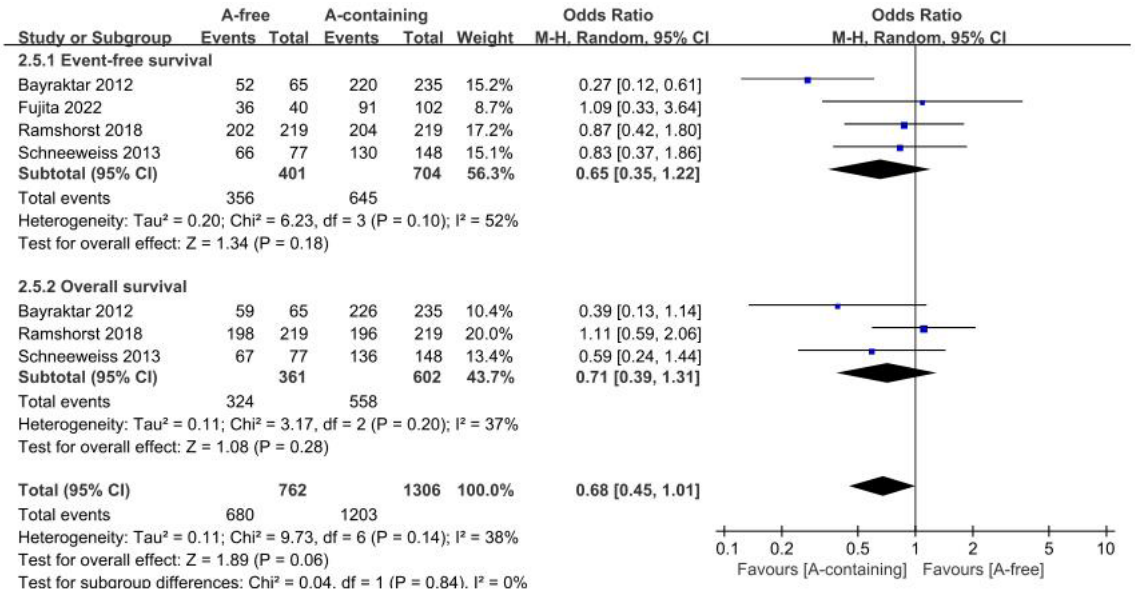

Figure S4 Forest plot showing the pooled odds ratios of event-free survival (EFS) and overall survival (OS).

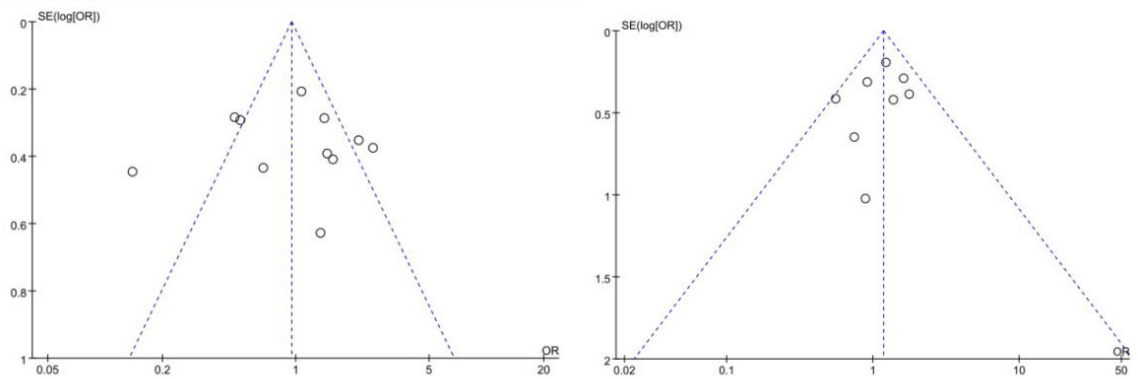

Figure S5 Funnel plot to assess the publication bias of the included studies in group of pathologic complete response (pCR) and breast-conserving surgery (BCS).

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