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Contrast-enhanced ultrasound for evaluating the pathologic response of breast cancer to neoadjuvant chemotherapy

A meta-analysis

Kun Jia, MD*, Li Li, MD, Xiao Jing Wu, MD, Mei Jin Hao, MBBS, Hong Yuan Xue, MD

Abstract

Objective: Recent reports have suggested that contrast-enhanced ultrasound (CEUS) can be used to monitor the pathologic responses of breast cancer (BC) to neoadjuvant chemotherapy (NAC); however, the diagnostic performance of CEUS in BC has yet to be confirmed. Thus, we conducted a meta-analysis of related studies to explore the relationship between CEUS and pathologic responses of BC to NAC.

Materials and methods: We searched PubMed, Embase, Web of Science, ScienceDirect, and China National Knowledge Infrastructure databases for studies published until September 31, 2018. Study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and then ORs with 95% CIs were pooled to estimate the prognostic role of CEUS for the pathologic responses of BC to NAC.

Results: Pooled meta-analysis of the 9 eligible studies that included 424 patients indicated the high performance of CEUS for monitoring pathologic responses to NAC (OR = 31.83, 95% CI: 16.69–60.67, $P < .001$), with no significant heterogeneity ($I^2 = 0.0\%$, $P = .529$). The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 87% (95% CI: 0.81–0.92), 84% (95% CI: 0.74–0.91), 5.5 (95% CI: 3.3–9.2), 0.15 (95% CI: 0.10–0.23), and 36 (95% CI: 18–70), respectively. An area under the curve of 0.92 (95% CI: 0.89–0.94) suggests a high ability for prognostic detection. Although Begg's funnel plot ($P = .057$) indicated the presence of publication bias among the included studies, the trim-and-fill method verified the stability of the pooled outcomes. Sensitivity analysis suggested that the pooled OR was robust.

Conclusion: Our results suggest that CEUS has a high diagnostic performance for the pathologic responses of BC to NAC. Further and better-designed studies should be performed to verify the clinical applications of CEUS for monitoring BC responses to NAC.

Abbreviations: CEUS = contrast-enhanced ultrasound, CI = confidence interval, NAC = neoadjuvant chemotherapy, OR = odds ratio, pCR = pathological complete response.

Keywords: breast cancer, contrast-enhanced ultrasound, neoadjuvant chemotherapy, pathologic response, prognosis

1. Introduction

Breast cancer (BC) is a major health problem and is the most common cancer in women worldwide, affecting 12% of all women and leading to 450,000 deaths each year.[1] Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced BC and inflammatory BC. NAC not only reduces tumor size to make surgery feasible but may also allow breast conserving surgery in women requiring a mastectomy. Achieving a pathological complete response (pCR) is a predictor of an improved disease free and overall survival, and it is used as a surrogate clinical endpoint for long-term outcome.[2–4] Notably, BC is highly heterogeneous with distinct molecular subtypes, and the same NAC chemotherapy regimen yields diverse responses. Therefore, clinically applicable biomarkers should be developed to predict the response of BC to NAC.

Contrast-enhanced ultrasound (CEUS) has gained vast interest in the last decade because of its capability to gather macro- and microvascular information in various organs. Thus, this technique can be used to understand the complexity of angiogenesis in different types of tumors.[5,6] CEUS is a quantitative kinetic imaging modality that assesses intravascular blood flow in breast tumors even at the capillary level. Some previous studies[7–15] suggested that CEUS can be used to monitor the pathologic responses of BC to NAC. However, the small sample size of each study might lack statistical power to draw definitive conclusions. Thus, we conducted a meta-analysis of related studies to explore the relationship between CEUS and pathologic responses of BC to NAC.

2. Materials and methods

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist.[16] The present meta-analysis was based on

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The authors have no conflicts of interest to disclose.

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previously published studies, and no ethical approval or patient consent was required. This study has been registered in PROSPERO (CRD42018111899).

2.1. Literature search

The PubMed, Embase, Web of Science, ScienceDirect, and China National Knowledge Infrastructure databases were searched for studies published until September 31, 2018. The following terms were used as keywords in the literature search by 2 individual authors (KJ and LL): "breast cancer," "neoadjuvant chemotherapy," and "contrast-enhanced ultrasound." We also performed a full manual search of the bibliographies of selected studies to identify additional studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: the study subjects were pathologically diagnosed with BC; studies that evaluated the association between CEUS and pathologic responses of BC to NAC; sufficient data available for calculating standardized odds ratios (ORs) with 95% confidence intervals (CIs). When several studies were available for the same cohort, we retained the one with the largest number of cases for analysis.

The exclusion criteria were as follows: lack of sufficient survival data, inability to obtain the full text, reviews, letters, case reports, conference abstracts, and duplicate articles.

2.3. Data extraction

Two researchers (KJ and XJW) independently extracted detailed information using a predesigned data extraction form and assessed the quality of the individual studies. Disagreements were resolved by discussion or consensus with a third reviewer (HYX). After strict selection and evaluation, basic information, including first author, publication year, country, age, number of patients, pathologic response characteristics, tumor stage, and study period, was extracted from the included studies. The ORs and 95% CIs obtained directly from the published articles were integrated in the meta-analysis according to the study conducted.

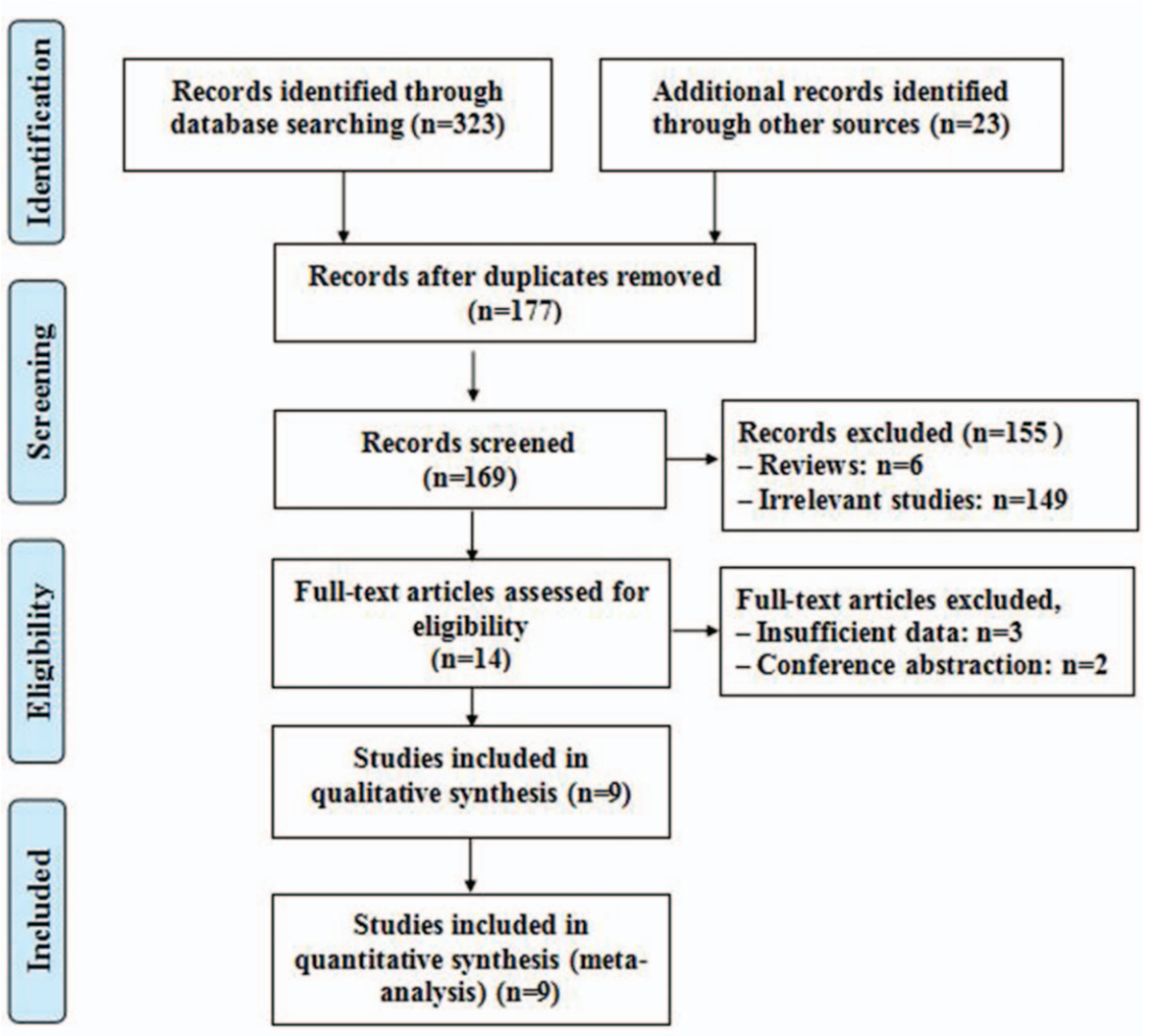

Figure 1. Flow diagram of the inclusion and exclusion of studies.

2.4. Quality assessment

The quality of the included studies was assessed by 2 authors (KJ and MJH) using the Newcastle–Ottawa quality assessment scale (NOS)[17] and studies awarded with 6 or higher were classified as high-quality studies.[18,19] Any disagreement was resolved by discussion and consensus.

2.5. Statistical analysis

STATA 14.0 software (StataCorp, College Station, TX) was used to analyze the extracted data. The predictive value of CEUS in this meta-analysis was performed using the pooled OR and its 95% CI. Heterogeneity between studies was evaluated using the Cochran Q test and the I^2 test. Studies were considered to have high, moderate, or low heterogeneity when I^2 was >75%, 50% to 75%, or 25% to 50%, respectively.[20] Fixed-effect models were adopted only for a $P>.1$ or $I^2<50\%$. Otherwise, random-effect models were applied to calculate the pooled OR. To evaluate publication bias, a funnel plot, Egger's test, and Begg's test were used. If the publication bias existed, we used the trim-and-fill method to add the potentially missing studies for adjustment for the funnel plot's asymmetry and observed the variation in the pooled OR (95% CI).[21] If the pooled OR (95% CI) changed weakly or remained unchanged, then the result was robust. Stability of results was analyzed and assessed by sensitivity analysis. Two-tailed test was applied, with a $P<.05$ level of significance.

3. Results

3.1. Literature search

Figure 1 shows the inclusion process, in which 346 potentially relevant studies were screened. After scanning titles and abstracts, 177 studies were excluded for duplication, leaving 14 to be read in full. Eventually, the 9 remaining articles involving 424 patients were in included in this meta-analysis.

3.2. Characteristics and quality assessment of the included studies

Table 1 shows the characteristics and quality assessment of the 9 included studies. The sample sizes of the 9 papers ranged from 18 to 63 with a total of 424 participants. Of these studies, 7 originated from China, one from Japan, and one from the United States. The scores of the eligible studies from the NOS ranged from 6 to 7, with a mean of 6.8, indicating that the included studies were of high quality.

3.3. Relationship between CEUS and the NAC response

The pooled results indicated the high performance of CEUS for monitoring pathologic responses to NAC (OR = 31.83, 95% CI: 16.69–60.67, $P<.001$; Fig. 2), with no significant heterogeneity ($I^2=0.0\%$, $P=.529$). The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic OR were 87% (95% CI: 0.81–0.92), 84% (95% CI: 0.74–0.91), 5.5 (95% CI: 3.3–9.2), 0.15 (95% CI: 0.10–0.23), and 36 (95% CI: 18–70), respectively (Fig. 3). The sROC AUC of CEUS for the pathologic responses of BC to NAC was 0.92 (95% CI: 0.89–0.94; Fig. 4).

3.4. Subgroup analyses

We performed 4 subgroup analyses (Table 2): with published language; with pCR or response; sample size; and country. No significant deviations from the main results were found for any of the subgroups.

3.5. Sensitivity analysis and publication bias assessment

Sensitivity analyses implied that the pooled results of our meta-analysis are robust (Fig. 5). Publication bias was observed among studies using Begg's ($P=.175$; Fig. 6A) and Egger's ($P=.057$; Fig. 6B) tests. Results of the trim-and-fill method showed that 3 necessary studies were missed. After filling these 3 in the comprehensive analysis, the adjusted fixed-effects pooled OR of 21.38 (95% CI: 11.760–38.885, $P<.001$; Fig. 6C) calculated using the trim-and-fill method was consistent with that in the original analysis (OR = 31.83, 95% CI: 16.69–60.67, $P<.001$).

4. Discussion

BC is a vascular-dependent lesion, and its growth, infiltration, and metastasis are closely related to neo-vascularization.[22] Folkman[22] proposed that the inhibition of angiogenesis arrests solid tumors. Angiogenesis occurs at the capillary level; thus, CEUS may be one of the most direct imaging tools for visualizing perfusion changes in the tumor. CEUS can objectively depict tumor vascularity and intratumoral perfusion by reconstructing stereoscopic images.[23]

Table 1

Characteristics of included studies.

First author	Publication year	Country	Age*, years	Number of patients	Pathological response	Clinical stage	Study period	NOS score
Amioka et al	2016	Japan	53.0 ± 10.2	63	pCR	I–III B	2012–2015	7
Cui et al	2014	China	45–62	48	pCR	NA	2011–2013	7
Guo et al	2015	China	58.2 ± 3.4	54	Response	II B–III	2013–2015	7
Han et al	2018	China	44.63 ± 11.25	55	Response	II A–III C	2015–2017	7
Jia et al	2016	China	28–63	48	pCR	II–III	2010–2012	7
Lee et al	2017	USA	24–64	18	pCR	NA	2014–2015	6
Li et al	2015	China	45.36 ± 3.40	60	pCR	II B–III	2011–2014	7
Wan et al	2018	China	50.9 ± 9.6	51	pCR	NA	2015–2016	6
Zhang et al	2014	China	44.04 ± 7.61	27	response	II B–III	2011–2013	7

NOS = Newcastle–Ottawa scale, pCR = pathological complete response.

* Continuous variable is presented as means ± SD or range.

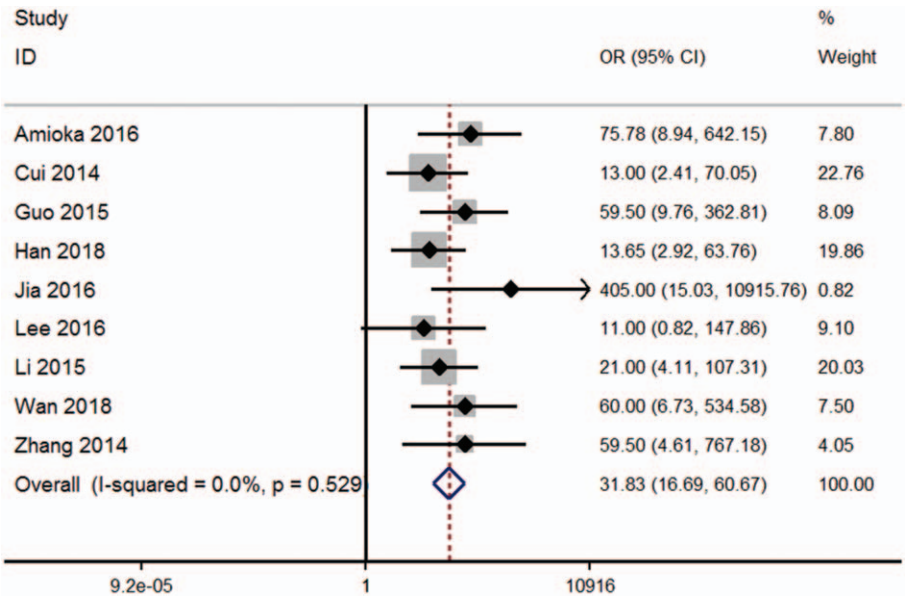

Figure 2. Forest plot of the association of CEUS with the neoadjuvant chemotherapy response. CEUS = contrast-enhanced ultrasound, NAC = neoadjuvant chemotherapy.

In the present meta-analysis, we searched several major databases for studies exploring the relationship between CEUS and pathological response of BC to NAC. By combining the data from the 9 studies, CEUS presented a diagnostic sensitivity of 87%, a specificity of 84%, and an AUC of 0.92. These 3 representative parameters confirmed the accuracy of CEUS as a valuable imaging method for assessing the response of BC to NAC. In addition, the diagnostic OR estimated for CEUS was 36 (95% CI: 18–70). This benign high-DOR value indicated that CEUS could monitor response in NAC accurately.

Various conventional imaging modalities are used in the preoperative setting, including mammography, ultrasound, and magnetic resonance imaging (MRI). A common potential limitation of mammography, ultrasound, and MRI imaging is their inability to distinguish viable tumor tissue from fibrotic scar tissue; thus, they are incapable of accurately predicting

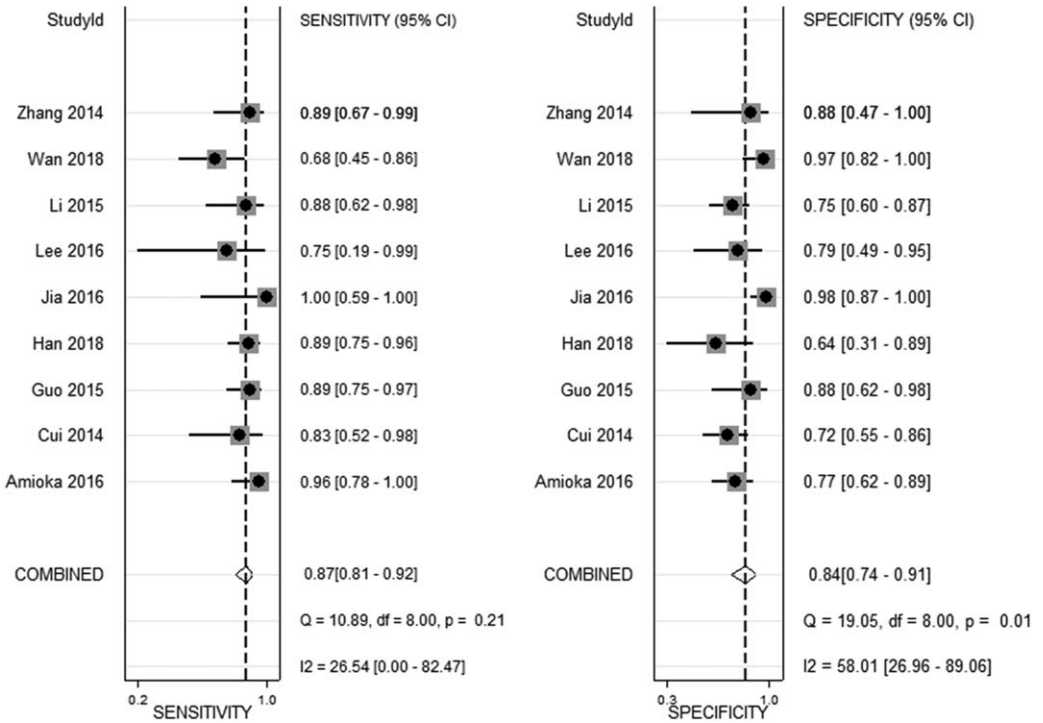

Figure 3. Forest plots of sensitivity and specificity for CEUS predicting NAC response. CEUS = contrast-enhanced ultrasound, NAC = neoadjuvant chemotherapy.

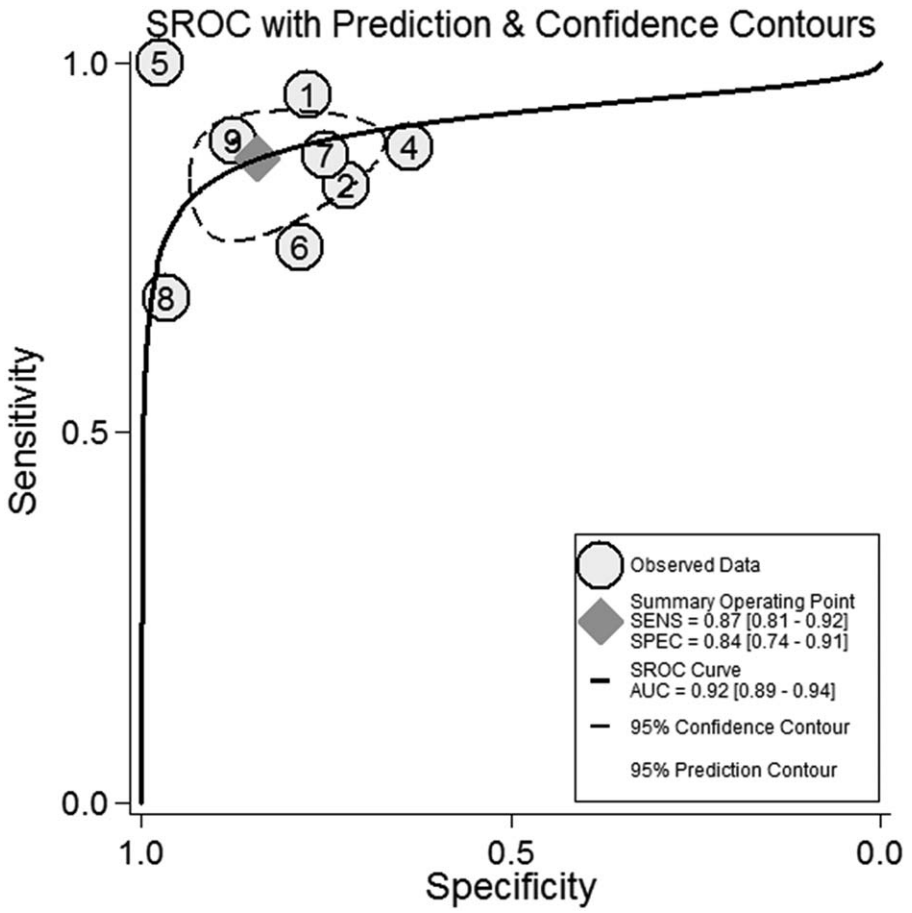

Figure 4. Summary ROC curve for the nine included studies. Numbers in brackets are 95% CIs. CEUS = contrast-enhanced ultrasound, NAC = neoadjuvant chemotherapy, AUC = area under ROC curve, SENS = sensitivity, SPEC = specificity.

response. Response as assessed by a reduction in tumor size often manifests later than changes in underlying tumor characteristics,[24] such as vascularization and vascular permeability, cellularity, metabolism, and biochemistry.[25,26] Thus, imaging modalities, such as CEUS, dynamic-contrast enhanced MRI (DCE-MRI), and fluorodeoxyglucose positron emission tomography, and computed tomography (FDG-PET/CT), which can quantify tumor functions, are becoming increasingly important in the evaluation and prediction of therapy response. Among different approaches, DCE-MR is especially promising due to its ability to quantitatively measure kinetic parameters related to perfusion and permeability of tumor.[25,27] Several clinical studies in the NAC setting have demonstrated that tumor reduction measured by DCE-MRI is in concordance with pathologic response, and the measurement can be a prognostic indicator of survival.[27–30] However, a recently published

Table 2

Subgroup analysis.

	Number of studies	OR (95% CI)	*P*	I^2 (*P* value)
Language				
English	4	58.40 (17.72–192.44)	<.001	0. 0%(.396)
Chinese	5	22.86 (10.45–50.00)	<.001	0.0% (.647)
Pathological response				
pCR	6	32.19 (14.26–72.71)	<.001	4.4% (.388)
Response	3	31.04 (11.06–87.13)	<.001	0.0% (.399)
Sample size				
≥50	5	34.99 (15.83–77.35)	<.001	0.0% (.579)
<50	4	26.37 (8.75–79.45)	<.001	27.6% (.246)
Country				
China	7	29.98 (14.78–60.79)	<.001	23.1% (.254)
Non-China	2	40.90 (8.45–198.02)	<.001	0.0% (.453)

CI = Confidence interval, OR = odds ratios, pCR = pathological complete response.

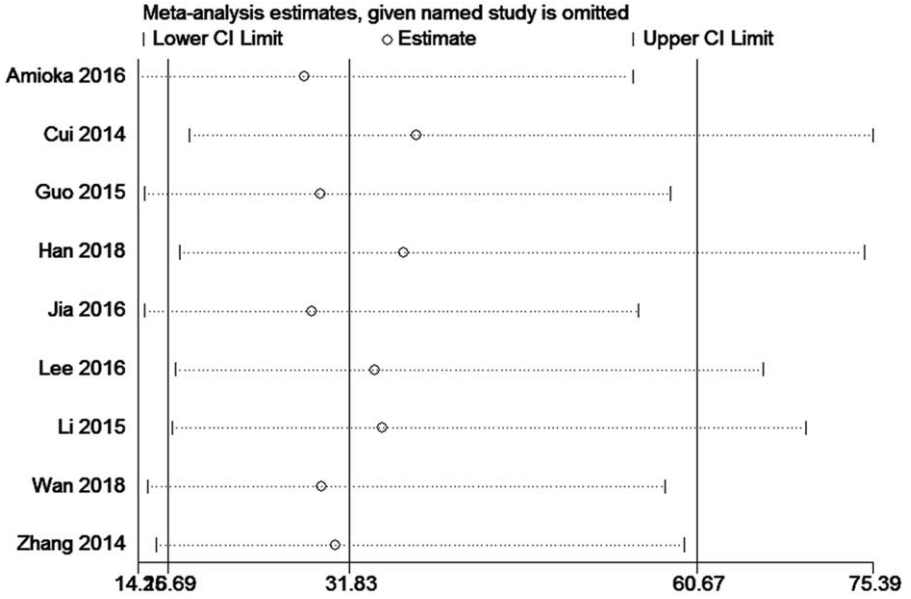

Figure 5. Sensitivity analysis of the relationships between CEUS and the NAC response. CEUS = contrast-enhanced ultrasound, NAC = neoadjuvant chemotherapy.

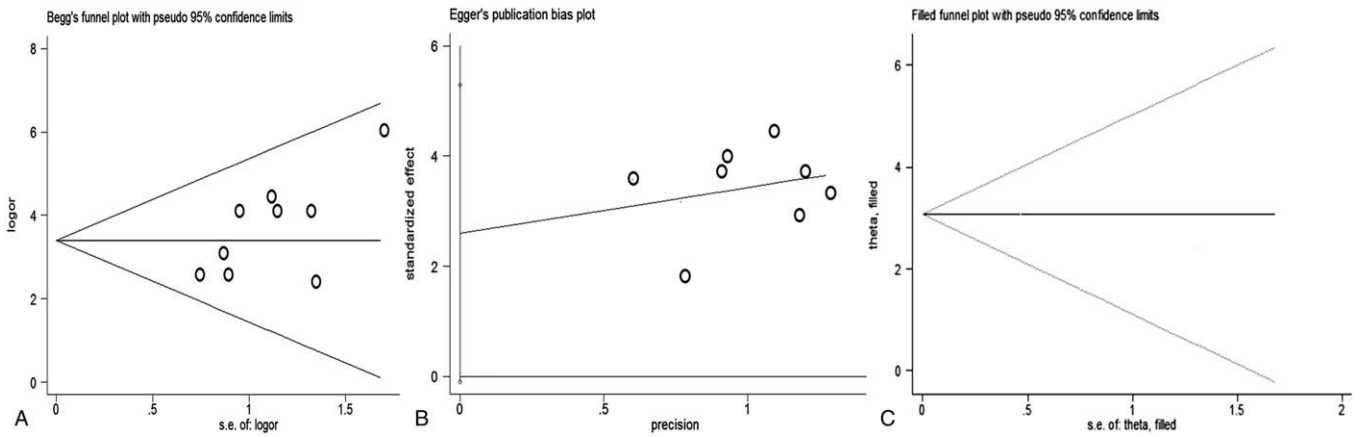

Figure 6. Funnel plots for publication bias. (A) Begg's test, (B) Egger's test, and (C) trim-and-fill method.

systematic review has shown that DCE-MRI has a high specificity (50%–97%) versus only moderate sensitivity (25%–100%) in the prediction for pCR. FDG-PET/CT is correlated with increased glucose metabolism in BC. Metabolic reduction detected between baseline and the early phase of NAC can provide early information on the potential BC response. By contrast, FDG-PET/CT has a high sensitivity (86%–90%) versus only moderate specificity (40%–85%) in pCR prediction.[31–33] The contrast agents used in CEUS remain only within the intravascular bed and do not diffuse into the interstitial space; hence, the reliability of CEUS is high. CEUS is widely available and can be performed in patients who cannot undergo DCE-MRI. Moreover, DCE-US can directly visualize perfusion status in the tumor. Notably, for deep-seated tumors and tumors with low vascularity, CEUS cannot delineate microvasculature and microcirculation features and monitor BC responses to NAC.[34] However, the varying results in the separate studies showed that the usefulness of the various imaging parameters in predicting the response to NAC in BC was still not clearly defined. Nevertheless, each modality offers unique and complementary information on several clinically relevant tumor characteristics.

We believe the conclusions drawn from this study are important but should be interpreted with caution because of several limitations. First, in a meta-analysis of published studies, publication bias is an inevitable problem. Second, the analysis used pooled data (individual data were not available), which restricted us from performing a more detailed relevant analysis and obtaining more comprehensive results. Third, the sample sizes of comparative studies available in the literature are relatively small, which may contribute to an overestimation of diagnostic accuracy. Fourth, most of the included studies were conducted in China and published in unknown magazines, and this may lead to limited generalizability.

In conclusion, the findings of our study demonstrated that CEUS modality holds a relatively high sensitivity and specificity in the evaluation and prediction of the response of BC to NAC. Nonetheless, a variety of issues should be considered when assessing CEUS techniques for estimating BC responses to NAC, and large-scale and well-designed clinical trials are needed to assess the technique's diagnostic value.

Author contributions

Conceptualization: Kun Jia, Li Li.
Data curation: Li Li, Xiao Jing Wu, Mei Jin Hao, Hong Yuan Xue.
Methodology: Mei Jin Hao.
Software: Hong Yuan Xue.
Writing – original draft: Xiao Jing Wu.
Writing – review & editing: Kun Jia.

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