Original Article

Diagnostic performance of contrast-enhanced ultrasound combined with shear wave elastography in differentiating benign from malignant breast lesions: a systematic review and meta-analysis

Xinyu Chen[1], Hairong Yu[1], Na Wei[1], Berat Bersu Ozcan[2], Guifang An[1], Qiong Wu[1], Ning Wang[1]

[1]Department of Ultrasound, Dongzhimen Hospital of Beijing University of Chinese Medicine, Beijing, China; [2]Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Contributions: (I) Conception and design: X Chen, N Wang; (II) Administrative support: N Wang; (III) Provision of study materials or patients: X Chen, G An; (IV) Collection and assembly of data: H Yu, Q Wu; (V) Data analysis and interpretation: X Chen, N Wei; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ning Wang, MM. Department of Ultrasound, Dongzhimen Hospital of Beijing University of Chinese Medicine, Hai Yun Cang on the 5th, Dongcheng District, Beijing 100700, China. Email: A3018@bucm.edu.cn.

Background: The value of contrast-enhanced ultrasound (CEUS), shear wave elastography (SWE) and their combination in the diagnosis of benign and malignant breast lesions have not been systematically evaluated. This study aimed to evaluate the diagnostic value of CEUS combined with SWE in benign and malignant breast lesions.

Methods: We searched six electronic databases for literature to evaluate the value of CEUS combined with SWE in the diagnosis of benign and malignant breast lesions from inception to May 2023. Review Manager 5.4 (Cochrane), Meta-DiSc 1.4, and Stata 14.0 (StataCorp) were used for meta-analysis. The pooled sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and the area under the curve (AUC) were calculated to evaluate the diagnostic performance.

Results: Ultimately, 17 studies were analyzed including 1,962 lesions in total. The overall quality of the included literature was acceptable, and no significant publication bias was found among the included studies. The pooled diagnostic performance measures for CEUS were as follows: SEN: 0.86 [95% confidence interval (CI): 0.84–0.88], SPE: 0.78 (95% CI: 0.75–0.80), PLR: 4.10 (95% CI: 2.86–5.90), NLR: 0.20 (95% CI: 0.15–0.25), DOR: 23.68 (95% CI: 16.77–33.44), and AUC: 0.90 (95% CI: 0.87–0.93); while, for SWE, SEN: 0.83 (95% CI: 0.81–0.86), SPE: 0.81 (95% CI: 0.78–0.83), PLR: 4.36 (95% CI: 3.18–5.97), NLR: 0.22 (95% CI: 0.17–0.29), DOR: 23.13 (95% CI: 14.70–36.40), and AUC: 0.90 (95% CI: 0.87–0.92). The measures for the pooled diagnostic performance of CEUS combined with SWE were as follows: SEN: 0.92 (95% CI: 0.90–0.94), SPE: 0.87 (95% CI: 0.85–0.89), PLR: 7.10 (95% CI: 5.24–9.61), NLR: 0.11 (95% CI: 0.07–0.16), DOR: 83.51 (95% CI: 49.67–140.39), and AUC: 0.96 (95% CI: 0.94–0.98). There was no statistically significant difference in SEN, SPE, and accuracy (ACC) between CEUS and SWE ($P>0.05$), but they were significantly lower than those of CEUS combined with SWE ($P<0.001$).

Conclusions: The diagnostic performance of CEUS combined with SWE is higher than that of using CEUS or SWE alone and can further improve the diagnosis of breast lesions.

Keywords: Contrast-enhanced ultrasound (CEUS); shear wave elastography (SWE); diagnosis; breast lesions; meta-analysis

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Introduction

Breast cancer is a malignant tumor originating from the ductal epithelium of the breast and the peripheral ductal epithelium. It is one of the most common malignant tumors and the main cause of cancer-related death in women in the United States (1). The incidence of breast cancer in women is second only to that of uterine cancer, with a tendency toward a greater incidence in younger individuals. After early treatment, the 10-year survival rate can reach more than 90% (2). Early detection and diagnosis can provide a scientific reference for the clinical treatment of patients with breast cancer in a timely manner and is thus critical to optimize the recovery of patients (3).

Mammography is the first choice for clinical screening and diagnosis of breast masses (4). In the past, conventional ultrasound was used to differentiate between benign and malignant breast lesions. However, it is largely limited by the scope of conventional morphological diagnosis, insufficient observation indicators, strong subjectivity in diagnosis, and susceptibility to factors such as machine performance and operator manipulation; thus, relying solely on conventional ultrasound to diagnose and grade tumors may not be sufficient (5). In recent years, rapid contrast-enhanced ultrasound (CEUS) and shear wave elastography (SWE) have been applied to the clinical diagnosis of breast lesions (6). CEUS can dynamically observe the blood supply in the tumor, qualitatively and quantitatively evaluate the blood flow changes in the tumor, and discern between benign and malignant breast lesions (7). SWE is able to differentiate between benign and malignant lesions via the elastic hardness of tissues according to elastic grading, elastic parameters, and the elastic parameter strain rate (8).

A few researchers have studied the value of CEUS, SWE, and their combination in the diagnosis of benign and malignant breast lesions (9,10), but they have not systematically evaluated their diagnosis performance. The advantages and disadvantages of these methods for the diagnosis of benign and malignant breast lesions cannot yet be confirmed. Therefore, the purpose of this study was to evaluate the diagnostic value of CEUS combined with SWE in differentiating between benign and malignant breast lesions. We present this article in accordance with the PRISMA-DTA reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-333/rc).

Highlight box

Key findings
- The combination of contrast-enhanced ultrasound (CEUS) and shear wave elastography (SWE) has high value in distinguishing between benign and malignant breast lesions.

What is known and what is new?
- Both CEUS and SWE have certain diagnostic value for breast cancer.
- Our study aimed to determine whether the combined use of CEUS and SWE can help improve diagnostic performance.

What is the implication, and what should change now?
- The diagnostic value of combining CEUS and SWE is higher than that of using CEUS or SWE alone, which can further improve the accuracy of breast lesion diagnosis.

Methods

Literature search strategy

PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI) database, and Wanfang Database were searched systematically from inception to May 2023. The search terms and strategy were based on the combination of the following keywords: (“breast lesions” or “breast tumor” or “breast cancer” or “breast neoplasm”) AND (“diagnosis” or “diagnostic”) AND (“contrast-enhanced ultrasound” or “CEUS” or “shear wave elastography” or “SWE” or “ultrasound elastography”). A comprehensive search of the literature was carried out, which had no limitation on the publishing language or publishing status.

Study selection

The inclusion criteria were as follows (11,12): (I) benign and malignant breast lesions not clearly definable before diagnosis; (II) diagnosis of the same group of lesion by CEUS, SWE, and their combination, respectively; (III) a gold standard of pathological and histological diagnosis, such as puncture biopsy or surgical pathological examination; (IV) 4-grid table data directly or indirectly derivable from the literature [true-positive (TP) lesions, false-positive (FP) lesions, false-negative (FN) lesions, and true-negative (TN) lesions]; and (V) total number of lesions ≥20. Meanwhile, the exclusion criteria were as follows: (I) total number of lesions <20; (II) a gold standard other than pathological histology; and (III) case reports, reviews, or other literature from which 4-grid table data could not be derived.

Data extraction

The search and data extraction were performed by two reviewers (Chen X and Wei N), and any disagreements were resolved by consulting a third reviewer (Wang N). The following characteristics of studies were extracted: the first author, year of publication, country, study design, reference standard and breast lesions, sample size of patients and lesions, patient characteristics (mean age), CEUS and SWE information, and diagnostic performance. The primary outcomes were sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and area under curve (AUC).

Quality assessment

Two authors (Yu H and Wu Q) independently assessed the risk bias and applicability concerns of each article based on the Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) tool (13). The QUADAS-2 tool is principally composed of four parts: patient selection, index test, reference standard, flow, and timing. All components were evaluated in terms of bias risk, and the first three components were evaluated in terms of clinical applicability.

Statistical analysis

A meta-analysis was performed using Review Manager 5.4 (Cochrane), Meta-DiSc 1.4, and Stata 14.0 (StataCorp, College Station, TX, USA). The overall diagnostic accuracy (ACC) of CEUS, SWE, and their combination for benign and malignant breast lesions was evaluated by calculating the pooled SEN, SPE, PLR, NLR, and DOR and by drawing the summary receiver operating characteristic (SROC) curve, drafting forest plots, and calculating the AUC. We calculated the Spearman correlation coefficient to evaluate whether there was threshold effect among the included literature. If the Spearman correlation coefficient was less than 0 and $P>0.05$, it indicated that there was no threshold effect between the studies, so the study could be combined for homogeneous analysis. Otherwise, the study indicators could not be combined due to the presence of the threshold effect. We further combined the I^2 value to quantitatively determine the size of the heterogeneity. If $P<0.1$ or $I^2>50\%$, then a high degree of heterogeneity between the studies was indicated, and a random effects model would be required for statistical analysis; otherwise, a fixed effects model would be used. In addition, the Deeks' funnel plot was used to detect the potential publication bias.

Results

Search process

Figure 1 illustrates the process of evaluating articles for inclusion in our review and meta-analysis. The search strategy yielded a total of 609 articles from all databases, and 134 duplicate records were removed after the initial screening. During the screening of the titles and abstracts, 386 records were excluded. After careful full-text review, 72 articles were excluded from the screening, including 12 review articles, 45 articles lacking relevant data, and 15 articles with an ineligible study design. A total of 17 eligible studies were included in our systematic review and meta-analysis (14-30).

Characteristics of the included studies

The detailed characteristics of the 17 eligible studies are summarized in *Table 1*. Apart from 1 (5.9%) study from Austria, all the articles were all from China. The study design included 8 (47.1%) retrospective studies and 9 (52.9%) prospective studies. The reference standard for the diagnosis of benign and malignant breast lesions in all studies was pathology. A total of 1,908 patients with 1,962 lesions were included in the study, comprising 935 (47.7%) malignant lesions and 1,027 (52.3%) benign lesions.

Results of the quality assessment

The quality evaluation of the included literature was conducted based on the QUADAS-2 tool, and the results are shown in *Figure 2*. All studies had clear reference standards, and the participants had undergone reference standard examination, which indicated no confirmation bias was present. Some studies (15,16,19-21,23,26,27) demonstrated risk of bias and applicability concerns in the "patient selection" and "index test" items, but they were all at an "uncleared risk". The above evaluation results indicated that the overall quality of the included studies was acceptable.

Results of the meta-analysis

Heterogeneity analysis

The Spearman correlation coefficient and P value were

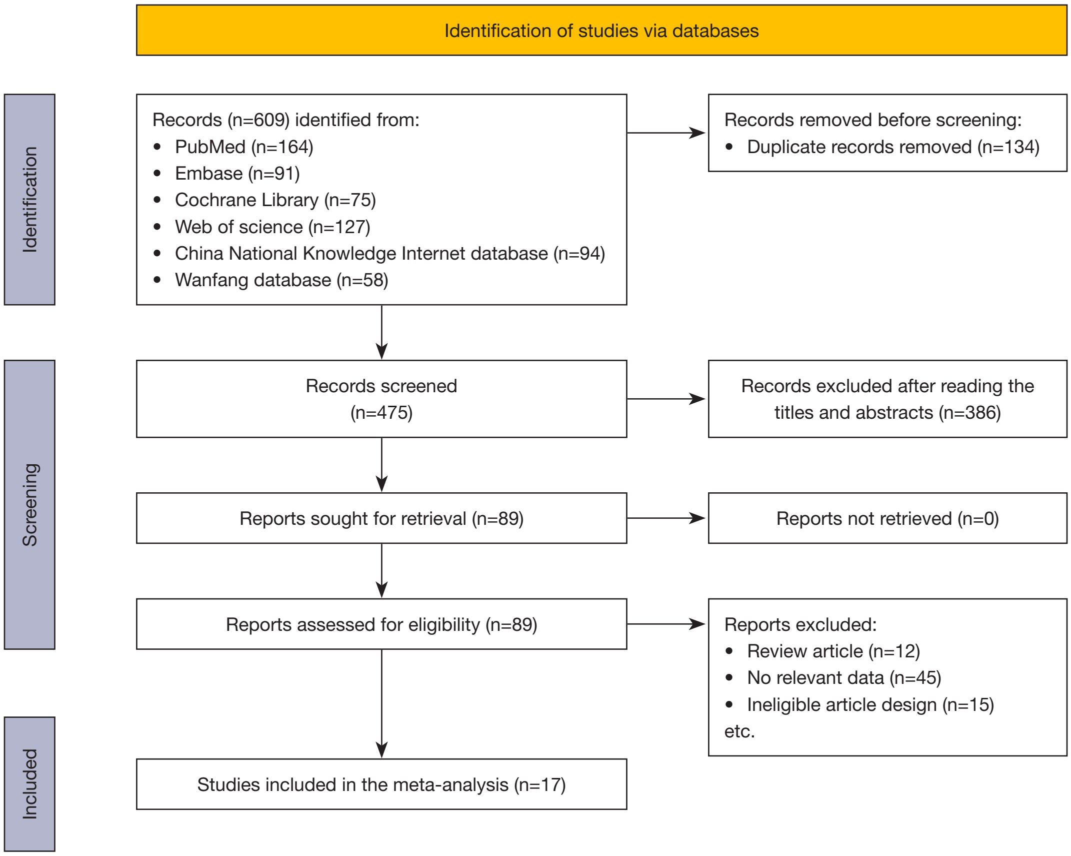

Figure 1 Flowchart of the literature search and study selection.

used to test the threshold effect. The results showed that Spearman correlation coefficient was 0.209 (P=0.372) for CEUS, 0.133 (P=0.612) for SWE, and 0.020 (P=0.940) for the combination of CEUS and SWE, suggesting that no threshold effect was present for the three diagnostic methods. The I^2 value was >50%, indicating that there was heterogeneity between the studies, which might be related to the control population and the test method. Therefore, the random effects model was used for statistical analysis.

Diagnostic ACC for each included study

Information on the CEUS or SWE system information used and the diagnostic performance in differentiating benign from malignant breast lesions in each included study are presented in *Table 2*. The ranges of diagnostic ACC for CEUS, SWE, and their combination were 0.647–0.921, 0.706–0.962, and 0.769–0.972, respectively. The combination of CEUS and SWE yielded the highest SEN and SPE reported in a single study, with values of 0.984 and 1.000, respectively.

Pooled diagnosis ACC of CEUS

The overall pooled SEN and SPE were 0.86 (95% CI: 0.84–0.88; I^2=67.4%) and 0.78 (95% CI: 0.75–0.80; I^2=86.6%), respectively (*Figure 3*). The pooled PLR, NLR, and DOR were 4.10 (95% CI: 2.86–5.90; I^2=89.9%), 0.20 (95% CI: 0.15–0.25; I^2=50.0%), and 23.68 (95% CI: 16.77–33.44; I^2=39.6%), respectively. The AUC of the SROC was 0.8996, and the Q value of the SROC was 0.8308.

Pooled diagnosis ACC of SWE

The meta-analysis results of the ACC of SWE in the diagnosis of benign and malignant breast lesions are shown in *Figure 4*. The overall pooled SEN and SPE were 0.83 (95% CI: 0.81–0.86; I^2=72.3%) and 0.81 (95% CI: 0.78–0.83; I^2=84.8%), respectively. The pooled PLR, NLR, and DOR were 4.36 (95% CI: 3.18–5.97; I^2=82.3%), 0.22 (95% CI: 0.17–0.29; I^2=68.3%), and 23.13 (95% CI: 14.70–36.40; I^2=64.3%), respectively. The AUC of the SROC was 0.8982,

Table 1 Main characteristics of the studies included in the meta-analysis

Study	Country	Study design	Reference standard	No. of patients	No. of lesions	Malignant lesions	Benign lesions	Age (years)†
Liu 2019 a	China	Prospective	Pathology	118	118	44	74	42.78±10.32
Li 2023	China	Prospective	Pathology	204	218	96	122	45 (22 to 74)
He 2023	China	Retrospective	Pathology	26	26	7	19	41.16±13.50
Xiang 2017	China	Retrospective	Pathology	62	66	13	53	49.3±12.1
Chen 2022	China	Prospective	Pathology	78	78	16	62	NR
Kapetas 2019	Austria	Prospective	Pathology	124	124	65	59	52 (18 to 82)
Li 2020	China	Retrospective	Pathology	178	181	67	114	NR
Ding 2021	China	Retrospective	Pathology	109	109	78	31	48.5±10.4
Hou 2021	China	Retrospective	Pathology	120	120	64	56	NR
Wang 2022	China	Prospective	Pathology	102	128	86	42	41.89±10.26
Wu 2021	China	Retrospective	Pathology	98	98	42	56	41.15±12.21
Shen 2022	China	Prospective	Pathology	85	76	44	32	46.2±12.6
Qi 2021	China	Prospective	Pathology	158	170	114	56	53.34±13.33
Liu 2019 b	China	Retrospective	Pathology	85	85	39	46	43.6±14.4
Gong 2021	China	Prospective	Pathology	112	112	47	65	NR
Hu 2021	China	Retrospective	Pathology	134	138	49	89	49±14
Yan 2019	China	Prospective	Pathology	115	115	64	51	53.95±8.9

†, value was presented as mean ± SD or median (range). NR, not reported; SD, standard deviation.

and the Q value of the SROC was 0.8293.

Pooled diagnosis ACC of CEUS combined with SWE

The meta-analysis results of the ACC of CEUS combined with SWE in the diagnosis of benign and malignant breast lesions are shown in *Figure 5*. The overall pooled SEN and SPE were 0.92 (95% CI: 0.90–0.94; I^2=66.5%) and 0.87 (95% CI: 0.85–0.89; I^2=73.8%), respectively. The pooled PLR, NLR, and DOR were 7.10 (95% CI: 5.24–9.61; I^2=67.1%), 0.11 (95% CI: 0.07–0.16; I^2=67.1%), and 83.51 (95% CI: 49.67–140.39; I^2=53.5%), respectively. The AUC of the SROC was 0.9565, and the Q value of the SROC was 0.8995.

Pairwise comparisons

The pooled results of the meta-analysis of CEUS, SWE, and their combination in diagnosing benign and malignant breast lesions are presented in *Table 3*, while their pairwise comparisons for the diagnostic performance are presented in *Table 4*. It can be seen that CEUS has a higher SEN than does SWE, a lower SPE, and a similar DOR and AUC; meanwhile CEUS combined with SWE has a higher SEN, SPE, DOR, and AUC than does CEUS alone or SWE alone (*Table 3*). In the comparison of the diagnostic performance of the three techniques in pairs, no statistical difference in the diagnostic outcomes of SEN, SPE, or ACC between CEUS and SWE was found (P>0.05). However, the SEN, SPE, and ACC of CEUS combined with SWE were indeed higher than those of CEUS alone or SWE alone (P<0.001).

Publication bias

By drawing Deeks' funnel plots separately and using linear regression to test the symmetry of the funnel plots, we found that the asymmetry-testing P values for the diagnostic performance of CEUS, SWE, and their combination for benign and malignant breast lesions were 0.64, 0.58, and 0.82, respectively, indicating that the funnel plots were symmetric and that there was no publication bias, as shown in *Figure 6*.

Discussion

Ultrasound has become a common clinical tool for

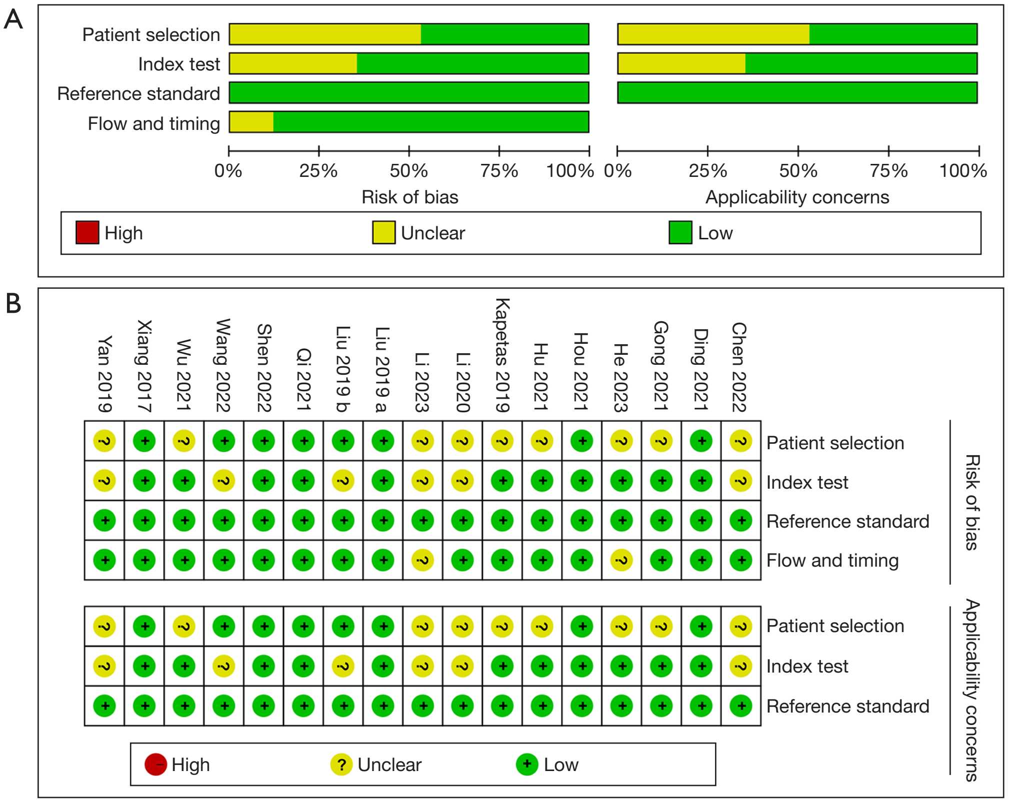

Figure 2 Risk of bias according to the Quality Assessment of Diagnostic Accuracy Studies questionnaire. (A) Review authors' judgements concerning each domain presented as percentages across included studies. (B) Review authors' judgements concerning each domain for each included study.

examining breast tumors. However, the conventional 2-dimensional ultrasound images of both benign and malignant breast masses often share similar features, leading to situations where different diseases may exhibit varying shadow characteristics or where the same characteristics may be present across different diseases. Moreover, with Doppler ultrasound, it is challenging to display new microvessels in solid breast tumors and malignant breast masses due to a low flow rate and blood supply, with unsatisfactory diagnostic ACC, SEN, and SPE (31). The application of CEUS and SWE can compensate for the deficiency in conventional ultrasound to a large degree. With the intravenous injection of contrast media, CEUS can enhance the contrast resolution of the images, thus significantly improving the detection ability of ultrasound as it pertains to the microcirculation perfusion of diseased tissues. Ultrasound elastography is a relatively novel imaging technology and has clinical value in differentiating benign from malignant breast lesions. According to the different elastic coefficients of different tissues, SWE can judge the benign and malignant tumors by comparing the ultrasound before and after compression, the hardness of lesions and surrounding tissues, and the subjectivity of clinical palpation.

Although the use SWE or CEUS independently has a higher degree of SPE in the diagnosis of breast lesions, it also has a higher FP rate than does conventional ultrasound as well as certain other limitations. For example, when SWE is performed, the small size, deep location and growth of the tumor in the duct may be factors that affect the ACC of the hardness test, thus making the SWE index unreliable (32). Meanwhile, for CEUS, the small size of the tumor, a superficial position, and improper manipulation may contribute to a poor imaging effect (33). The main focus of our study was thus to determine whether the combination of these two methods has a higher diagnostic value in the differential diagnosis of benign and malignant breast lesions compared

Table 2 CEUS and SWE information used in each included study and their diagnostic performance for benign and malignant breast lesions

Study	No. of lesions	CEUS system	Contrast agent	Probe	SWE system	SWE parameters	Cutoff value (Kpa)	CEUS			SWE			CEUS + SWE		
								SEN	SPE	ACC	SEN	SPE	ACC	SEN	SPE	ACC
Liu 2019 a	118	Philips Medical Systems	SonoVue	4–12 MHz	SuperSonic Imagine	Emean	NR	0.864	0.946	0.915	0.886	0.905	0.898	0.977	0.932	0.949
Li 2023	218	Mindray Medical International	SonoVue	4–9 MHz	SuperSonic Imagine	Emean	NR	0.832	0.885	0.862	0.895	0.926	0.912	0.927	0.902	0.913
He 2023	26	Mindray Medical International	SonoVue	3–11 MHz	Mindray Medical International	Emean	NR	0.857	0.684	0.731	0.714	0.790	0.769	0.714	0.790	0.769
Xiang 2017	66	General Electric Healthcare	SonoVue	6–15 MHz	SuperSonic Imagine	Emean	NR	0.923	0.604	0.667	0.615	0.981	0.909	0.615	1.000	0.924
Chen 2022	78	Mindray Medical International	SonoVue	5–14 MHz	SuperSonic Imagine	Emax	57.38 Kpa	0.750	0.919	0.885	0.875	0.984	0.962	0.938	0.919	0.923
Kapetas 2019	124	NR	SonoVue	4–9 MHz	NR	Max SWV	3.2 m/s	0.965	0.297	0.647	0.962	0.441	0.714	0.912	0.712	0.817
Li 2020	181	Mindray Medical International	SonoVue	5–14 MHz	Mindray Medical International	NR	NR	0.804	0.717	0.749	0.938	0.734	0.809	0.929	0.788	0.840
Ding 2021	109	Mindray Medical International	SonoVue	3–9 MHz	Mindray Medical International	Emax	98 Kpa	0.885	0.742	0.844	0.654	0.839	0.706	0.859	0.903	0.872
Hou 2021	120	General Electric Healthcare	SonoVue	NR	General Electric Healthcare	Emean	NR	0.781	0.857	0.817	0.859	0.857	0.858	0.953	0.964	0.958
Wang 2022	128	SuperSonic Imagine	SonoVue	NR	SuperSonic Imagine	Emean	60 Kpa	0.930	0.714	0.859	0.807	0.762	0.792	0.984	0.762	0.911
Wu 2021	98	Mindray Medical International	SonoVue	NR	Mindray Medical International	SWV	3.7 m/s	0.762	0.857	0.816	0.714	0.821	0.776	0.881	0.911	0.898
Shen 2022	76	General Electric Healthcare	SonoVue	9 MHz	SuperSonic Imagine	Emax	NR	0.818	0.750	0.789	0.795	0.687	0.750	0.886	0.875	0.881
Qi 2021	170	General Electric Healthcare	SonoVue	NR	SuperSonic Imagine	Emax	60 Kpa	0.947	0.714	0.871	0.860	0.750	0.823	0.974	0.750	0.900
Liu 2019 b	85	Siemens Acuson S3000	SonoVue	4–9 MHz	Siemens Acuson S3000	Mean SWV	3.77 m/s	0.795	0.804	0.800	0.769	0.804	0.788	0.897	0.935	0.918
Gong 2021	112	MyLab Twice	SonoVue	NR	SuperSonic Imagine	Emean	41.43 Kpa	0.851	0.785	0.813	0.809	0.723	0.759	0.915	0.877	0.893
Hu 2021	138	Philips Medical Systems	SonoVue	5–12 MHz	Siemens Acuson S3000	SWV	3.7 m/s	0.673	0.831	0.775	0.714	0.775	0.753	0.796	0.854	0.833
Yan 2019	115	General Electric Healthcare	SonoVue	NR	Mindray Medical International	Emax	140 Kpa	0.937	0.902	0.921	0.922	0.843	0.887	0.981	0.961	0.972

CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography; SEN, sensitivity; SPE, specificity; ACC, accuracy; Emean, mean stiffness; NR, not, reported; Emax, maximum stiffness; SWV, shear wave velocity.

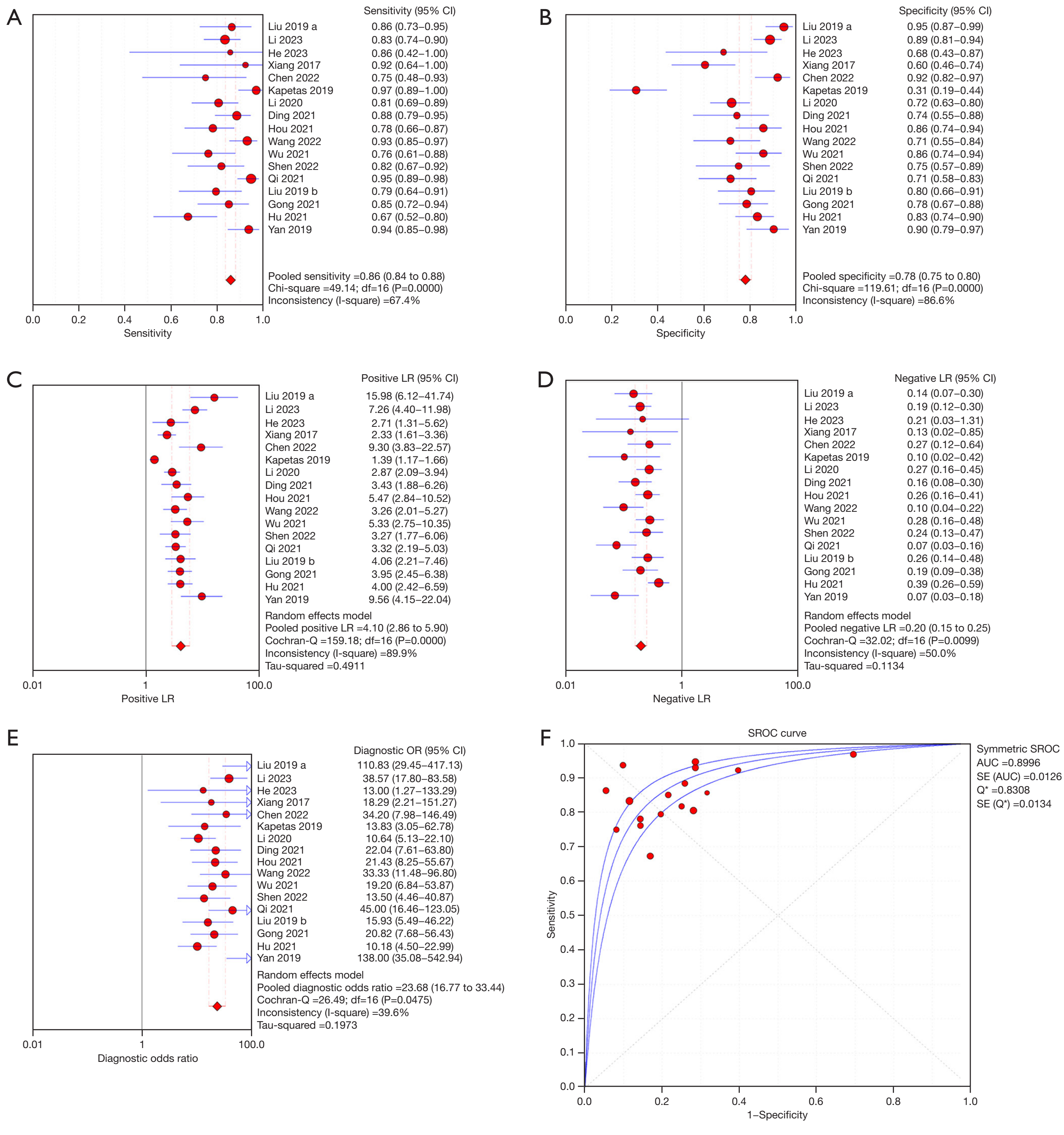

Figure 3 Plots of meta-analysis for differentiating benign and malignant breast lesions with CEUS. (A) SEN. (B) SPE. (C) Positive LR. (D) Negative LR. (E) Diagnostic OR. (F) SROC curve. Q*, Q test of heterogeneity. CI, confidence interval; LR, likelihood ratio; OR, odds ratio; SROC, summary receiver operating characteristic; AUC, area under the curve; SE, standard error; CEUS, contrast-enhanced ultrasound; SEN, sensitivity; SPE, specificity.

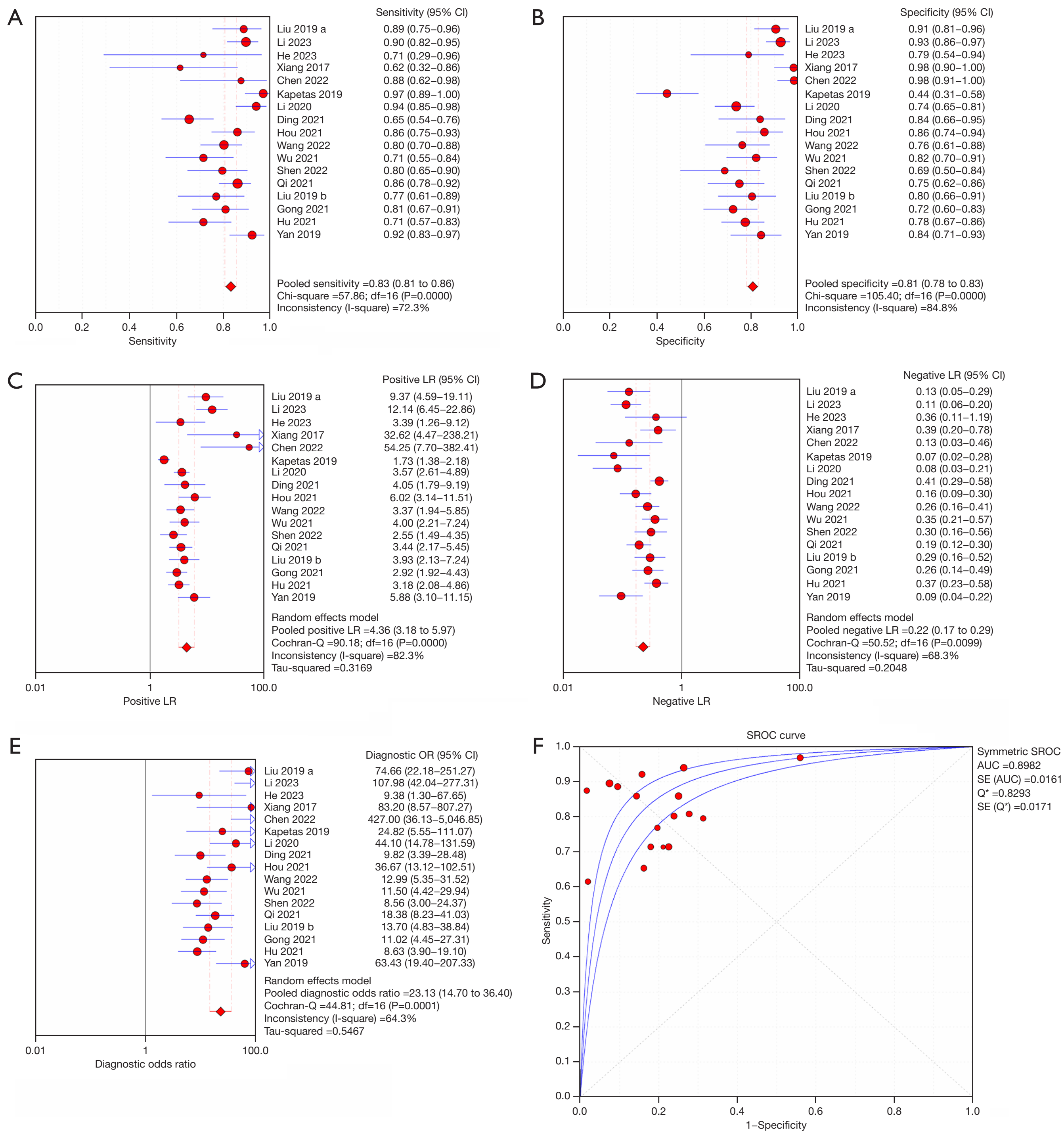

Figure 4 Plots of meta-analysis for differentiating benign and malignant breast lesions with SWE. (A) SEN. (B) SPE. (C) Positive LR. (D) Negative LR. (E) Diagnostic OR. (F) SROC curve. Q*, Q test of heterogeneity. CI, confidence interval; LR, likelihood ratio; OR, odds ratio; SROC, summary receiver operating characteristic; AUC, area under the curve; SE, standard error; SWE, shear wave elastography; SEN, sensitivity; SPE, specificity.

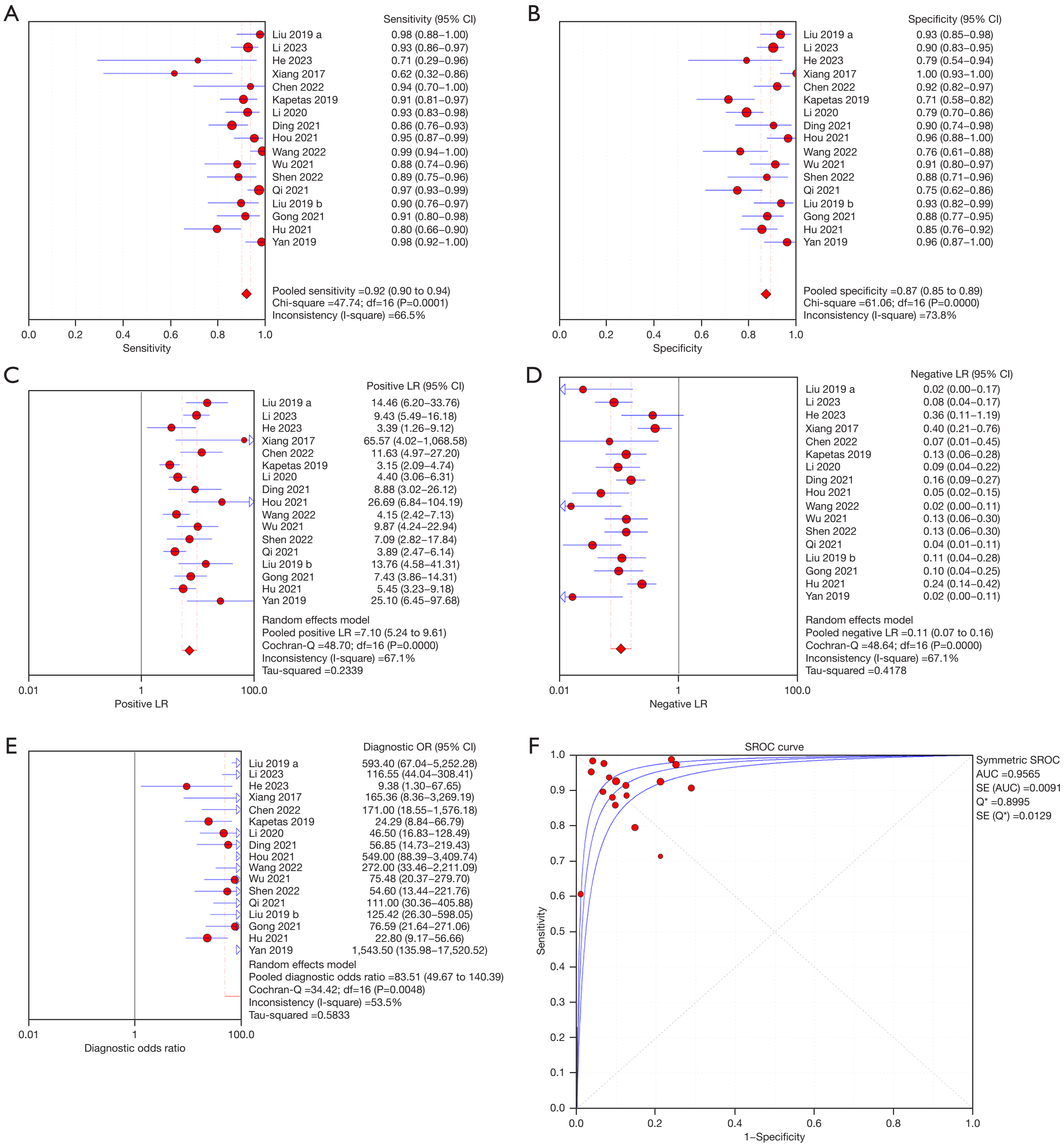

Figure 5 Plots of meta-analysis for differentiating benign and malignant breast lesions using CEUS combined with SWE. (A) SEN. (B) SPE. (C) Positive LR. (D) Negative LR. (E) Diagnostic OR. (F) SROC curve. Q*, Q test of heterogeneity. CI, confidence interval; LR, likelihood ratio; OR, odds ratio; SROC, summary receiver operating characteristic; AUC, area under the curve; SE, standard error; CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography; SEN, sensitivity; SPE, specificity.

Table 3 Pooled results of the meta-analysis of diagnostic performance for benign and malignant breast lesions using CEUS, SWE, and their combination

Test	Pooled SEN (95% CI)	Pooled SPE (95% CI)	Pooled PLR (95% CI)	Pooled NLR (95% CI)	Pooled DOR (95% CI)	Pooled AUC (95% CI)
CEUS	0.86 (0.84, 0.88)	0.78 (0.75, 0.80)	4.10 (2.86, 5.90)	0.20 (0.15, 0.25)	23.68 (16.77, 33.44)	0.90 (0.87, 0.93)
SWE	0.83 (0.81, 0.86)	0.81 (0.78, 0.83)	4.36 (3.18, 5.97)	0.22 (0.17, 0.29)	23.13 (14.70, 36.40)	0.90 (0.87, 0.92)
CEUS + SWE	0.92 (0.90, 0.94)	0.87 (0.85, 0.89)	7.10 (5.24, 9.61)	0.11 (0.07, 0.16)	83.51 (49.67, 140.39)	0.96 (0.94, 0.98)

CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography; SEN, sensitivity; CI, confidence interval; SPE, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under curve.

Table 4 Pairwise comparisons of the diagnostic performance for benign and malignant breast lesions by CEUS, SWE and their combination

Pairwise comparisons	Value	P value
CEUS *vs.* SWE		
Pooled SEN	0.86 *vs.* 0.83	0.073
Pooled SPE	0.78 *vs.* 0.81	0.092
Pooled ACC	0.82 *vs.* 0.82	0.908
CEUS *vs.* CEUS + SWE		
Pooled SEN	0.86 *vs.* 0.92	<0.001
Pooled SPE	0.78 *vs.* 0.87	<0.001
Pooled ACC	0.82 *vs.* 0.89	<0.001
SWE *vs.* CEUS + SWE		
Pooled SEN	0.83 *vs.* 0.92	<0.001
Pooled SPE	0.81 *vs.* 0.87	<0.001
Pooled ACC	0.82 *vs.* 0.89	<0.001

CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography; SEN, sensitivity; SPE, specificity; ACC, accuracy.

to either method used alone.

Hu *et al.* (34) and Liu *et al.* (35) conducted a meta-analysis on the diagnosis of benign and malignant breast lesions with CEUS and SWE, respectively. The results suggest that CEUS and SWE had high SEN (CEUS: 0.86, 95% CI: 0.83–0.89; SWE: 0.97, 95% CI: 0.94–0.99) and SPE (CEUS: 0.79, 95% CI: 0.75–0.83; SWE: 0.80, 95% CI: 0.73–0.86) in the differential diagnosis of benign and malignant breast lesions. However, without comparing and evaluating CEUS, SWE, and its combination for the same group of breast lesions, it is impossible to determine which modality is more advantageous in the diagnosis of benign and malignant breast lesions. Therefore, our study included 17 articles comprising 1,962 lesions regarding CEUS, SWE, and CEUS combined with SWE in the diagnosis of the same group of breast lesions and quantitatively summarized the diagnostic indices of CEUS combined with SWE to differentiate benign and malignant breast lesions. Our results showed that the SEN, SPE, and AUC of using CEUS to distinguish benign from malignant breast lesions were 0.86 (0.84, 0.88), 0.78 (0.75, 0.80), and 0.90 (0.87, 0.93), respectively; the SEN, SPE, and ACC of using SWE were 0.83 (0.81, 0.86), 0.81 (0.78, 0.83), and 0.90 (0.87, 0.92), respectively; and the SEN, SPE, and ACC of using CEUS combined with SWE were 0.92 (0.90, 0.94), 0.87 (0.85, 0.89), and 0.96 (0.94, 0.98), respectively. The diagnostic SEN of CEUS was higher than that of SWE, the SPE of CEUS was lower than that of SWE, and their overall ACC was similar, but there was no statistical difference in the SEN, SPE, or ACC between CEUS and SWE. The SEN, SPE, and ACC of CEUS combined with SWE were higher than those of CEUS and SWE alone, and the difference was statistically significant. The DOR of CEUS and SWE was 23.68 and 23.13, respectively, indicating that both have strong diagnostic ability, while the DOR for CEUS combined with SWE was 83.51, indicating a strong improvement in diagnostic performance. The AUC of CEUS, SWE, and their combined use was 0.90, 0.90, and 0.96, respectively.

One of the important contributors to heterogeneity in diagnostic trials is the threshold effect (36). The diagnostic thresholds used in the same diagnostic trial studies published by different authors often differ, and different diagnostic thresholds can lead to the threshold effect. All studies included in this study used pathological examination as a reference standard. By calculating the Spearman correlation coefficient, it was found that there was no heterogeneity caused by threshold effects. However, the meta-analysis revealed moderate to high heterogeneity among the

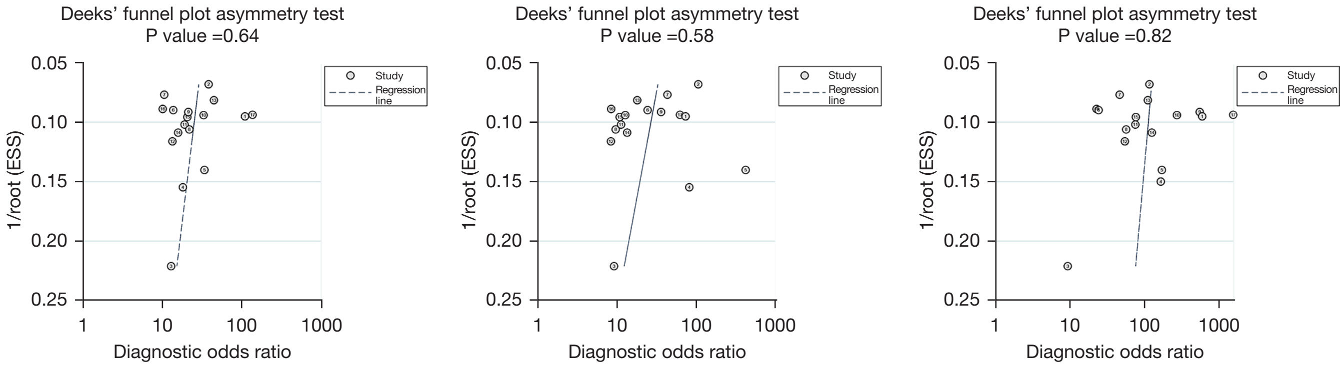

Figure 6 Deeks' funnel plots for differentiating benign and malignant breast lesions using (A) CEUS, (B) SWE, and (C) CEUS combined with SWE. ESS, effective sample size; CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography.

included studies (all P values >50%), indicating that they were influenced by other factors, such as different breast mass sizes, pathological type composition ratios, ultrasound instruments, diagnostic experience of the clinicians, dosages of contrast agents, imaging analysis software, and imaging conditions. Therefore, there is an urgent need for a series of SWE and CEUS diagnostic guidelines to standardize the examination conditions and facilitate the creation of objective tools for diagnosing breast benign and malignant lesions.

Some limitation to this study should be noted. First, of the 17 papers included, 16 were from China, which may be related to the high use of SWE technology in China; nonetheless, any generalization of the results should be undertaken with caution. Second, different ultrasound instruments, dosages of contrast media, imaging software, and imaging conditions constituted a degree of heterogeneity in each study, which affected the ACC of meta-analysis results. However, this meta-analysis was based on strict inclusion, exclusion, and evaluation criteria; a quantitative combination of multiple similar studies; and an expanded sample size. As a consequence, the findings produced have a greater research validity and credibility than do those produced by any single study.

Conclusions

Both SWE and CEUS techniques have certain diagnostic value for breast cancer, but the combined application of these two techniques has higher diagnostic value for breast cancer. Our findings can provide a reference for the clinical evaluation of breast cancer and selection of treatment schemes.

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Footnote

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