Contrast-Enhanced Ultrasound (CEUS) vs. Conventional Ultrasound for Differentiation of Benign and Malignant Breast Lesions: A Meta-Analysis

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Abstract

Background: High-frequency ultrasonography (US) has become the first-line imaging modality in evaluation of breast lesions however; it faces some limitations in differentiating benignity from malignancy **; Aim of work:** The aim of this meta-analysis was to estimate and compare the validity of contrast-enhanced ultrasound versus conventional ultrasound for differentiation of benign and malignant breast lesions; **Patients and Methods:** Quantitative, formal, epidemiological study design used to systematically assess the results of previous research to derive conclusions about that body of research. The study is based on randomized, controlled clinical trials. Participants will be adult females (over the age of 45 years old with breast lump dedicated for ultrasound study; **Results:** Both contrast-enhanced and conventional ultrasound demonstrated high PPV, with contrast-enhanced ultrasound showing a slightly higher pooled value. Despite the observed heterogeneity in both methods, there was no significant publication bias. Both contrast-enhanced and conventional ultrasound demonstrated high NPV, with contrast-enhanced ultrasound showing a slightly higher pooled value. The minimal heterogeneity in conventional ultrasound suggests more consistent results across studies. Contrast-enhanced ultrasound demonstrated higher accuracy compared to conventional ultrasound. Both methods exhibited significant heterogeneity, but no substantial publication bias was detected for either; **Conclusion:** Contrast-enhanced ultrasound demonstrated higher sensitivity and specificity compared to conventional ultrasound, Also, both contrast-enhanced and conventional ultrasound demonstrated high PPV and NPV, with contrast-enhanced ultrasound showing a slightly higher pooled value. Contrast-enhanced ultrasound demonstrated higher accuracy compared to conventional ultrasound. Both methods exhibited significant heterogeneity.

Keywords: Breast; Contrast, Ultrasound, Meta-analysis

Introduction:

Globally, breast cancer is the most common cancer and the leading cause of cancer death among women, necessitating accurate diagnosis for effective management [1].

Early detection of breast cancer can improve patients' survivability, select more cost-effective treatment, and reduce the economic burden of the family and country [2].

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High-frequency ultrasonography (US) has become the first-line imaging modality in evaluation of breast lesions however; it faces some limitations in differentiating benignity from malignancy [3]. Unlike conventional US, the newly emerging contrast-enhanced ultrasound (CEUS) helps evaluate blood distribution and perfusion of tumors, thus offering more valuable information for lesion differentiation. However, the capability of CEUS to accurately diagnose breast cancer remains Unclear [4].

With the use of contrast agents, vascular signals at Doppler US improved obviously and the microvascular architecture of breast lesions could be clearly delineated [5].

This meta-analysis aims to provide clarity regarding the diagnostic capabilities of these ultrasound techniques and their potential contributions to improving breast lesion diagnosis, particularly in the context of breast cancer detection and management.

Patients and Methods:

Quantitative, formal, epidemiological study design used to systematically assess the results of previous research to derive conclusions about that body of research. The study is based on randomized, controlled clinical trials. Participants were adult females (over the age of 45 years old with breast lump dedicated for ultrasound study. This study did not involve patient consent, so ethical approval is not necessary for this study.

Search Strategy: The following electronic databases were searched from 2000 to 2024: PubMed, Google Scholar search engine, Medline, EMBASE and Science Direct, using keywords such as contrast-enhanced ultrasound, conventional ultrasound, and breast lesions.

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Inclusion criteria of this meta-analysis were included studies have been published from 2000 till now, studies of patients suspected of having one breast mass or more, using US and CEUS, or US and US+CEUS as diagnostic methods, histopathological or cytological results for comparison, and reporting true positive (TP), false positive (FP), true negative (TN), and false negative (FN), and the study type was diagnostic test.

Exclusion criteria were case reports or case series, review articles, studies of contrast-enhanced power or color Doppler sonography, duplicate publications in different studies, fewer than 15 cases confirmed by reference standard and postsurgical studies.

Methods of this meta-analysis:

a) Locating and selecting studies:

- Locating and selecting studies

- Studies were in search engines like PubMed and Google Scholar in the duration from 2000 till now. These search engines were searched for studies only in the English language.

b) Statistical considerations:

- The data synthesis was performed using methods recommended by the working group of the Cochrane Collaboration on systematic reviews of diagnostic test accuracy. Any identified clinical or statistical heterogeneity was explored visually or using the chi-square test.

- In case of heterogeneity, subgroup analyses according to these different categories was conducted.

c) Evidence of publication bias:

- The studies were revised by a special committee for possible publication bias.

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Study	Year	Journal	Sample Size	Study Design	Patient Demographics	Lesion Details
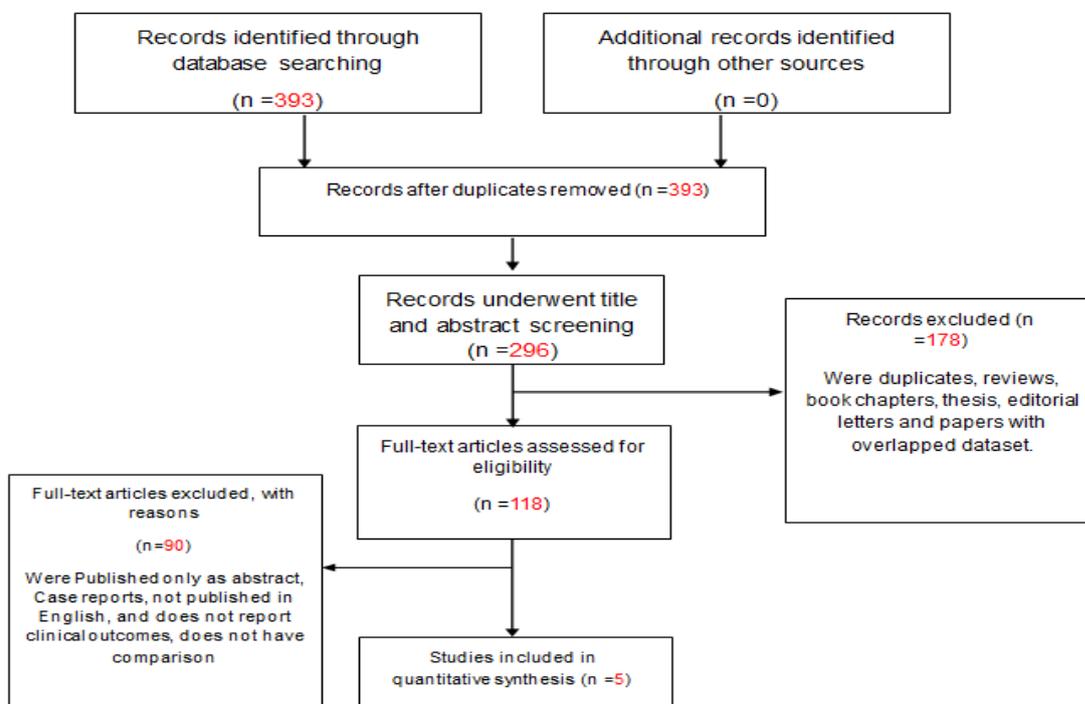
Results:

We obtained 393 articles from PubMed, 155 articles from Scopus, 29 articles from Cochrane library and 110 from web of science. 97 duplicated articles were removed using Endnote X8 program (Tompson Reuter, USA), 296 articles manually underwent titles and abstracts screening and 118 articles underwent full-text review as shown (Figure 1). Five studies finally met our inclusion criteria.

Figure (1): PRISMA flow diagram showing process of studies selection

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Cuiying Li,[6]	2018	Journal of Biomedical Research	117 patients	Prospective	Female, aged 22-76 years (median 43 years); Lesion sizes: 4-40 mm	Single hospital, March 2011 to September 2016
Xin Li,[7]	2023	Clinical Breast Cancer	86 patients	Prospective	Not specified; Classified into 4 molecular subtypes	Quantitative CEUS analysis performed
Qian Li,[8]	2018	Ultrasound in Medicine and Biology	2469 patients	Meta-analysis	Group 1: 1545 patients with 1609 breast masses (46.7% malignant); Group 2: 924 patients with 959 breast masses (52.6% malignant)	Various studies compared CEUS vs US and US+CEUS vs US
Jianghao Lu,[9]	2014	PLoS ONE	5276 patients	Meta-analysis	Mean patient age: 47.8 years	Mean of 199 lesions per study (range 15-1023); Studies published from 2006 to 2019
Daniela Stanzani,[10]	2014	Clinics	64 patients	Prospective	64 women, aged 18-78 years (median 49.12 years)	Single institution, March 2007 to January 2008

Table (1): Study Characteristics

Pooled Sensitivity (%)

1- Contrast enhanced ultrasound group (CEUS)

The meta-analysis for sensitivity of contrast-enhanced ultrasound demonstrated a pooled sensitivity of 91.25% (95% CI: 90.61% to 91.86%) using fixed effects and 94.67% (95% CI: 91.62% to 97.06%) using random effects.

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Cuiying2018	117	90.140	83.246 to 94.879	1.47	17.23

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Daniela Stanzani2014	64	100.000	94.399 to 100.000	0.81	13.16
Jianghao Lu2020	5276	90.000	89.159 to 90.797	65.82	27.42
Qian2018	2469	93.000	91.921 to 93.975	30.81	27.01
Xin Li 2024	86	100.000	95.801 to 100.000	1.09	15.18
Total (fixed effects)	8012	91.248	90.608 to 91.857	100.00	100.00
Total (random effects)	8012	94.668	91.615 to 97.062	100.00	100.00

Test for heterogeneity

Q	**56.2601**
DF	4
Significance level	P < 0.0001
I² (inconsistency)	92.89%
95% CI for I²	86.37 to 96.29
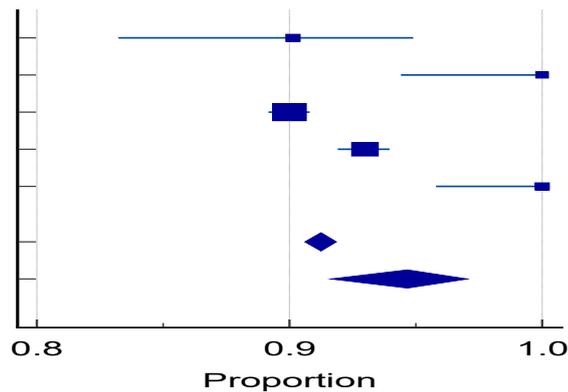
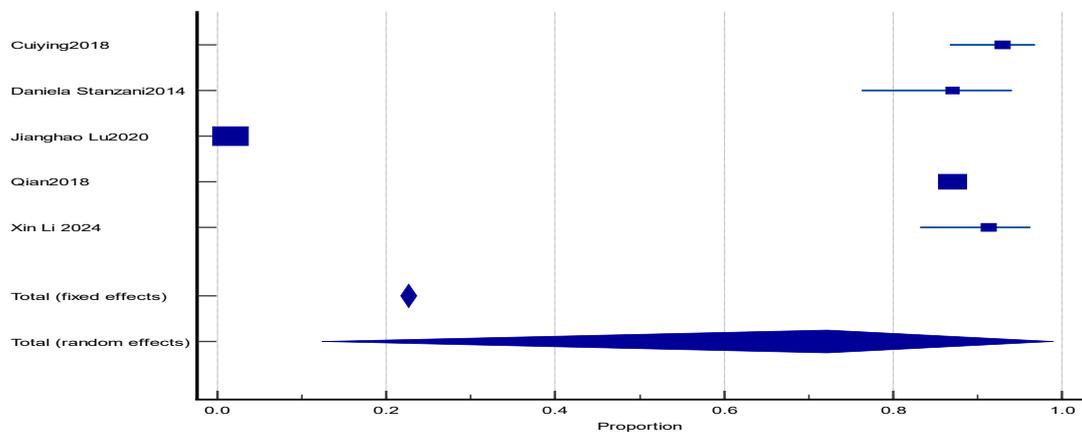## 2- Conventional ultrasound group (CUS)

In contrast, the meta-analysis for conventional ultrasound sensitivity revealed a significantly lower pooled sensitivity of 22.64% (95% CI: 21.73% to 23.57%) using fixed effects and 72.20% (95% CI: 12.39% to 98.99%) using random effects.

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Cuiying2018	117	92.960	86.716 to 96.866	1.47	19.99
Daniela Stanzani2014	64	87.000	76.245 to 94.103	0.81	19.93
Jianghao Lu2020	5276	1.581	1.262 to 1.955	65.82	20.06
Qian2018	2469	87.000	85.609 to 88.302	30.81	20.06

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Xin Li 2024	86	91.300	83.241 to 96.299	1.09	19.96
Total (fixed effects)	8012	22.642	21.729 to 23.574	100.00	100.00
Total (random effects)	8012	72.195	12.388 to 98.998	100.00	100.00

Test for heterogeneity

Q	8436.4790
DF	4
Significance level	$P < 0.0001$
I^2 (inconsistency)	99.95%
95% CI for I^2	99.95 to 99.96

Overall, contrast-enhanced ultrasound demonstrated higher sensitivity compared to conventional ultrasound, although both methods showed considerable variability in sensitivity estimates across studies.

Pooled Specificity (%)

1- Contrast enhanced ultrasound group (CEUS)

The meta-analysis of specificity for contrast-enhanced ultrasound yielded a pooled specificity of 83.74% (95% CI: 82.91% to 84.54%) using fixed effects and 79.25% (95% CI: 72.62% to 85.18%) using random effects.

| Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Cuiying2018	117	95.920	90.570 to 98.707	1.47	18.57
Daniela Stanzani2014	64	67.000	54.118 to 78.250	0.81	15.42

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Study	Sample size	Proportion (%)	95% CI	Weight Fixed	Weight Random
Jianghao Lu2020	5276	83.000	81.959 to 84.005	65.82	24.59
Qian2018	2469	86.000	84.568 to 87.346	30.81	24.38
Xin Li 2024	86	46.030	35.221 to 57.120	1.09	17.05
Total (fixed effects)	8012	83.738	82.912 to 84.540	100.00	100.00
Total (random effects)	8012	79.252	72.624 to 85.175	100.00	100.00

Test for heterogeneity

Q	99.8951
DF	4
Significance level	P < 0.0001
I^2 (inconsistency)	96.00%
95% CI for I^2	93.07 to 97.69
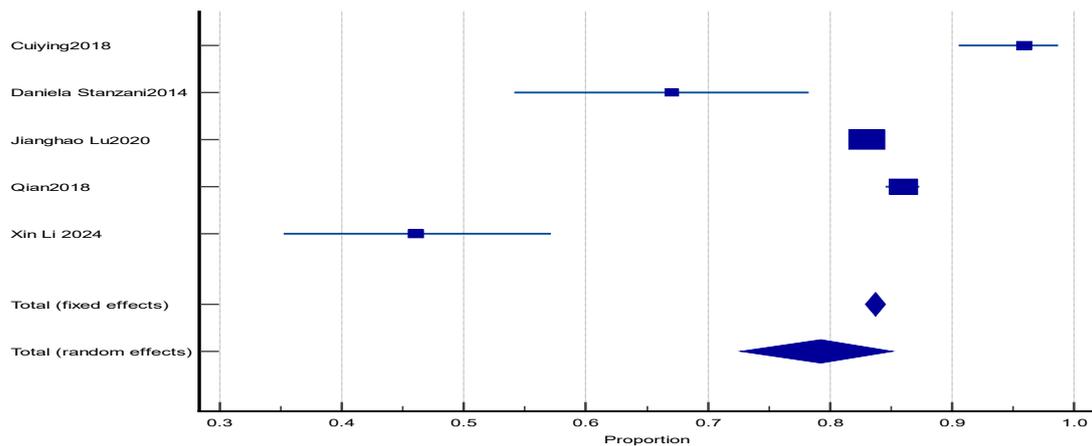


2- Sensitivity for the Conventional ultrasound (CUS)

For conventional ultrasound, the meta-analysis revealed a pooled specificity of 16.92% (95% CI: 16.10% to 17.76%) using fixed effects and 51.30% (95% CI: 6.50% to 94.73%) using random effects.

Study	Sample size	Proportion (%)	95% CI	Weight (%) Fixed	Weight (%) Random
Cuiying2018	117	81.630	73.410 to 88.184	1.47	19.98
Daniela Stanzani2014	64	71.000	58.310 to 81.669	0.81	19.89
Jianghao Lu2020	5276	1.427	1.125 to 1.785	65.82	20.09
Qian2018	2469	72.000	70.183 to 73.764	30.81	20.09

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Xin Li 2024	86	45.330	34.558 to 56.433	1.09	19.94
Total (fixed effects)	8012	16.917	16.102 to 17.755	100.00	100.00
Total (random effects)	8012	51.302	6.495 to 94.728	100.00	100.00

Test for heterogeneity	
Q	**5729.6267**
DF	4
Significance level	P < 0.0001
I^2 (inconsistency)	99.93%
95% CI for I^2	99.92 to 99.94
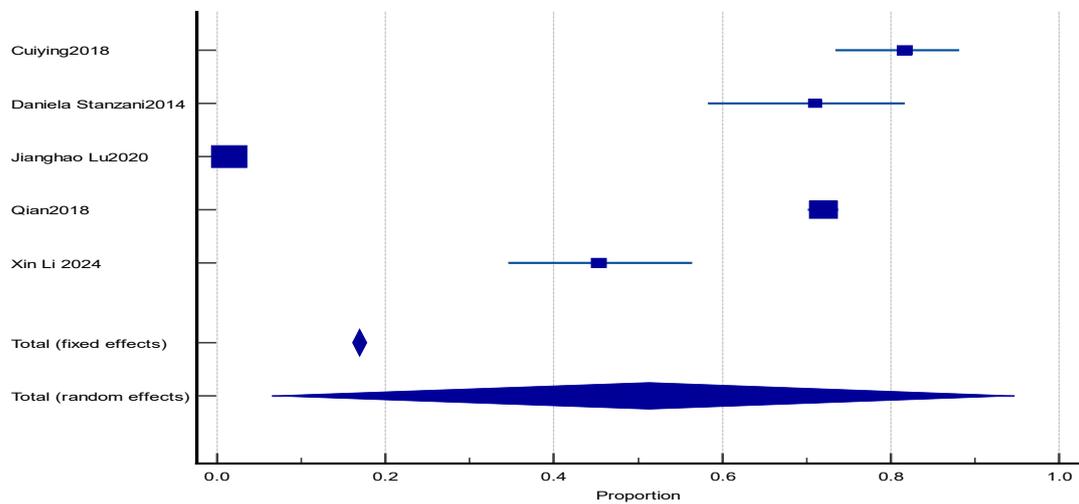
Overall, contrast-enhanced ultrasound demonstrated higher specificity compared to conventional ultrasound, although both methods exhibited considerable variability and heterogeneity in their specificity estimates across studies.

Accuracy (%)

1- Contrast enhanced ultrasound group (CEUS)

The meta-analysis for accuracy of contrast-enhanced ultrasound yielded a pooled accuracy of 94.13% (95% CI: 93.58% to 94.64%) using fixed effects and 94.21% (95% CI: 92.41% to 95.77%) using random effects.

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Cuiying2018	117	92.520	86.164 to 96.568	1.50	11.97
Jianghao Lu2020	5276	93.540	92.843 to 94.189	67.09	45.57

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Study	Sample size	Proportion (%)	95% CI	Fixed	Random
Qian2018	2469	95.400	94.498 to 96.192	31.40	42.47
Total (fixed effects)	7862	94.125	93.583 to 94.635	100.00	100.00
Total (random effects)	7862	94.205	92.414 to 95.769	100.00	100.00

Test for heterogeneity

Q	**11.7957**
DF	2
Significance level	P = 0.0027
I² (inconsistency)	83.04%
95% CI for I²	48.40 to 94.43

2- Conventional ultrasound group (CUS)

For conventional ultrasound, the pooled accuracy was 90.19% (95% CI: 89.51% to 90.84%) using fixed effects and 89.56% (95% CI: 87.11% to 91.78%) using random effects.

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Cuiying2018	117	88.330	81.088 to 93.527	1.50	13.05
Jianghao Lu2020	5276	91.039	90.236 to 91.796	67.09	44.81
Qian2018	2469	88.400	87.071 to 89.637	31.40	42.14
Total (fixed effects)	7862	90.188	89.510 to 90.837	100.00	100.00
Total (random effects)	7862	89.561	87.107 to 91.783	100.00	100.00

Test for heterogeneity

Q	**13.3996**
DF	2
Significance level	P = 0.0012
I² (inconsistency)	85.07%
95% CI for I²	55.95 to 94.94

In summary, contrast-enhanced ultrasound demonstrated higher accuracy compared to conventional ultrasound. Both methods exhibited significant heterogeneity, but no substantial publication bias was detected for either.

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Discussion

Breast cancer diagnosis relies heavily on imaging techniques, and while conventional ultrasound (US) is the most common method for diagnosing breast diseases its application in differentiating between benign and malignant breast lesions is limited [11]. Contrast-enhanced ultrasound (CEUS) provides more information regarding the tumor blood supply, thus, it may be more helpful for the identification of breast diseases, which are often indicative of malignancy[12].

Therefore, this meta-analysis was conducted to estimate and compare the validity of contrast-enhanced ultrasound versus conventional ultrasound for differentiation of benign and malignant breast lesions.

We concluded 5 studies in this meta-analysis, the pooled sensitivity in the Contrast enhanced ultrasound group (CEUS) demonstrated a pooled sensitivity of 91.25% (95% CI: 90.61% to 91.86%) using fixed effects and 94.67% (95% CI: 91.62% to 97.06%) using random effects.

Similar results were reported in the meta analysis of **Li et al.,** [8] found that as regards the sensitivity analysis, the pooled sensitivity of CEUS in studies published in English were 0.93 (95%CI:0.91-0.95). Also, another study by **Zhang et al.,** [13] reported that the pooled value related to the sensitivity of CEUS in the differential diagnosis of breast lesions and breast cancer were computed by 88.00 which is lower than reported in our meta-analysis.

Regarding conventional ultrasound group (CUS), the meta-analysis for conventional ultrasound revealed a significantly lower pooled sensitivity of 22.64% (95% CI: 21.73% to 23.57%) using fixed effects and 72.20% (95% CI: 12.39% to 98.99%) using random effects.

In contrast, the pooled sensitivity reported in the meta-analysis by **Li et al.,** [8] in studies using conventional ultrasound was 0.87 (95%CI: 0.83-0.90) which is much higher than reported in our meta-analysis. Also, in contrast by the study of **Wubulihasimu et al.** [14] found that the pooled sensitivity for conventional US imaging in detecting breast lesions was: 0.87 (95% CI: 0.84 -0.91).

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Overall, contrast-enhanced ultrasound demonstrated higher sensitivity compared to conventional ultrasound, although both methods showed considerable variability in sensitivity estimates across studies. **Li et al.,** [8] reported the same results as sensitivity of conventional US is lower when compared to contrast-enhanced ultrasound.

The meta-analysis of specificity for contrast-enhanced ultrasound yielded a pooled specificity of 83.74% (95% CI: 82.91% to 84.54%) using fixed effects and 79.25% (95% CI: 72.62% to 85.18%) using random effects.

This came in accordance with a meta-analysis by **Chong et al.,** [15] showed that the specificity of CEUS was 0.86 (95 % CI 0.82–0.89). Similarly, this study agreed with **Dong et al.,** [16] reported that the specificity, of CEUS was 82.4%.

For conventional ultrasound, the meta-analysis revealed a pooled specificity of 16.92% (95% CI: 16.10% to 17.76%) using fixed effects and 51.30% (95% CI: 6.50% to 94.73%) using random effects.

In contrast, our findings disagreed with **Wubulihasimu et al.** [14] found that the pooled specificity for conventional US imaging in detecting breast lesions was: 0.80 (95% CI: 0.76 - 0.84).

Overall, contrast-enhanced ultrasound demonstrated higher specificity compared to conventional ultrasound, although both methods exhibited considerable variability and heterogeneity in their specificity estimates across studies. Similar results were reported by **Li et al.,** [8]. Similarly, it has been reported that, compared to color Doppler in conventional US (sensitivity 83.8-95.3%, specificity 57.7-77.7%), CEUS alone has superior diagnostic performance in differentiating between benign and malignant breast lesions (sensitivity 91.4-95.5%, specificity 81.6-88.3%) **(Liu et al.**[17]**; Miyamoto et al.** [18]**; Xiao et al.**[19]**)**

Contrast-enhanced ultrasound demonstrated higher accuracy compared to conventional ultrasound. Both methods exhibited significant heterogeneity, but no substantial publication bias was detected for either.

Similar results were obtained by **Li et al.,** [8] who reported that the AUC of SROC of US+CEUS (AUC=0.965, SE=0.009) was significantly higher than that of US (Group 2) (AUC=0.911, SE=0.011) (Z=3.826, P=0.000). Also, **Wubulihasimu et al.** [14]

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reported that the pooled accuracy of CEUS had significantly higher accuracy than usual conventional US.

limitations

Several limitations were identified in this study. First, the analysis included a small number of studies and participants. Second, there was no objective classification of enhancement patterns for breast lesions, and sonologist skill could impact CEUS diagnostic accuracy. Third, the analysis was conducted at the study level, limiting detailed subgroup analyses.

Conclusions

Contrast-enhanced ultrasound demonstrated higher sensitivity and specificity compared to conventional ultrasound. Contrast-enhanced ultrasound demonstrated higher accuracy compared to conventional ultrasound. Both methods exhibited significant heterogeneity.

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