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Diagnostic efficacy of sentinel lymph node in breast cancer under percutaneous contrast-enhanced ultrasound: An updated meta-analysis

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Abstract

Background: To investigate the diagnostic efficacy of sentinel lymph nodes (SLN) in breast cancer by percutaneous contrast-enhanced ultrasound (CEUS) through pooled analysis of relevant studies published before June 2021.

Methods: We conducted a systematic review and meta-analysis of relevant studies by searching the electronic databases of PubMed, Embase, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang and VIP and the studies were screened according to their inclusion and exclusion criteria. Sensitivity (SEN), specificity (SPE), positive likelihood ratio (+LR), negative likelihood ratio (−LR) and diagnostic odds ratio (DOR) were calculated by Meta-disc 1.4 software and the summary receiver operating characteristic (SROC) curve and area under the curve of ROC (AUC) were constructed.

Results: Twenty-two publications evaluating the diagnostic efficacy of SLN in breast cancer under percutaneous CEUS were included in the meta-analysis. The diagnostic sensitivity, specificity were 0.86 (95% CI: 0.83–0.88) and 0.89 (95% CI: 0.87–0.91) for SLN in breast cancer detected by percutaneous CEUS respectively using a random effect model. The +LR and –LR were combined in a random effect model due to significant statistical heterogeneity ($p < 0.05$). The pooled +LR, −LR were 7.06 (95% CI: 4.34–11.50), and 0.17 (95% CI: 0.12–0.24), respectively. The combined DOR was 53.32 (95% CI: 29.74–95.61) for SLN diagnosis in breast cancer by percutaneous CEUS under a random effect model. The AUC was 0.94 which indicated that CEUS had high diagnostic efficacy of SLN in patients with breast cancer.

Conclusions: CEUS is a noninvasive method for the detection SLN in patients of breast cancer with relative high prediction efficacy.

KEYWORDS
breast cancer, contrast-enhanced ultrasound, meta-analysis, sentinel lymph node

INTRODUCTION

Breast cancer is one of the leading causes of cancer-related death globally in women. It has been estimated 281 550 new cases and 43 600 deaths as a result of breast cancer will be diagnosed in the year 2021 in the US according to the annual cancer statistical analysis.[1] Breast cancer is the leading cause of cancer deaths in women under 45 years of age.[2] Most of the lymphatic drainage of the breast is to the axillary lymph nodes, which are most important in treatment planning and procedures such as surgery, radiotherapy and chemotherapy. In addition, axillary lymph node metastasis is an important independent prognostic factor for patient prognosis.[3]

The sentinel lymph node (SLN) is the first lymph node that receives lymphatic drainage from an organ or tissue, through which the tumor metastasizes to other lymph nodes.[4,5] Lymph node skipping metastasis rarely occurs in the tumor. Therefore, the pathological status of axillary SLNs in breast cancer can represent the whole lymph node status in the axillary region. Preoperative detection of lymph node metastasis status is of great importance for surgical procedures and patient prognosis, and avoids unnecessary complications caused by extensive lymph node dissection.[6,7] Studies have shown that SLN status is usually representative of the pathological status of axillary lymph nodes. For SLN negative breast cancer patients, axillary lymph node dissection (ALND) is not necessary, thereby reducing operative complications and improving the quality of life of breast cancer patients.[8] Contrast-enhanced ultrasound (CEUS) is the application of ultrasound contrast medium to traditional medical sonography, which is widely applied in the detection of SLN for cancer cell metastasis in breast cancer patients.

METHODS

Systematic database search

The electronic databases of PubMed, Embase, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang and VIP were comprehensively searched for relevant studies published before June 2021. Electronic searching was performed using the free text word of "breast cancer", "breast neoplasm", "breast carcinoma", "sentinel lymph node", "contrast-enhanced ultrasound" and "CEST". The references of the included studies were also reviewed to identify any further potential suitable studies for inclusion.

Inclusion and exclusion criteria

The study inclusion criteria was focused on the aspects of: (1) study type: prospective diagnostic studies relevant to diagnostic efficacy of SLN in breast cancer under percutaneous contrast-enhanced ultrasound. (2) Subjects: the subjects included were limited to those with pathologically confirmed breast cancer. (3) Diagnostic method: limited to percutaneous contrast-enhanced ultrasound. (4) Outcome: the original study provided the exact number of true positive, false positive, false positive and true negative SLN cases detected. (5) The gold diagnostic standard for SLN was pathology. (6) The studies were published in Chinese or English. The exclusion criteria were: (1) retrospective, case reports or review studies. (2) Duplicated publications. (3) Animal studies. (4) The true positive,

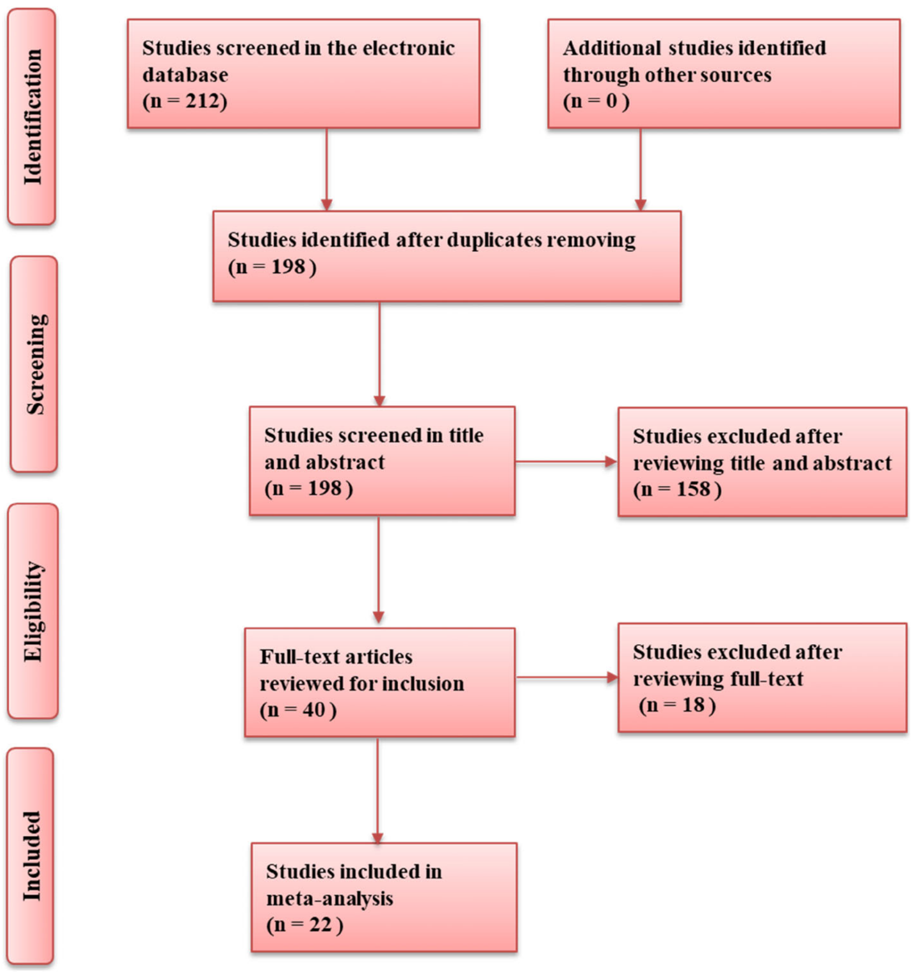

FIGURE 1 The studies screened and identified in the electronic databases

TABLE 1 General characteristics of publications included

Author	Year	Area	Age	Equipment	TP	FP	FN	TN
Zhong et al.[9]	2007	China	48.4 ± 14.4	Siemens	10	2	1	19
Mi et al.[10]	2010	China	23–67	Philips	25	5	7	5
Zhang and Gu[11]	2012	China	41.2 ± 5.6	Philips	8	1	0	14
Sun and Mi[12]	2012	China	20–57	Siemens	32	8	4	13
Yu et al.[13]	2013	China	47.8 ± 16.2	Esaote	12	0	1	13
Podkrajsek and Hocevar[14]	2011	Snovenia	26–73	Toshiba	22	0	1	3
Ouyang et al.[15]	2010	China	30–78	Esaote	25	6	2	18
Sever et al.[16]	2009	U.K	NA	GE	43	0	5	6
Cox et al.[17]	2013	U.K	62(25–93)	Siemens	35	0	22	238
Sever et al.[18]	2012	U.K	NA	Siemens	17	0	9	100
Wang et al.[19]	2013	China	47(29–80)	Siemens	37	6	7	39
Fu et al.[20]	2015	China	28–67	Esaote	18	1	2	17
Xie et al.[21]	2015	China	54(22–82)	GE	27	9	6	56
Lin et al.[22]	2017	China	50.82 ± 9.52	Philips	18	2	3	7
Lu et al.[23]	2014	China	26–69	Esaote	9	9	8	55
Giacomo[24]	2017	Italy	Na	Philips	28	4	0	18
Liu et al.[25]	2019	China	NA	Philips	50	33	1	32
Qiao et al.[8]	2021	China	47.5(29–72)	Philips	61	17	6	124
Zhou et al.[26]	2021	China	47(8–70)	NA	27	5	7	60
Hu et al.[27]	2013	China	NA	Esaote	13	0	1	17
Chen et al.[28]	2020	China	48.23 ± 10.37	Philips	49	5	6	73
Fang et al.[29]	2021	China	49.26 ± 9.18	GE	33	2	1	46

false positive, false negative and true negative cases could not be extracted or calculated from the original studies.

Data extraction from original studies

The primary data of the original studies included were extracted by two reviewers independently. The extracted data included: (1) first author of the included study, (2) region or country in which the experiment was performed, (3) age of included subjects, (4) ultrasonic equipment, (5) sample size or number of lymph nodes, and (6) the exact number of true positive, false positive, false negative and true negative cases.

Statistical methods

The statistical analysis was performed using MetaDiSc 1.4 statistical software. Diagnostic sensitivity and specificity was calculated using the equation of sensitivity = true positive/(true positive+ false negative), specificity = true negative/(true negative + false positive). The area under the receiver operating characteristic (ROC) curve was used to evaluate the diagnostic efficacy of SLN in breast cancer under percutaneous CEUS. Before data pooling, the statistical heterogeneity across the included studies was evaluated by chi-square text and demonstrated by I^2. If $I^2 > 50\%$, the data was pooled by random effect otherwise by fixed effect model.

RESULTS

Characteristics of studies

After removing studies unsuitable for inclusion, 22 publications evaluating the diagnostic efficacy of SLN metastasis in breast cancer under percutaneous contrast-enhanced ultrasound were included in the meta-analysis (Figure 1). The publication year ranged from 2007 to 2021 with 17 studies performed in the Chinese population, one in Slovenia, three in the UK and one in Italy. The general characteristics of the 22 publications included are shown in Table 1.

Diagnostic sensitivity

The diagnostic sensitivity was pooled in a random effect model because of obvious statistical heterogeneity ($I^2 = 71.9\%$, $p < 0.05$). The pooled results indicated that the diagnostic sensitivity was 0.86 (95% CI: 0.83–0.88) for SLN metastasis in breast cancer under percutaneous CEUS (Figure 2).

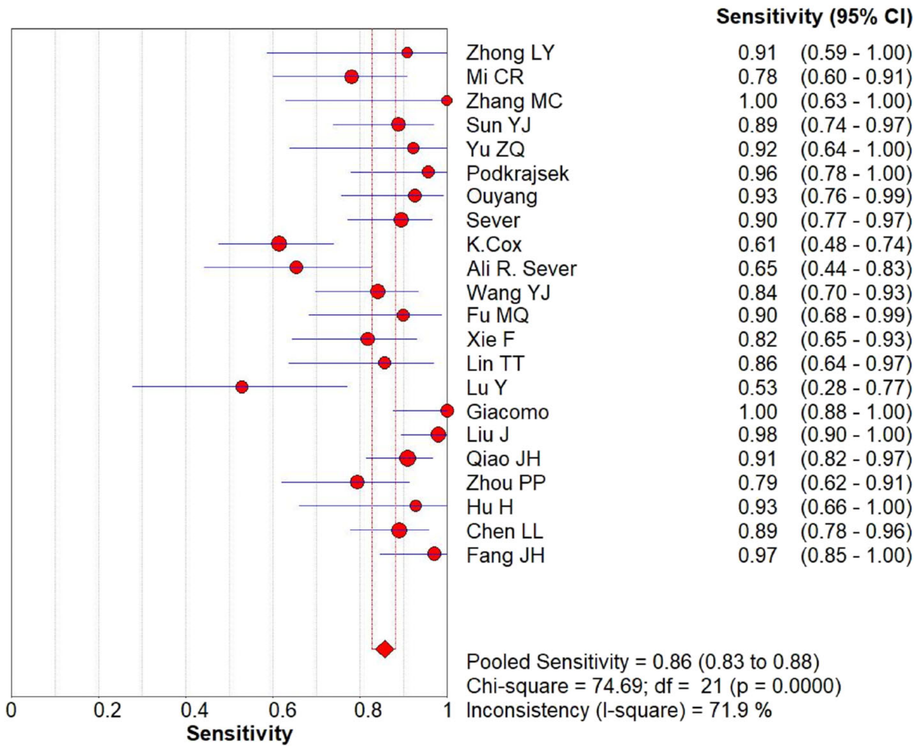

FIGURE 2 Forest plot of diagnostic sensitivity of sentinel lymph nodes in breast cancer under percutaneous contrast-enhanced ultrasound by pooling the 22 open published studies

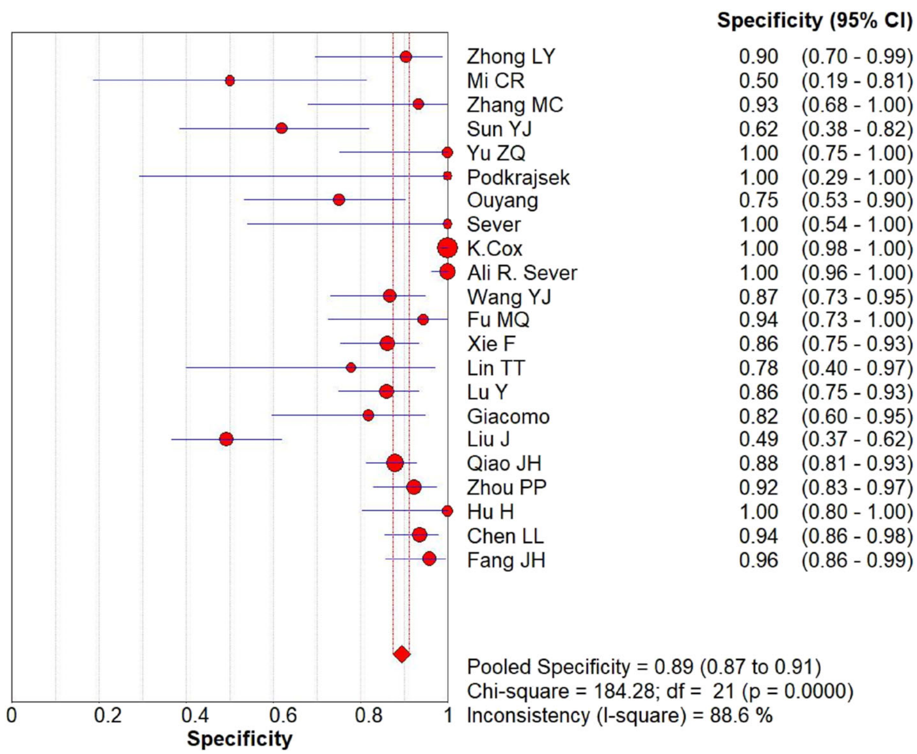

FIGURE 3 Forest plot of diagnostic specificity of sentinel lymph nodes in breast cancer under percutaneous contrast-enhanced ultrasound by pooling the 22 open published studies

Diagnostic specificity

In condition of significant statistical heterogeneity across the 22 studies ($I^2 = 88.6\%$, $p < 0.05$), the data was pooled in a random effect model. The pooled results showed the diagnostic specificity was 0.89 (95% CI: 0.87–0.91) for SLN metastasis in breast cancer under percutaneous CEUS (Figure 3).

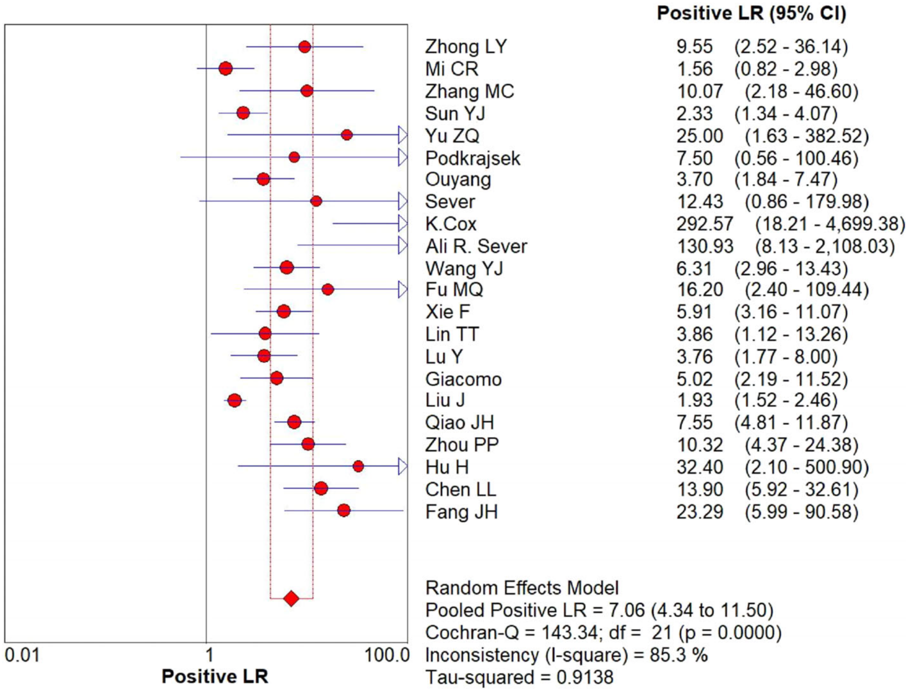

FIGURE 4 Forest plot of diagnostic +LR of sentinel lymph nodes in breast cancer under percutaneous contrast-enhanced ultrasound by pooling the 22 open published studies

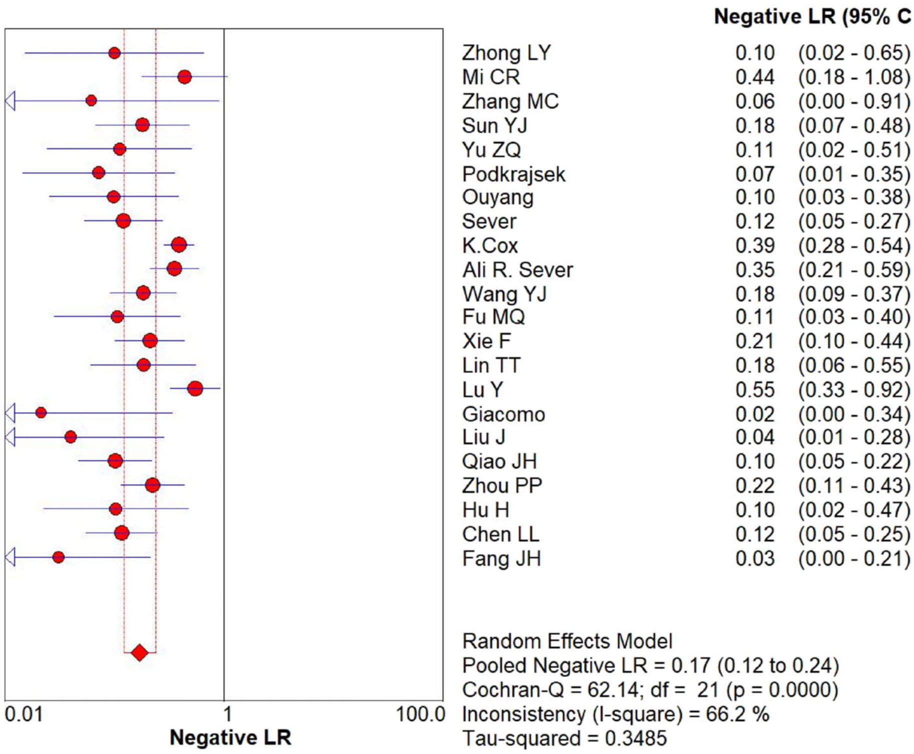

FIGURE 5 Forest plot of diagnostic -LR of sentinel lymph nodes in breast cancer under percutaneous contrast-enhanced ultrasound by pooling the 22 open published studies

Positive and negative likelihood ratio

The +LR and –LR were combined in a random effect model due to significant statistical heterogeneity ($p < 0.05$). The pooled +LR, −LR were 7.06 (95% CI: 4.34–11.50), (Figure 4) and 0.17 (95% CI: 0.12–0.24), (Figure 5), respectively.

Diagnostic odds ratio

Under condition of obvious statistical heterogeneity, the DOR was combined in a random effects model. The combined DOR was 53.32 (95% CI: 29.74–95.61) for SLN metastasis in breast cancer under percutaneous CEUS, Figure 6.

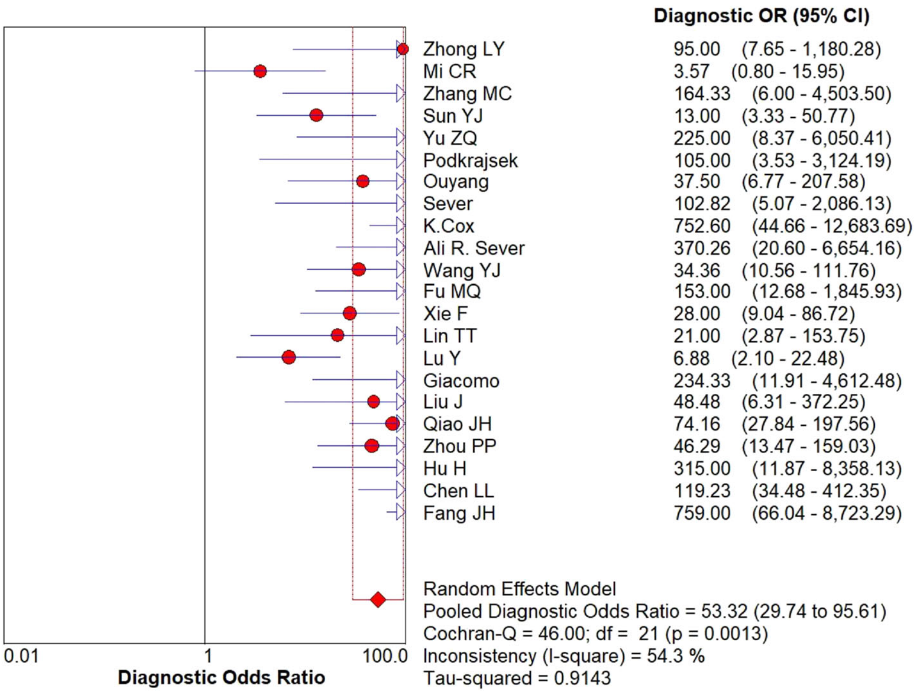

FIGURE 6 Forest plot of DOR of sentinel lymph nodes in breast cancer under percutaneous contrast-enhanced ultrasound by pooling the 22 open published studies

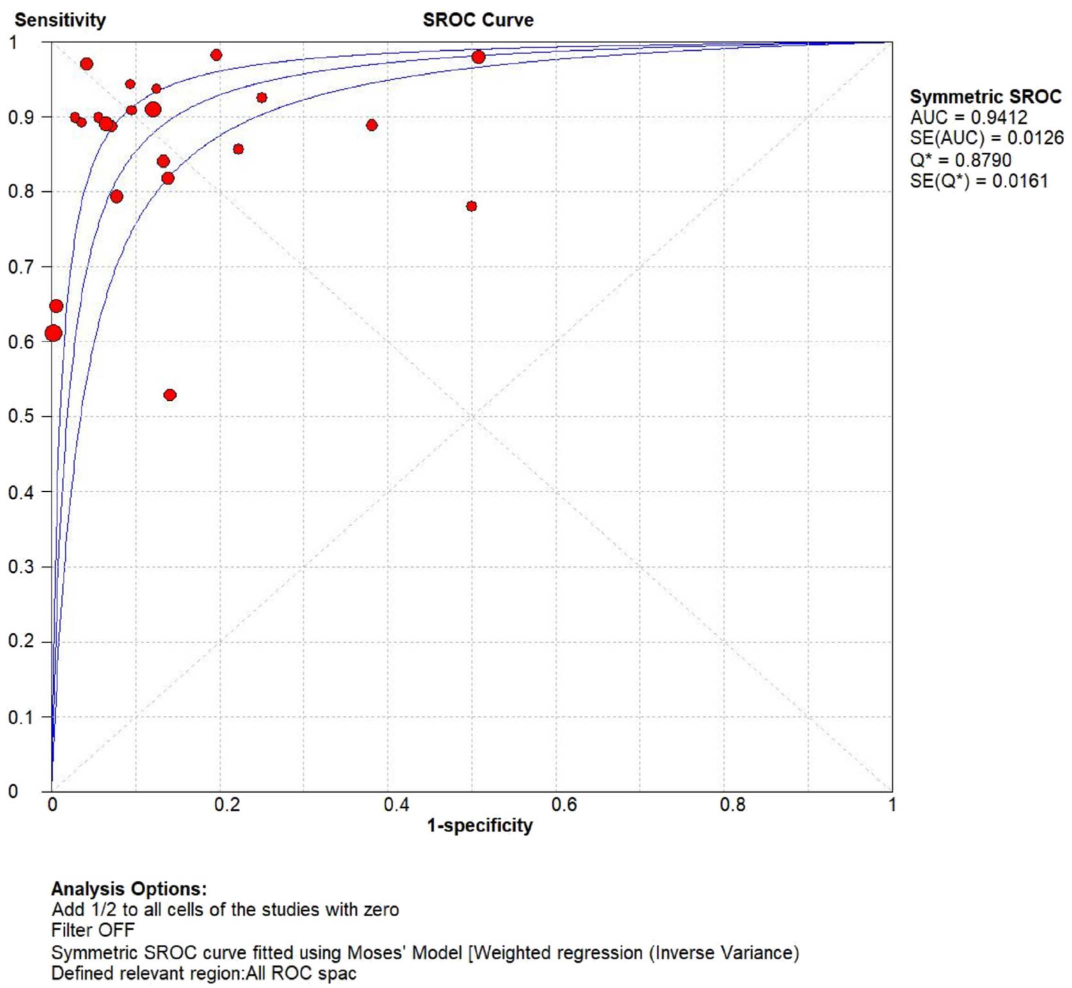

FIGURE 7 The summary receiver operating characteristic (SROC) curve of sentinel lymph nodes in breast cancer under percutaneous contrast-enhanced ultrasound by pooling the 22 open published studies

Area under the ROC

The SROC was constructed using the Moses' Model (Figure 7). The area under the ROC (AUC) was 0.94 which indicated that CEUS had high diagnostic efficacy of SLN metastasis in patients with breast cancer.

DISCUSSION

Contrast-enhanced ultrasound (CEUS) provides a new method for the detection and diagnosis of SLNs.[30] The principle of CEUS is that microbubble contrast agents generate a nonlinear harmonic signal in the sound field with a small mechanical index. Using this characteristic, different pulse coding techniques are used to selectively extract the nonlinear harmonic signal of microbubbles and filter out the linear fundamental signal generated by tissues, so as to realize real-time blood perfusion imaging of organs and tissues.[31] The CEUS technique has been extensively applied clinically especially in the diagnosis of cancer and metastatic lymph nodes. Recent studies have shown that CEUS has great potential in the diagnosis of SLNs in breast cancer.[9–11] However, due to the small sample size and different CEUS technique, the results have not been conclusive across different studies. Therefore, we performed this meta-analysis in order to further evaluate the diagnostic efficacy of SLN in breast cancer by CEUS. In our present study, 22 prospective diagnostic studies were included and made data combination. The pooled results indicated that the diagnostic sensitivity, specificity, +LR, −LR, DOR and AUC were 0.86 (95% CI: 0.83–0.88), 0.89 (95% CI: 0.87–0.91), 7.06 (95% CI: 4.34–11.50), 0.17 (95% CI: 0.12–0.24), 53.32 (95% CI: 29.74–95.61) and 0.94, respectively for SLN in breast cancer detected by percutaneous CEUS under a random effect model. The pooled diagnostic efficacy was satisfied with relative high sensitivity and specificity.

At present, the gold standard of SLN identification in breast surgery is isotope tracer and the methylene blue staining method.[32] Compared with the two methods, contrast-enhanced ultrasound has the advantages of less trauma, safety and convenience. It can track the flow direction of contrast agent in real time and display lymphatic vessels and metastatic lesions in lymph nodes. Compared with the above SLN detection methods, CEUS is a non- or minimally invasive method with relative high sensitivity and specificity and has potential clinical application value.

In conclusion, CEUS is a non- or minimally invasive method for the detection of SLN in breast cancer patients with relative high prediction efficacy. However, the current study also has some limitations. (1) Significant statistical heterogeneity across the included studies which may decrease the statistical power. (2) Only studies published in English or Chinese were included. (3) Although pathology was applied as the gold standard in all the included studies, the "gold standard" was not unified across the included studies. (4) The contrast agent injection methods of the included studies were different which may cause clinical heterogeneity. Due to these limitations, further well designed prospective multicenter diagnostic studies are needed to investigate the diagnostic efficacy of SLNs in breast cancer using percutaneous contrast-enhanced ultrasound.

CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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