Systematic Review and Meta-Analysis

Medicine

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Which combination of different ultrasonography modalities is more appropriate to diagnose breast cancer?

A network meta-analysis (a PRISMA-compliant article)

Yang Zhou, Jialing Wu*

Abstract

Background: Abundant amount of literature that analyze the various detection of different ultrasound methods, no comprehensive literature that investigates the diagnostic values of breast cancer (BC) by different ultrasonography modalities through a network meta-analysis (NMA) has been made available. Each imaging diagnostic examination has its own advantages and disadvantages, and any imaging examination is not enough to make an accurate diagnosis of the disease. Thus, this study aimed to compare diagnostic values among different ultrasonography modalities, including the information of 2-dimension, stiffness and blood flow, by a network meta-analysis in the hopes of understanding which imaging methods are better and which combination of different ultrasonography modalities is more appropriate to diagnose BC.

Methods: We made use of Cochrane Library, PubMed, and Embase in order to obtain literature and papers. The combination analysis of both direct and indirect evidence in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value(NPV) and accuracy was conducted so as to assess the odds ratios (ORs) and surface under the cumulative ranking curve (SUCRA) values of the 8 different ultrasound methods.

Results: A total of 36 eligible diagnostic tests regarding 8 ultrasound methods were included in the study. According to this network meta-analysis, Breast Imaging Reporting and Data System (BI-RADS) 4b exhibited higher specificity, PPV, and accuracy and lower sensitivity and NPV than BI-RADS 4a. Contrast-enhanced ultrasound (CEUS) had the highest sensitivity, PPV, NPV and accuracy and superb microvascular imaging (SMI) had the highest specificity among color Doppler flow imaging (CDFI), power Doppler imaging(PDI), SMI and CEUS. There was no significant difference in diagnostic indexes between SMI and CEUS. Shear wave elastrography (SWE) had higher PPV and accuracy and lower sensitivity, specificity NPV than strain elastography (SE).

Conclusion: The results of this network meta-analysis suggested more appropriate combination of different ultrasound modalities is BI-RADS 4b, SMI, and SWE for the diagnosis of breast cancer.

Abbreviations: BI-RADS = Breast Imaging Reporting and Data System, BC = breast cancer, CDFI = color Doppler flow imaging, CEUS = contrast-enhanced ultrasound, CI = confidence intervals, NMA = network meta-analysis, NPV = negative predictive value, ORs = odds ratios, PDI = power Doppler imaging, PPV = positive predictive value, QUADAS = quality assessment of studies of diagnostic accuracy studies, SE = strain elastography, SMI = superb microvascular imaging, SUCRA = surface under the cumulative ranking curve, SWE = shear wave elastrography.

Keywords: breast cancer, BI-RADS, CEUS, CDFI, ultrasonography, SMI, SWE, SE

1. Background

Breast cancer is the second largest malignancy in women, next to uterine cancer. The incidence rate is about 8% of malignant tumors, and it is increasing all over the world.[1] Young adults are often in advanced stage when they are diagnosed with BC, and the 5-year survival rate and quality of life of patients are not optimistic.[2] Therefore, early diagnosis is the key to determine the prognosis of BC patients. With the advantages of high resolution, simple, convenient, low cost, and no radiation, ultrasound has become an important imaging method for early detection of breast lesions and differentiation of benign and malignant.[3] Initially developed in 1993, the American College of Radiology Breast Imaging Reporting and Data System

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All data generated or analyzed during this study are included in this published article.

Ultrasound department of the First Affiliated Hospital of Dalian Medical University.

**Correspondence: Jialing Wu, No. 222 Zhongshan Road, Xigang District, Dalian City, Liaoning Province, China (e-mail: wc027214@163.com).*

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(BI-RADS) lexicon serves to standardize breast imaging reports, improve communication with referring physicians, and provide a quality assurance tool.[4] However, BI-RADS 4 malignant risk is 3%–94%, the span is large, and the ultrasonic diagnosis is easily affected by the operator subjectively, so there is a lack of a relatively unified specific standard for the classification of breast lesions.

Two dimensional color Doppler ultrasound is the basis of ultrasound diagnosis of breast lesions, but with the promotion and wide application of new techniques, more and more atypical lesions in 2-dimensional ultrasound can be accurately diagnosed in the differential diagnosis of breast lesions.[5,6] The stiffness difference between tissues is much greater than the acoustic resistance difference, which is the basis of 2 dimensional ultrasound imaging, and the stiffness or elasticity of tissue is closely related to histopathology.[7] Thus, ultrasound elastography, including strain elastography (SE) and (shear wave elastrography) SWE, provides a new method for the diagnosis of BC through extracting the information of tissue stiffness.[8] Neovascularization and microvessel density are closely related to the degree of malignancy, invasiveness, recurrence, metastasis and the prognosis of tumor patients.[9] Color Doppler flow imaging (CDFI) is often used to show the blood flow inside the tumor, but CDFI is not good for some low-velocity microvessels.[10] Contrast-enhanced ultrasound (CEUS) has high spatial and temporal resolution, and microbubbles have the same fluidity as red blood cells, and some scholars use CEUS to detect neovascularization in BC as reliable evidence for the diagnosis, but it is an invasive examination requiring injection of contrast medium.[11] As a novel ultrasonic technique, superb microvascular imaging (SMI) can quickly, simply and noninvasively observe the microvascular distribution in the tumor and evaluate the microvascular perfusion.[12]

Despite the abundant amount of literature that analyze the various detection of different ultrasound methods, no comprehensive literature that investigates the diagnostic values of BC by different ultrasonography modalities through a NMA has been made available. Each imaging diagnostic examination has its own advantages and disadvantages, and any imaging examination is not enough to make an accurate diagnosis of the disease. Thus, this study aimed to compare diagnostic values among different ultrasonography modalities, including the information of 2-dimension, stiffness and blood flow, by a network metaanalysis in the hopes of understanding which imaging methods are better and which combination of different modalities is more appropriate to diagnose BC.

2. Materials and Methods

2.1. Literature search

We searched the Cochrane Library, PubMed and EMBASE databases to obtain literature relevant to this from the beginning of this investigation up until March 2021. Literature was manually searched using different combinations of keywords and free words. The search terms included: BC, SE, SWE, CEUS, SMI, BI-RADS, power Doppler imaging (PDI) and CDFI.

2.2. Inclusion and exclusion criteria

The inclusion criteria for the study were as follows: (1) the study designs must be diagnostic tests; (2) the imaging methods should include 2 or more of the following ultrasound methods: BI-RADS, SE, SWE, SMI, CEUS,PDI and CDFI; (3) study subjects were consecutive breast lesion patients aging from 12 to 100 years; (4) the outcome indicators studies include of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. The exclusion criteria included were as follows: (1) insufficient data integrity; (2) duplicate publications; (3) conference reports, systematic reviews and summary articles; (4) studies unrelated to BC; (5) nonEnglish studies; and (6) nonhuman studies.

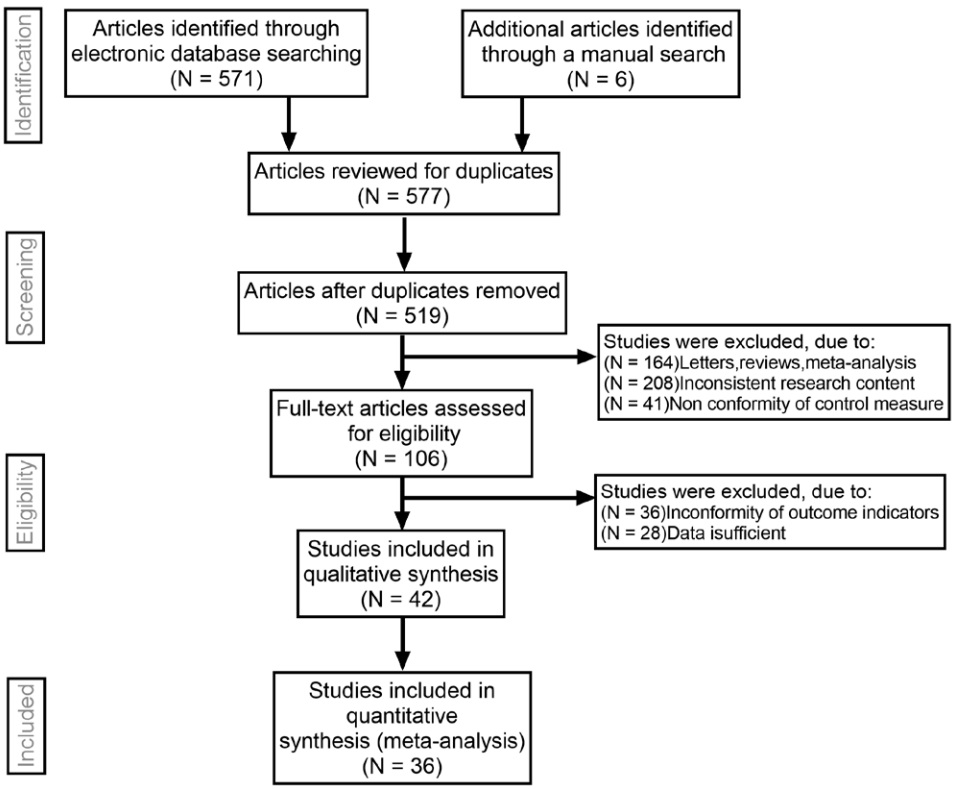

Figure 1. Flow chart of literature search and study selection. 36 studies were included in this net meta-analysis.

2.3. Data extraction and quality assessment

Relevant data were systematically extracted from all included studies by 2 researchers using a standardized form. The researchers collected the following data: the first author's surname, publication year, language of publication, age, sample size, gold standard, and diagnostic accuracy. The true positives, true negatives, false positives, and false negatives in the fourfold (2 × 2) tables were also collected. Methodological quality was independently assessed by 2 researchers based on the quality assessment of studies of diagnostic accuracy studies (QUADAS) tool. The QUADAS criteria included 14 assessment items. Each of these items was scored as "yes" (2), "no" (0), or "unclear"(1). The QUADAS score ranged from 0 to 28, and a score ≥22 indicated good quality.

2.4. Statistical analysis

Firstly, traditional pairwise meta-analyses were performed for studies to compare different diagnostic modalities using the Stata version 15.1 software (StataCorp, College Station, TX). The pooled estimates of odd ratios (ORs) and 95% confidence intervals (CI) for sensitivity, specificity, PPV, NPV and accuracy of BC were shown. Heterogeneity among studies was tested using the I-square and Chi-square tests. If the values of $P < .05$ or $I^2 > 50\%$ indicated that there was greater heterogeneity in the specimen, the random-effect model was used for further analysis, otherwise, a fixed-effect model was performed. Secondly, the R version 3.2.1 statistical computing software and network package were used to draw the network graphs, with each node representing different interventions, the node size reflecting the number of patients, and the thickness of lines between nodes indicating the number of included studies. Thirdly, Bayesian network meta-analyses were performed to combine the effective sizes of direct and indirect comparisons. The basis of each analysis was noninformative before gain-effect sizes and precision. After 4 chains and a 20,000-simulation burn-in stage, the convergence and subsequent lack of auto-correlation were examined and confirmed; finally, direct probability statements were obtained from an additional 50,000-simulation stage. The node-splitting method was adopted to evaluate the consistency between direct and indirect evidence, and the consistency or inconsistency model was selected based on the results of the aforementioned evaluation. To obtain a better interpretation of ORs, the probability of every intervention was calculated in order to find the most effective methods based on a Bayesian approach that employs probability values summarized as the surface under the cumulative ranking curve (SUCRA), the significance or difference in the larger the SUCRA value, the better the rank of the intervention. Cluster analyses were conducted to evaluate different imaging methods on the diagnostic value of BC treatment, by grouping different interventions according to

Table 1

Baseline characteristics of included studies.

Author	Year	Country	Standard method	Sample size	Age	Diagnostic modalities				QUADAS score
						M1	M2	M3	M4	
Evans A[14]	2012	England	Biopsy	175	56 (18–94)	SWE	BI-RADS			23
Jing Du[15]	2012	China	Resection or biopsy	61	48 (27–71)	CEUS	BI-RADS			24
Jung MC[16]	2013	Korea	Resection or biopsy	150	47.8 (22–75)	SWE	BI-RADS	SE		24
Lee EJ[17]	2013	Korea	Resection or biopsy	156	43.5 (21–88)	SWE	BI-RADS			22
Youk JH[18]	2013	Korea	Resection or biopsy	389	46 (22–87)	SWE	BI-RADS			23
Lee SH[19]	2013	Korea	Biopsy	144	49.1 (20–79)	SWE	BI-RADS			22
Wang ZL[20]	2013	China	Biopsy	114	42.8 (18–65)	SWE	BI-RADS			24
Ianculescu V[21]	2014	France	Biopsy or cytology	110	NR	SWE	BI-RADS			23
Xiao XY[22]	2014	China	Resection or biopsy	498	43 (16–84)	CEUS	BI-RADS	SE		25
Zhou J[23]	2014	China	Resection or biopsy	193	46 (18–82)	SWE	BI-RADS			22
Stanzani D[24]	2014	Brazil	Biopsy	70	NR	CEUS	BI-RADS	CDFI		23
Zhang JX[25]	2014	China	Resection	107	46 (25–71)	CEUS	BI-RADS			24
Klotz T[26]	2014	France	Resection or biopsy	167	57.7 (22–88)	SWE	BI-RADS			24
Shi XQ[27]	2015	China	Resection or biopsy	279	45.3 (22–87)	SWE	BI-RADS			23
Dobruch-Sobczak K[28]	2015	Poland	Resection or biopsy	84	53.9 (24–85)	SWE	BI-RADS			25
Ma Y[29]	2015	China	Resection or biopsy	123	44 (15–69)	SMI	CDFI			24
Zhao YF[30]	2016	China	Resection or biopsy	135	45 (18–65)	PDI	SMI			23
Li DD[31]	2016	China	Resection or biopsy	296	45.4 (16–84)	SWE	BI-RADS			25
Xiao XY[32]	2016	China	Resection or biopsy	132	44 (16–78)	SMI	CEUS	CDFI		23
Li XL[33]	2016	China	Resection or biopsy	116	48.5 (21–84)	SWE	SE	BI-RADS		24
Cong R[34]	2017	China	Biopsy	325	44.6 (18–81)	SWE	BI-RADS			24
Tian J[35]	2017	China	Resection or biopsy	210	43.1 (18–80)	SWE	BI-RADS			22
Lin X[36]	2018	China	Resection or biopsy	2262	43 (18–91)	SWE	BI-RADS			23
Zhu YC[37]	2018	China	Resection or biopsy	123	53 (16–64)	CDFI	SWE	SMI		22
Song EJ[38]	2018	Korea	Resection or biopsy	209	47 (17–78)	SWE	BI-RADS			24
Park AY[39]	2019	Korea	Resection or biopsy	98	45.6 (20–76)	SMI	CEUS			23
Han J[40]	2019	China	Resection or biopsy	278	44.7 (19–85)	SWE	SE			25
Huang Y[41]	2019	China	Resection or biopsy	278	42.0 ± 10.1	SWE	BI-RADS			22
Gürüf A[42]	2019	Turkey	Biopsy	87	49.6 (16–64)	BI-RADS	SE	SWE		23
Fujioka T[43]	2019	Japan	Resection or biopsy	148	54 (25–85)	BI-RADS	SE	SWE		24
Wang Q[44]	2019	China	Resection or biopsy	122	45 (33–56)	SWE	BI-RADS			24
Lee EJ[45]	2020	Korea	Resection or biopsy	200	49 (19–82)	SWE	SMI			23
Liang M[46]	2020	China	Resection or biopsy	177	44 (19–78)	BI-RADS	SE	SWE		25
Jiang H[47]	2020	China	Resection or biopsy	164	45 (15–81)	BI-RADS	SE	SWE		23
Diao X[48]	2020	China	Resection	85	54.2 (34–66)	CDFI	PDI	SMI	CEUS	25
Jia WR[49]	2021	China	Resection or biopsy	201	46.1 (18–82)	SWE	SE	BI-RADS		24

NR = not reported, QUADAS = the quality assessment of studies of diagnostic accuracy studies.

Table 2

Estimated OR and 95%CI of pairwise meta-analysis for sensitivity, specificity, PPV, NPV, and accuracy for BC.

		Heterogeneity assessment		Pairwise meta-analysis		
Included studies	**Comparisons**	**I2**	**Ph**	**OR (95%CI)**	**Z**	**P**
Sensitivity						
10 studies	G - A	45.60%	0.057	4.23 (2.30,7.78)	4.65	0.000
13 studies	H - A	77.67%	0.000	1.88 (1.04,3.39)	2.11	0.035
2 studies	F - A	1.80%	0.313	1.72 (0.94,3.15)	1.77	0.077
1 study	C - A	NA	NA	0.37 (0.15,0.91)	2.17	0.030
7 studies	B - A	54.20%	0.041	0.88 (0.50,1.55)	0.43	0.669
1 study	E - B	NA	NA	1.10 (0.60,2.01)	0.31	0.759
1 study	F - B	NA	NA	0.31 (0.13,0.75)	2.59	0.010
4 studies	G - B	24.00%	0.267	6.37 (1.67,24.21)	2.72	0.007
4 studies	H - B	81.60%	0.001	0.90 (0.36,2.26)	0.23	0.821
1 study	D - C	NA	NA	1.70 (0.69,4.23)	1.15	0.251
3 studies	E - C	72.10%	0.028	4.01 (0.91,17.64)	1.83	0.067
4 studies	F - C	73.00%	0.011	2.28 (0.94,5.52)	1.82	0.069
1 study	G - C	NA	NA	7.93 (0.39,162.07)	1.35	0.178
1 study	E - D	NA	NA	10.50 (2.75,40.10)	3.44	0.001
2 studies	F - D	0.00%	0.381	3.42 (1.59,7.39)	3.13	0.002
3 studies	F - E	60.20%	0.081	0.79 (0.42,1.51)	0.72	0.474
1 study	G - E	NA	NA	5.43 (0.25,118.96)	1.07	0.283
3 studies	H - E	65.50%	0.055	0.57 (0.22,1.44)	1.2	0.231
1 study	G - F	NA	NA	28.37 (3.71,217.11)	3.22	0.001
Specificity						
10 studies	G - A	85.10%	0.000	0.20 (0.11,0.37)	5.02	0.000
13 studies	H - A	94.40%	0.000	0.64 (0.28,1.44)	1.08	0.282
2 studies	F - A	93.50%	0.000	0.46 (0.06,3.46)	0.75	0.453
1 study	C - A	NA	NA	1.84 (0.89,3.83)	1.64	0.101
7 studies	B - A	69.20%	0.003	0.70 (0.41,1.19)	1.31	0.192
1 study	E - B	NA	NA	1.47 (0.87,2.48)	1.44	0.149
1 study	F - B	NA	NA	3.44 (1.31,9.09)	2.5	0.013
4 studies	G - B	73.70%	0.010	0.23 (0.10,0.54)	3.4	0.001
4 studies	H - B	85.60%	0.000	1.13 (0.47,2.69)	0.27	0.790
1 study	D - C	NA	NA	0.76 (0.27,2.13)	0.52	0.601
3 studies	E - C	85.00%	0.001	1.62 (0.41,6.34)	0.69	0.490
4 studies	F - C	81.20%	0.001	1.83 (0.67,5.00)	1.17	0.242
1 study	G - C	NA	NA	1.46 (0.62,3.44)	0.87	0.385
1 study	E - D	NA	NA	1.54 (0.53,4.48)	0.8	0.423
2 studies	F - D	0.00%	0.576	1.25 (0.58,2.67)	0.57	0.567
3 studies	F - E	0.00%	0.381	0.84 (0.46,1.53)	0.58	0.564
1 study	G - E	NA	NA	2.29 (0.97,5.36)	1.9	0.057
3 studies	H - E	7.60%	0.339	0.51 (0.33,0.79)	3.05	0.002
1 study	G - F	NA	NA	0.05 (0.02,0.12)	6.43	0.000
PPV						
10 studies	G - A	66.60%	0.001	0.40 (0.26,0.60)	4.39	0.000
13 studies	H - A	88.60%	0.000	0.78 (0.43,1.43)	0.80	0.424
2 studies	F - A	86.40%	0.007	0.59 (0.14,2.49)	0.72	0.471
1 study	C - A	NA	NA	1.15 (0.52,2.55)	0.35	0.728
7 studies	B - A	27.90%	0.216	0.70 (0.52,0.92)	2.51	0.012
1 study	E - B	NA	NA	1.42 (0.83,2.43)	1.29	0.196
1 study	F - B	NA	NA	2.44 (0.91,6.56)	1.77	0.076
4 studies	G - B	60.70%	0.054	0.45 (0.24,0.82)	2.61	0.009
4 studies	H - B	79.80%	0.002	1.09 (0.49,2.41)	0.20	0.841
1 study	D - C	NA	NA	1.07 (0.34,3.35)	0.11	0.912
3 studies	E - C	72.00%	0.028	2.04 (0.73,5.67)	1.36	0.174
4 studies	F - C	45.40%	0.139	1.99 (1.27,3.12)	2.99	0.003
1 study	G - C	NA	NA	1.44 (0.59,3.49)	0.80	0.421
1 study	E - D	NA	NA	2.50 (0.82,7.60)	1.62	0.106
2 studies	F - D	0.00%	0.436	1.68 (0.75,3.75)	1.27	0.205
3 studies	F - E	0.00%	0.799	0.87 (0.47,1.62)	0.43	0.666
1 study	G - E	NA	NA	1.74 (0.74,4.10)	1.26	0.206
3 studies	H - E	18.50%	0.293	0.47 (0.30,0.73)	3.34	0.001
1 study	G - F	NA	NA	0.15 (0.06,0.36)	4.17	0.000
NPV						
10 studies	G - A	20.80%	0.251	2.38 (1.28,4.43)	2.73	0.006
13 studies	H - A	63.70%	0.001	1.47 (0.99,2.17)	1.94	0.052
2 studies	F - A	0.00%	0.914	1.25 (0.70,2.26)	0.75	0.454
1 study	C - A	NA	NA	0.59 (0.25,1.38)	1.22	0.222
7 studies	B - A	5.80%	0.383	0.85 (0.59,1.22)	0.88	0.378
1 study	E - B	NA	NA	1.13 (0.63,2.05)	0.42	0.677
1 study	F - B	NA	NA	0.44 (0.18,1.04)	1.87	0.062

(*Continued*)

Table 2

(*Continued*)

Included studies	Comparisons	Heterogeneity assessment		Pairwise meta-analysis		
		I2	Ph	OR (95%CI)	Z	P
4 studies	G - B	5.20%	0.367	3.46 (1.09,11.05)	2.10	0.036
4 studies	H - B	76.60%	0.005	0.91 (0.42,1.96)	0.25	0.802
1 study	D - C	NA	NA	1.21 (0.57,2.60)	0.49	0.621
3 studies	E - C	38.10%	0.199	3.50 (1.68,7.31)	3.34	0.001
4 studies	F - C	0.00%	0.434	1.93 (1.25,2.99)	2.96	0.003
1 study	G - C	NA	NA	8.06 (0.40,163.21)	1.36	0.174
1 study	E - D	NA	NA	6.49 (1.77,23.84)	2.82	0.005
2 studies	F - D	0.00%	0.513	2.54 (1.23,5.25)	2.53	0.012
3 studies	F - E	24.10%	0.268	0.77 (0.41,1.43)	0.83	0.409
1 study	G - E	NA	NA	7.09 (0.32,155.28)	1.24	0.213
3 studies	H - E	55.30%	0.107	0.57 (0.26,1.25)	1.41	0.158
1 study	G - F	NA	NA	9.71 (1.27,74.55)	2.19	0.029
Accuracy						
10 studies	G - A	74.70%	0.000	0.45 (0.31,0.65)	4.22	0.000
13 studies	H - A	90.40%	0.000	0.89 (0.59,1.33)	0.57	0.569
2 studies	F - A	78.80%	0.030	0.80 (0.36,1.81)	0.53	0.598
1 study	C - A	NA	NA	0.96 (0.55,1.67)	0.14	0.888
7 studies	B - A	0.00%	0.680	0.72 (0.58,0.89)	3.00	0.003
1 study	E - B	NA	NA	1.30 (0.88,1.92)	1.30	0.195
1 study	F - B	NA	NA	0.96 (0.53,1.72)	0.15	0.882
4 studies	G - B	75.90%	0.006	0.58 (0.31,1.08)	1.71	0.087
4 studies	H - B	88.90%	0.000	1.04 (0.49,2.18)	0.11	0.914
1 study	D - C	NA	NA	1.17 (0.62,2.20)	0.48	0.629
3 studies	E - C	85.90%	0.001	2.34 (0.78,7.01)	1.52	0.128
4 studies	F - C	46.10%	0.134	1.96 (1.45,2.65)	4.35	0.000
1 study	G - C	NA	NA	1.68 (0.78,3.60)	1.34	0.182
1 study	E - D	NA	NA	3.68 (1.66,8.20)	3.19	0.001
2 studies	F - D	10.90%	0.289	2.05 (1.21,3.48)	2.66	0.008
3 studies	F - E	0.00%	0.838	0.81 (0.53,1.24)	0.97	0.331
1 study	G - E	NA	NA	2.17 (1.02,4.58)	2.02	0.043
3 studies	H - E	71.00%	0.032	0.62 (0.30,1.28)	1.29	0.197
1 study	G - F	NA	NA	0.38 (0.23,0.64)	3.68	0.000

95% CI = 95%confidence intervals, A = SWE, B = SE, C = CDFI, D = PDI, E = CEUS, F = SMI, G = BI-RADS 4A, H = BI-RADS 4B, NA = not available, NPV = negative predictive value, OR = odds ratios, PPV = positive predictive value.

similarities of 2 variables to judge the efficacies by comparing the advantages and disadvantages of different imaging methods. Comparison-adjusted funnel plots were performed to detect the small study effects on data. R (V.3.2.1) package gemtc (V.0.6) and Markov Chain Monte Carlo engine Open BUGS (V.3.4.0) are both used for making all necessary computations.[13]

3. Results

3.1. Characteristics of included studies

Initially, the searched keywords identified 577 articles. We Reviewed the titles and abstracts of all articles and excluded 471 articles; full texts and data integrity were also reviewed and 70 were further excluded. Finally, 36 studies that met all inclusion criteria were included in this meta-analysis.[14–49] Figure 1 showed the selection process of eligible articles. A total of 8466 breast lesions were assessed. We summarized the study characteristics and methodological quality in Table 1. The QUADAS scores of all included studies were ≥22.

3.2. Pairwise meta-analysis

We conducted a direct-paired comparison of the diagnostic value of 8 different ultrasound methods for the treatment of BC. The results revealed CEUS exhibited higher sensitivity, specificity, PPV, NPV, and accuracy among CDFI, PDI, SMI, and CEUS. SWE had higher sensitivity, specificity, PPV, NPV, and accuracy than SE (Table 2).

3.3. Evidence network

In terms of sensitivity, we can make the indication that both SWE and BI-RADS(4b) methods were used by a relatively large number of patients (Fig. 2).

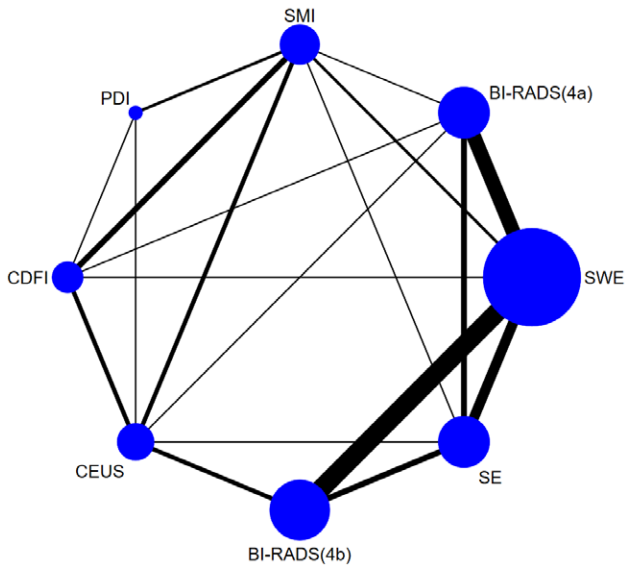

Figure 2. Evidence network plot of diagnostic value of 8 ultrasound modalities for BC.

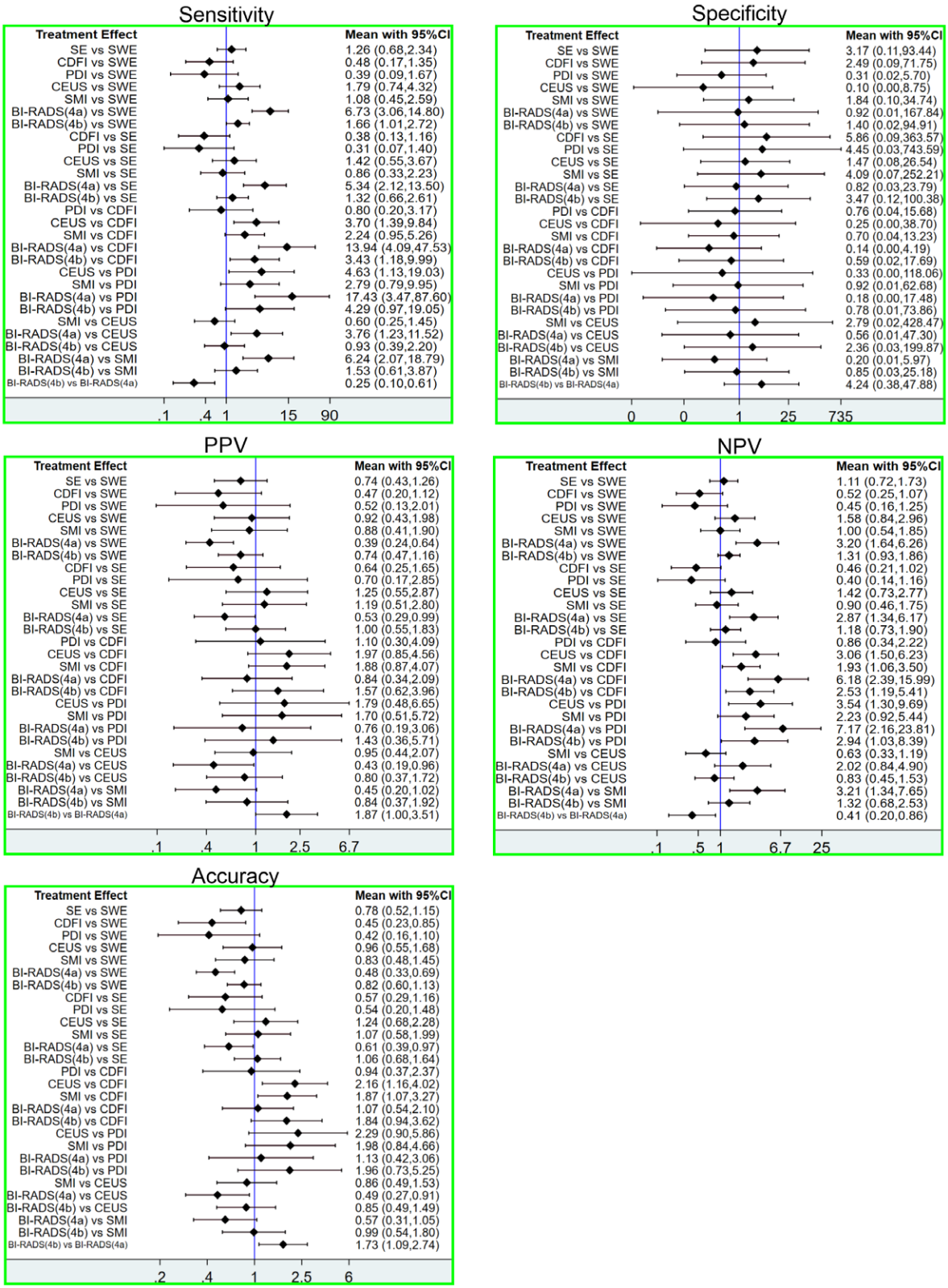

Figure 3. Forest plots of diagnostic value of 8 ultrasound modalities for BC.

Table 3

SUCRA values of 8 diagnostic modalities under 5 endpoint outcomes.

Treatments	Sensitivity	Specificity	PPV	NPV	Accuracy
SWE	37.6	**84**	**82.4**	40.5	**86.4**
SE	**53.7**	53.7	53.6	**52.1**	56.8
CDFI	11.6	34.5	23.1	10.2	15.6
PDI	8.8	46.4	34.3	8.1	17.5
CEUS	**72.5**	61.6	**72.6**	**78.5**	**79.1**
SMI	45.2	**64.5**	69.8	44.5	65.4
BI-RADS(4a)	**99.8**	4.9	11.4	**98.9**	17.8
BI-RADS(4b)	70.9	**50.5**	**52.8**	67.3	**61.4**

Maximum SUCRA value of hardness (SE,SWE), blood flow (CDFI, PDI, CEUS, SMI) and two-dimensional(BI-RADS) information of breast tumor.
NPV = negative predictive value, PPV = positive predictive value.

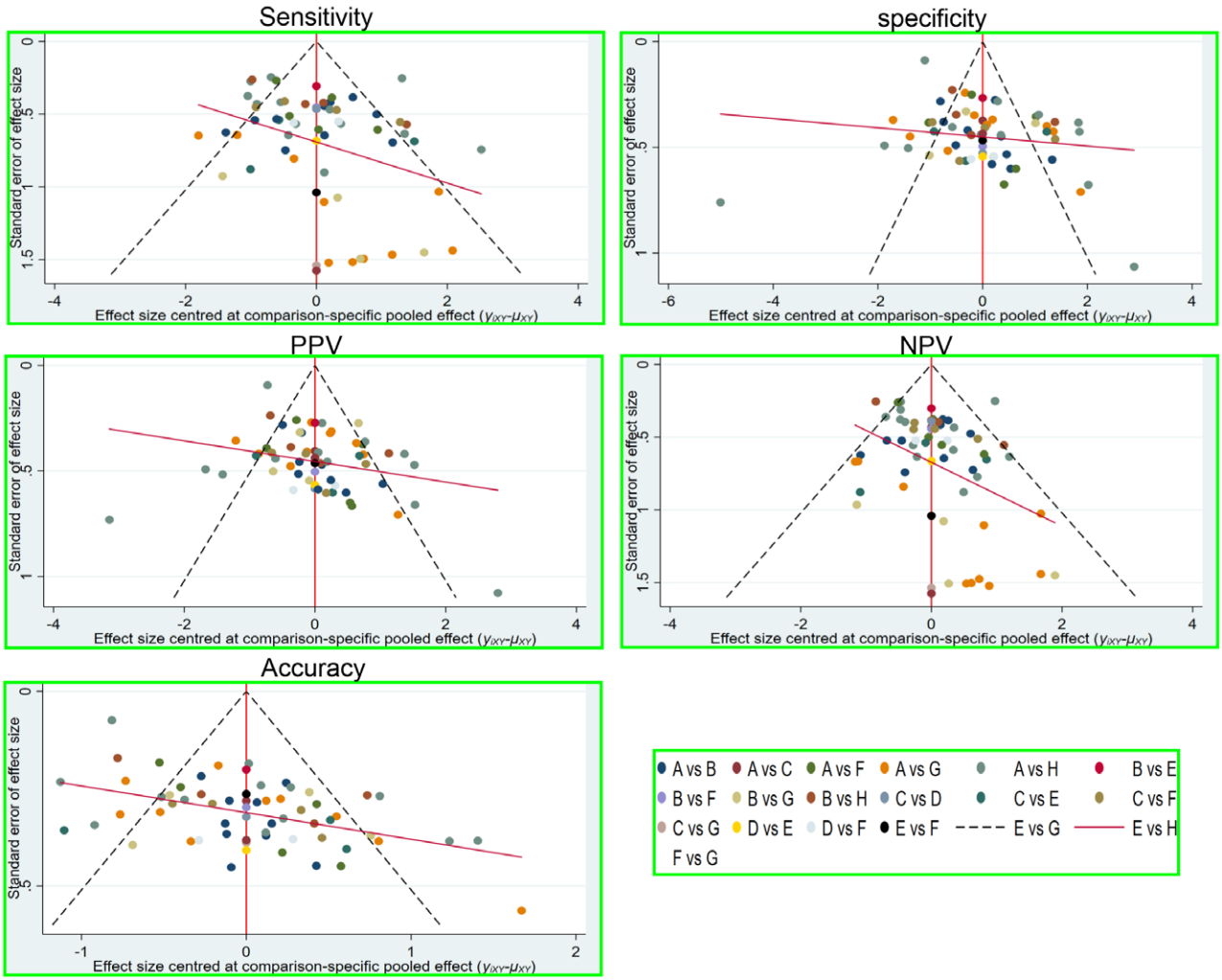

Figure 4. Comparison-adjusted funnel plot for diagnostic value of 8 ultrasound modalities for BC. A = SWE; B = SE; C = CDFI; D = PDI; E = CEUS; F = SMI; G = BI-RADS 4a; H = BI-RADS 4b.

3.4. Inconsistency test

The results showed no inconsistencies among the studies thanks to a node-splitting method in terms of sensitivity, specificity, PPV, NPV, and accuracy (all $P > .05$). Therefore, due to the consistent nature of the results, logically the consistency model was applied.

3.5. Network meta-analysis

BI-RADS 4b exhibited higher specificity, PPV, and accuracy and lower sensitivity and NPV than BI-RADS 4a. CEUS had the highest sensitivity, PPV, NPV, and accuracy and SMI had the highest specificity among CDFI, PDI, SMI, and CEUS. There was no significant difference in diagnostic indexes between SMI and CEUS. SWE had higher PPV and accuracy and lower sensitivity, specificity NPV than SE (Fig. 3).

3.6. SUCRA values of the diagnostic value for BC

The SUCRA values of different ultrasound methods were summarized and shown in Table 3. SWE, CEUS, SMI, BI-RADS 4b exhibited higher accuracy.

3.7. Assessment of publication bias

The results of assessment of publication bias showed symmetrical distribution, indicating no small sample effect or publication bias in this network meta-analysis for specificity, PPV, and accuracy (Fig. 4).

3.8. Ethics and dissemination

We will not obtain ethic documents because this study will be conducted based on the data of published literature. We expect to publish this study on a peer-reviewed journal.

4. Discussion

Use of standardized terminology, report organization, and assessment structures allows radiologists to communicate breast imaging findings to referring physicians clearly and succinctly.[4] Mainly based on conventional 2 dimensional color Doppler ultrasound as before, the fifth edition of the ACR BI-RADS lexicon was released in February 2014, and subdivision of category 4, which was always focused on, included Category 4A (low suspicion for malignancy, >2–10% likelihood of malignancy), Category 4B (moderate suspicion for Malignancy, >10–50% likelihood of malignancy) and Category 4C (high suspicion for malignancy, >50%–<95% likelihood of malignancy).[50] But as a diagnostic test, the diagnostic threshold was a fixed value, BI-RADS 4a or BI-RADS 4b, in some literature. Which diagnostic threshold has higher diagnostic value is our concern, that is lack of direct comparison. In this article through a NMA, we found BI-RADS 4B exhibited higher specificity and PPV and lower sensitivity and NPV than BI-RADS 4A, but the accuracy of BI-RADS 4B was higher.

Blood flow information is very important for tumor diagnosis. Conventional color Doppler ultrasound can detect the nutrient vessels with a diameter of 200 mm or more, but can not show the vessels with low velocity.[10] By intravenous injection of contrast agent, CEUS could increase the contrast of tissue blood flow, dynamically observe the number, distribution and course of blood vessels in tissues, organs or tumors in real time, improve the detection rate of microvessels, and increase the display of tissues, organs and lesions.[11] It has good diagnostic efficiency in the differential diagnosis of breast tumors, and the image features of benign lesions were regular shape, clear boundary, blood vessels distributed around the lesions, and the lumen was uniform in thickness and distribution, while the malignant lesions were irregular in shape, with radial enhancement on the edge, uneven thickness, distortion or penetration of blood vessels around, and uneven distribution, and filling defect in the lesions.[39] SMI is a noninvasive Doppler technique for detecting tumor blood flow, and can display low-speed microvessels with a minimum diameter of 0.1 mm.[30] Conventional ultrasound imaging needs to filter the clutter signal, including the Doppler signal generated by the low-speed movement of tissue and low-speed blood flow, while the principle of SMI technology is to use adaptive technology to separate and display the low-speed blood flow signal from the filtered clutter signal. The advantage is that it can display the micro vessels with slow flow velocity without using contrast agent. It has the characteristics of low flow velocity display, high resolution, less motion artifacts and high frame rate.[48] In this NMA, CEUS exhibited the best diagnostic efficacy about blood flow information, but because it was invasive and relatively expensive and its diagnostic efficacy has no significant difference with SMI, SMI was considered more appropriate for the diagnosis for BC.

There are significant differences in the texture between benign and malignant breast tumors.[51] In malignant breast lesions, cancer cells infiltrate into the surrounding stroma, interstitial tissue fibers proliferate intensively with a small amount of adenoid tissue; while benign lesions are usually composed of proliferative glands and fibrous stroma, which are loose due to rich polysaccharides, so the hardness of malignant tumors is usually higher than that of benign tumors.[46] SE is base on the difference in strain after external force according to the elastic coefficient of different tissues, which is imaged by color coding, while according to the different propagation speed of shear wave in different hardness tissues, SWE uses ultra fast imaging technology to record the tissue movement caused by shear wave propagation in real time and accurately, and then calculates the propagation speed of shear wave through each particle of tissue through autocorrelation algorithm, and then measures the stiffness of the tissue.[38] In this article, either pairwise meta-analysis or NMA showed SWE had better diagnostic efficacy than SE.

Advantages of our study included the wide range of comparison, allowing us to compare all 8 different imaging methods in order to assess the diagnostic values of BC in patients. However, several limitations need to be acknowledged. Firstly, Sensitivity and NPV demonstrated positive publication bias, indicating the presence of potential unpublished studies that might influence the outcome. Secondly, the retrospective nature of a meta-analysis can lead to subject selection bias. Thirdly, significant heterogeneity was noticed across studies, which might be attributed to several factors, such as different diagnostic criteria, different instrument, and variations in patients' characteristics.

5. Conclusion

The results of this network meta-analysis suggested more appropriate combination of different ultrasound modalities is BI-RADS 4B, SMI, and SWE for the diagnosis of BC.

Author contributions

Conceptualization: Yang Zhou.
Data curation: Jialing Wu.
Methodology: Yang Zhou.
Writing – original draft: Jialing Wu.
Writing – review & editing: Yang Zhou.

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