Systematic Review and Meta-Analysis

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The diagnostic accuracy of contrast-enhanced ultrasound for the differentiation of benign and malignant thyroid nodules

A PRISMA compliant meta-analysis

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Abstract

Background: Contrast-enhanced ultrasound (CEUS) is a non-invasive method that has been used in the diagnosis of several diseases. Recently, CEUS has been used in the differentiation of benign and malignant thyroid nodules. However, the performance of CEUS in thyroid nodules has not been studied clearly.

Methods: The databases of Pubmed, Embase, Cochrane library and the unpublished studies were systematically searched for candidate inclusions, with the use of CEUS in differentiating the benign and malignant thyroid nodules. The quality of included studies was assessed using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) questionnaire. The pooled estimates of sensitivity, specificity, diagnostic odds ratio (DOR), positive and negative likelihood ratio (NLR) were calculated using STATA software version 14.0.

Results: Totally 33 diagnostic studies were included for further analysis. The quality of included studies was relatively high using QUADAS method. The pooled estimates of sensitivity and specificity were 0.88 (95% CI 0.85, 0.91) and 0.88 (95% CI 0.83, 0.91), respectively. In addition, the DOR, the positive and NLRs were pooled positive LR and the negative LR were 54 (95% CI 33, 89), 7.1% (5.2%, 9.8%), and 0.13% (0.10%, 0.18%). No significant publication bias was observed.

Conclusions: Our meta-analysis further indicated that CEUS is a useful tool in differentiating benign and malignant thyroid nodules, with high sensitivity and specificity.

Abbreviations: CEUS = contrast-enhanced ultrasound, DOR = diagnostic odds ratio, FN = false-negative, FNA = fine-needle aspiration, FP = false-positive, HSROC = hierarchical summary ROC model, NLR = negative likelihood ratio, PLR = positive likelihood ratio, QUADAS = Quality Assessment of Diagnostic Accuracy Studies, SROC = summary receiver operating characteristic, TN = true-negative, TP = true-positive.

Keywords: contrast-enhanced ultrasound, diagnostic accuracy, meta-analysis, thyroid nodules

1. Introduction

Thyroid nodules have a high prevalence of 19% to 67% among different populations, of which the malignant nodules account for almost 5% to 10% according to previous reports.[1,2] Since the early trend of lymphatic metastasis, the diagnosis and distinguish between the benign and malignant thyroid nodules become important for doctors.[3] Currently, the most commonly used diagnostic tools for thyroid nodules were the ultrasound (US) and the fine-needle aspiration (FNA). Conventional sonographic technique has been used to distinguish between benign and malignant thyroid nodules by exhibiting the echogenicity, margins, presence of microcalcifications, and vascular flow, which is the choice of first-screen by doctors. Although widely used due to the features of non-invasiveness and inexpensiveness, the diagnostic sensitivity and specificity are not satisfactory, since the sonograms of some lesions were overlapped between the benign and the malignant nodules.[4–6] On the other hand, FNA is widely adopted by clinicians as a simple, minimally invasive way of diagnosing thyroid nodules with sensitivity and specificity ranged from 65% to 98% and 72% to 100%, respectively. However, this technique is invasive and still have false positive or negative outcomes, with relatively poor sensitivity.[7–9] It is reported approximately 10% to 20% of thyroid nodules could not be diagnosed and some patients refuse to undergo FNA biopsy. Therefore, finding a way to increase the diagnostic accuracy would spare a large number of patients an unnecessary invasive procedure and other effective US examinations are needed for the diagnosis of benign and malignant thyroid nodules.

Recent advances in technology increase the accuracy of US in the diagnosis of thyroid nodules. Especially the contrast-enhanced ultrasound (CEUS) could exhibit both of the micro- and macro-vascularization and the perfusion assessment over-time, with the help of microbubble contrast material to investigate the dynamic enhancing pattern.[10,11] CEUS allows studying dynamic enhancement patterns of focal thyroid nodules in real time and thus provides much better characterization of focal thyroid nodules than conventional US. The technique of CEUS has been shown to play important roles in different fields,

Editor: Kou Yi.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:49(e13325)

Received: 30 May 2018 / Accepted: 24 October 2018

http://dx.doi.org/10.1097/MD.0000000000013325

especially in liver lesions.[12,13] However, the diagnostic value of CEUS on the characterization of thyroid nodules have not been reported very much and not been incorporated to the published guidelines on non-liver application.[14] The 2013 NCCN guidelines did not discuss the role of CEUS on the diagnosis of the thyroid lesions while the Chinese thyroid cancer diagnosis and therapy guidelines in 2012 stated that CEUS on thyroid nodules need further investigation.[15] Previous meta-analyses showed that CEUS might improve the diagnostic accuracy of thyroid nodules, but these studies are not up-to-date and the number of these studies is quite few.[16,17] In this meta-analysis, we searched the diagnostic studies of CEUS on the distinction of benign and malignant nodules and summarized the pooled estimates of different parameters, including the sensitivity, specificity, the diagnostic odds ratio (DOR) and the posttest probabilities, while drawing the summary receiver operating characteristic (SROC) and hierarchical summary receiver operating characteristic (HSROC) curves. This meta-analysis may help further investigating the diagnostic roles of CEUS on the thyroid nodules and provide some insights into the differentiation of thyroid nodules.

2. Materials and methods

2.1. Literature search

In this meta-analysis, major databases (Pubmed, Embase and the Cochrane library) and unpublished data (*www.clinicaltrials.gov*) were searched for possible candidate articles published until May, 2018. MESH terms and other terms were both used for literature searching using different combinations. The terms used included "thyroid nodules", "thyroid neoplasm", "thyroid", "diagnosis", "diagnostic", "contrast-enhanced ultrasound", and "CEUS". The searches were limited to identify the diagnostic studies without language restrictions. Two authors (Q Liu and J Cheng) conducted the literature searching independently with a third investigator (J Li) solved any discrepancy. The study was approved by the Ethics Committee of the People's Hospital of Rizhao.

2.2. Study selection

After searching the candidate studies for inclusion, we set the inclusion and exclusion criteria for further identification. Publications were selected if they met the following criteria:

1. The studies that assessed the diagnostic accuracy of CEUS for the distinction between benign and malignant thyroid nodules, that is, the studies using CEUS to evaluate the nature of thyroid nodules to be benign or malignant, elucidating the diagnostic accuracy of CEUS with reference methods such as FNA or pathological results;
2. The studies that adopted the appropriate reference diagnostic standard, the pathology diagnosis, defined as the histology and cytology of biopsy specimens or histology of the surgical specimens;
3. The studies that provided the diagnostic data that were sufficient for us to calculate the values of true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) results for the 2×2 contingency table.

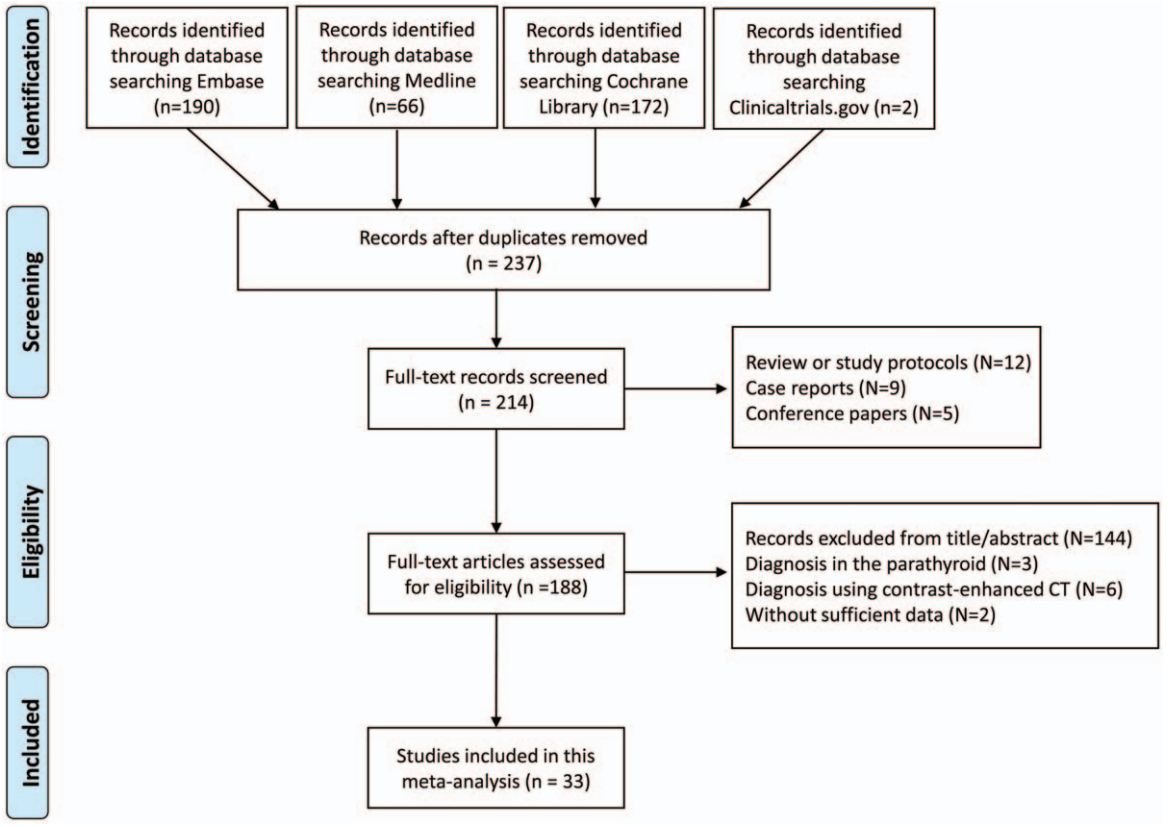

Figure 1. The flow diagram of literature searching and selection of studies according to the PRISMA criteria.

Table 1

The baseline characteristics and the data extracted from the included studies.

Study	Publication	Number of nodules (Benign vs Malignant)	Mean age and gender (Male%)	Study region	Gold standard	Contrast agent	TP	FP	FN	TN
Acharya 2011	Technol Cancer Res Treat	20 (10 vs 10)	53.5 years 50.0%	Singapore	FNA biopsy	SonoVue	39	0	1	40
Acharya 2012	Ultrasonics	240 (120 vs 120)	51.8 years 50.0%	Singapore	FNA biopsy	SonoVue	117	1	3	119
Acharya 2013	Proc Inst Mech Eng H	30 (5 vs 25)	51.8 years 50.0%	Singapore	FNA biopsy	SonoVue	25	0	0	5
Bartolotta 2006	Eur Radiol	18 (5 vs 9)	44.3 years 44.4%	Italy	Histology of resected specimens	2.4 mL SonoVue	10	0	3	5
Cantisani 2013	Eur J Radiol	53 (34 vs 19)	49 years 72.9%	Italy	FNA cytology	4.8 mL SonoVue	15	3	4	31
Chen 2016	Mol Clin Oncol	319 (183 vs 136)	43.6 years 34.0%	China	Surgical histopathology	25 mg SonoVue	158	17	25	119
Deng 2014	PLOS One	175 (119 vs 56)	46.3 years 28.8%	China	FNA biopsy	2.4 mL SonoVue	46	18	10	111
Diao 2017	Transl Cancer Res	87 (32 vs 55)	52.4 years -	China	Surgical histopathology	1.5 mL SonoVue	51	6	4	26
Ferrari 2008	J Ultrasound	16 (7 vs 9)	44 years 21.7%	Italy	FNA cytology	2.4 mL SonoVue	9	2	0	5
Friedrich-Rust 2009	Exp Clin Endocrinol Diabetes	53 (46 vs 7)	53.5 years 26.0%	USA	FNA cytology	4.8 mL SonoVue	6	6	1	40
Giusti 2013	J Zhejiang Univ-Sci B (Biomed & Biotechnol)	33 (16 vs 17)	55.9 years 19.0%	Italy	FNA biopsy	4.8 mL SonoVue	12	5	5	11
Jiang 2014	J Ultrasound Med	122 (60 vs 62)	45 years 30.3%	China	Pathological diagnosis	2.4 mL SonoVue	60	3	2	57
Jiang 2015	Kaohsiung J Med Sci	122 (73 vs 49)	46 years 30.3%	China	Pathological diagnosis	2.4 mL SonoVue	44	6	5	67
Jin 2016	Ultrasound in Med. & Biol	77 (41 vs 36)	44 years 25.7%	China	FNA biopsy or Surgery	1.5–2.5 mL SonoVue	30	14	6	27
Ke 2017	Chin J Interv Image Ther	69 (37 vs 32)	49.9 years 16.7%	China	Pathological diagnosis	SonoVue	21	3	11	34
Li 2013	Exp Ther Med	310 (98 vs 212)	47.2 years 27.1%	China	FNA biopsy	2.4 mL SonoVue	199	41	13	57
Li 2017	Ultrasound Q	89 (33 vs 56)	43.2 years 23.6%	China	Pathological diagnosis	2.4 mL SonoVue	52	4	4	29
Liu 2017	Oncol Lett	125 (65 vs 57)	40.3 years 33.0%	China	Pathological diagnosis	SonoVue	34	7	23	58
Ma 2013	Thyroid	172 (94 vs 78)	48.7 years 27.1%	China	Pathology of surgical specimens	SonoVue	70	6	8	88
Ma 2017	Acta Radiologica	135 (56 vs 79)	48.6 years 23.0%	China	Pathological diagnosis	2.4 mL SonoVue	70	3	9	53
Nemec 2012	Eur J Radiol	42 (29 vs 13)	52.1 years 21.7%	Australia	Histology of surgical specimens	2.4 mL SonoVue	8	3	5	26
Wang 2017	Chin J Med Image Tech	95 (20 vs 75)	41.2 years 18.9%	China	Pathological diagnosis	1.6 mL SonoVue	62	8	13	12

(*continued*)

Table 1
(continued).

Study	Publication	Number of nodules (Benign vs Malignant)	Mean age and gender (Male%)	Study region	Gold standard	Contrast agent	TP	FP	FN	TN
Wu 2015	Clin Hemorheol Microcirc	96 (92 vs 4)	53 years 41.7%	China	FNA or Histology of surgical specimens	1.2 mL SonoVue	3	14	1	78
Wu 2016	Endocrine	133 (48 vs 85)	46.3 years 33.7%	China	FNA biopsy or Histology of surgical specimens	1.2 mL SonoVue	81	16	4	32
Yuan 2015	J Cancer Res Ther	78 (41 vs 37)	39.9 years 41.0%	China	Pathological diagnosis	2.5 mL SonoVue	35	5	2	36
Zhan 2017	Ultrasound in Med & Biol	40 (12 vs 28)	49.6 years 22.9%	China	Pathological diagnosis	2.0 mL SonoVue	26	2	2	10
Zhang 2008	J Zhejiang University (Medical science)	40 (11 vs 25)	–	China	Pathological diagnosis	2.4 mL SonoVue	16	1	9	10
Zhang 2010	Thyroid	104 (53 vs 51)	44.2 years 22.1%	China	Pathological diagnosis	1.2 mL SonoVue	45	4	6	49
Zhang 2016	Med Sci Monit	157 (75 vs 82)	45.4 years -	China	FNA biopsy	2.4 mL SonoVue	72	26	10	49
Zhang 2016	Medicine	111 (57 vs 54)	48.0 years 18.0%	China	Pathological diagnosis	SonoVue	46	18	8	39
Zhang 2017	Eur Radiol	319 (244 vs 75)	46.1 years 34.6%	China	FNA biopsy	2.4 mL SonoVue	58	15	17	229
Zhao 2015	Ultrasound in Med & Biol	83 (25 vs 58)	45.7 years 26.5%	China	FNA biopsy or Histology of surgical specimens	1.2 mL SonoVue	53	4	5	21
Zhou 2013	Chin J Otorhinolaryngol Head Neck Surg	179 (110 vs 69)	45.0 years 31.85	China	FNA biopsy or Histology of surgical specimens	2.4 mL SonoVue	64	10	5	100

FN = false-negative, FNA = fine needle aspiration, FP = false-positive, TN = true-negative, TP = true-positive.

Table 2

Quality assessment of the studies included in our meta-analysis.

Publication and reference number	Item number on QUADAS Systematic Review—Assessment Tool*													
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Acharya, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acharya, 2012	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Acharya, 2013	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bartolotta, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cantisani, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen, 2016	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Deng, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Diao, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Ferrari, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Friedrich-Rust, 2009	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Giusti, 2013	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Jiang, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jiang, 2015	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Jin, 2016	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Ke, 2017	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Li, 2013	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Li, 2017	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Liu, 2017	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Ma, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ma, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Nemec, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang, 2017	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Wu, 2015	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wu, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yuan, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Zhan, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Zhang, 2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhang, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Zhang-1, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhang-2, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhang, 2017	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhao, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhou, 2013	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
No. of "Yes" answers	33	20	33	33	33	32	31	33	20	30	33	33	33	33
No. of "No" answers	0	13	0	0	0	1	2	0	13	3	0	0	0	0

* Data are from our use of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) systematic review-assessment tool, which has 14 items that evaluate study design-related issues and the validity of the results of the selected study. The items are as follows, by question (Q) number (Adapted from: Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003; 3: 25).

Q1: Was the spectrum of patients representative of the patients who will receive the test in practice?

Q2: Were selection criteria clearly described?

Q3: Is the reference standard likely to correctly classify the target condition?

Q4: Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?

Q5: Did the whole sample receive verification using a reference standard of diagnosis?

Q6: Did patients receive the same reference standard?

Q7: Was the reference standard independent of the index test?

Q8: Was the execution of the index test described in sufficient detail to permit replication of the test?

Q9: Was the execution of the reference standard described in sufficient detail to permit its replication?

Q10: Were the index test results interpreted without knowledge of the results of the reference standard?

Q11: Were the reference standard results interpreted without knowledge of the results of the index test?

Q12: Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?

Q13: Were interpretable/intermediate test results reported?

Q14: Were withdrawals from the study explained?

The publications were excluded if:

1. they did not provide sufficient data for calculating the TP, FP, TN, and FN parameters;
2. the thyroid lesions were not measured;
3. repeated or updated reports of studies with same group of participants;
4. the articles were case reports, reviews, editorials, or meta-analysis that did not meet the inclusion criteria.

2.3. Data extraction and quality assessment

Two investigators (Q Liu and J Cheng) extracted the data from the included studies with a third investigator (J Li) solved any discrepancy by consensus. The data extracted were as follows: journals, authors, year of publication, country, participant characteristics (number of patients, age, and sex), number of thyroid nodules, reference methods adopted, the concrete data of TP, FP, TN, and FN. In the data extraction process, the values of these

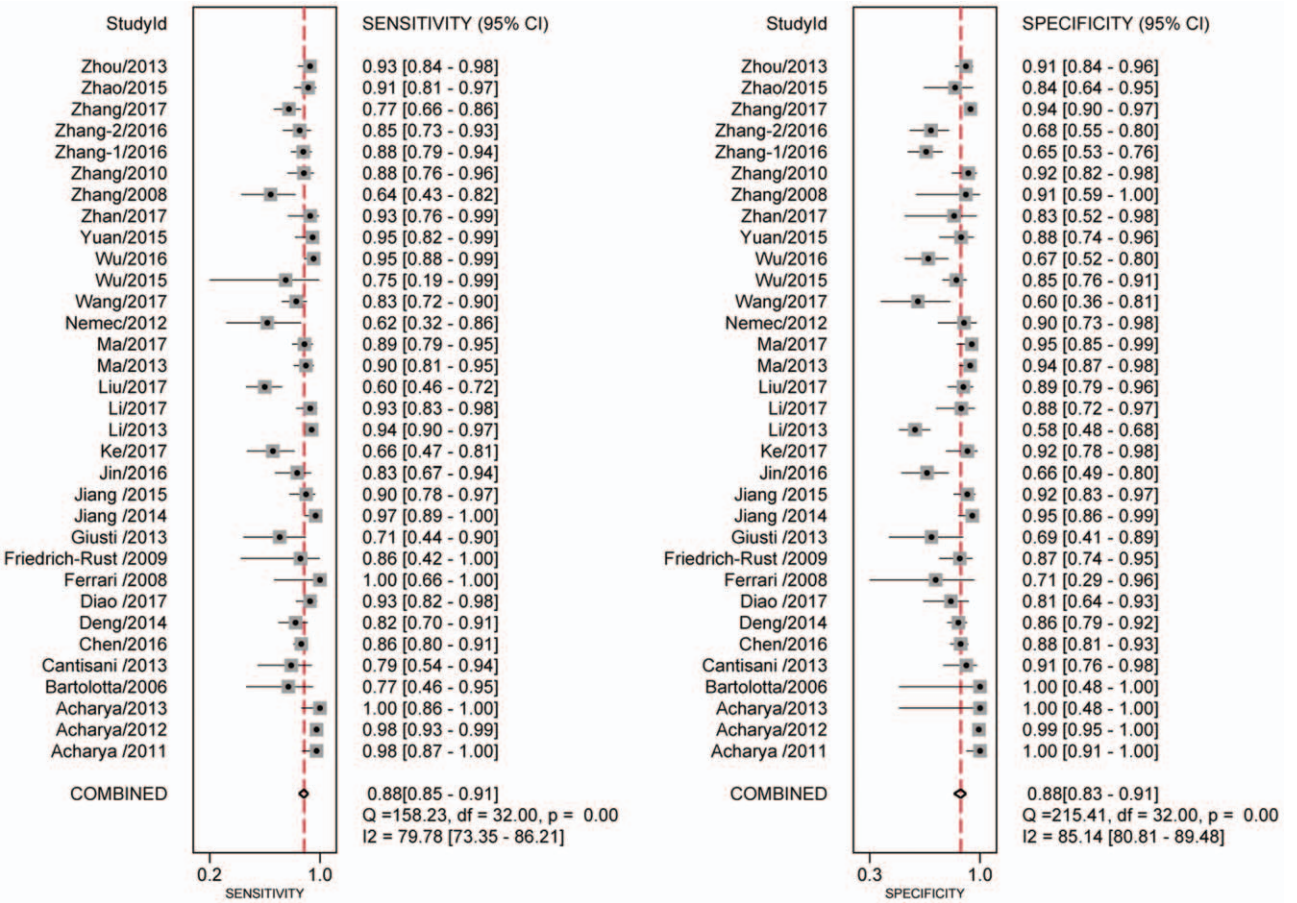

Figure 2. Forest plot for the pooled estimates of sensitivity and specificity of CEUS on the differentiation of thyroid nodules. CEUS = contrast-enhanced ultrasound.

parameters could by extracted directly or indirectly through the studies included. If no direct data of TP, FP, TN, and FN, these values could be calculated backward through the sensitivity and specificity rates, the positive predictive value (PPV), and the negative predictive value (NPV). The quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADS) questionnaire according to previous study.[18]

2.4. Data synthesis and statistical analysis

After data extraction, the bivariate model and the HSROC model were used to estimate the pooled sensitivity, specificity, positive likelihood ratio (PLR) and the negative likelihood ratio (NLR). The post-test probabilities were calculated by the PLR and NLR and plotted on a Fagan nomogram. The HSRPC curve was also plotted to illustrate the relationship between sensitivity and specificity. In addition, the publication bias was assessed using the Deeks' method.[19] All the data analysis and the graphs were made using the STATA version 14.0 software for Windows (StataCorp, College Station, TX) with the commands MIDAS and METANDI. $P < .05$ was regarded as statistically significant.

3. Results

3.1. Characteristics of included studies

After searching the literature in the databases, totally 33 studies were included for further analysis[3,10,15,20–49] (Fig. 1). Table 1 showed the basic characteristics of included studies, including the number of patients and thyroid nodules, mean age and gender ratio, study region, gold standard, contrast agent and the 4 important parameters for further analysis (TP, FP, TN, and FN values). It showed that the mean age of patients included ranged from 39.9 to 55.9 years, with 3 studies conducted in Singapore, 4 studies in Italy, 1 in the USA, 1 in Australia and 24 studies performed in China. The contrast agent used of the included studies were all Sonovue, with different doses, ranging from 1.2 to 4.8 mL.

3.2. Quality assessment

In this meta-analysis, the qualities of included studies were assessed using QUADS questionnaire, showed in Table 2. The study quality was defined as high when at least 9 of the total 14 items in the QUADAS checklist were considered "yes". It showed that the overall quality of the included studies was high. For item 2, about whether the inclusion criteria were clearly described, 13 studies were answered with "No" while the other 20 studies were answered with "yes". For item 6, 1 study was answered with "No" and the other studies were answered with "yes". For item 7, concerning whether the reference standard was independent of the gold standard, was rated "no" for 2 studies, of which the gold standard consists of the reference standard. For item 9, about whether the details of the reference standard were clearly described, it showed that 13 studies were rated with answer "No", without sufficient information of the reference standard. In addition, for item 10, concerning whether the index test results interpreted without knowledge

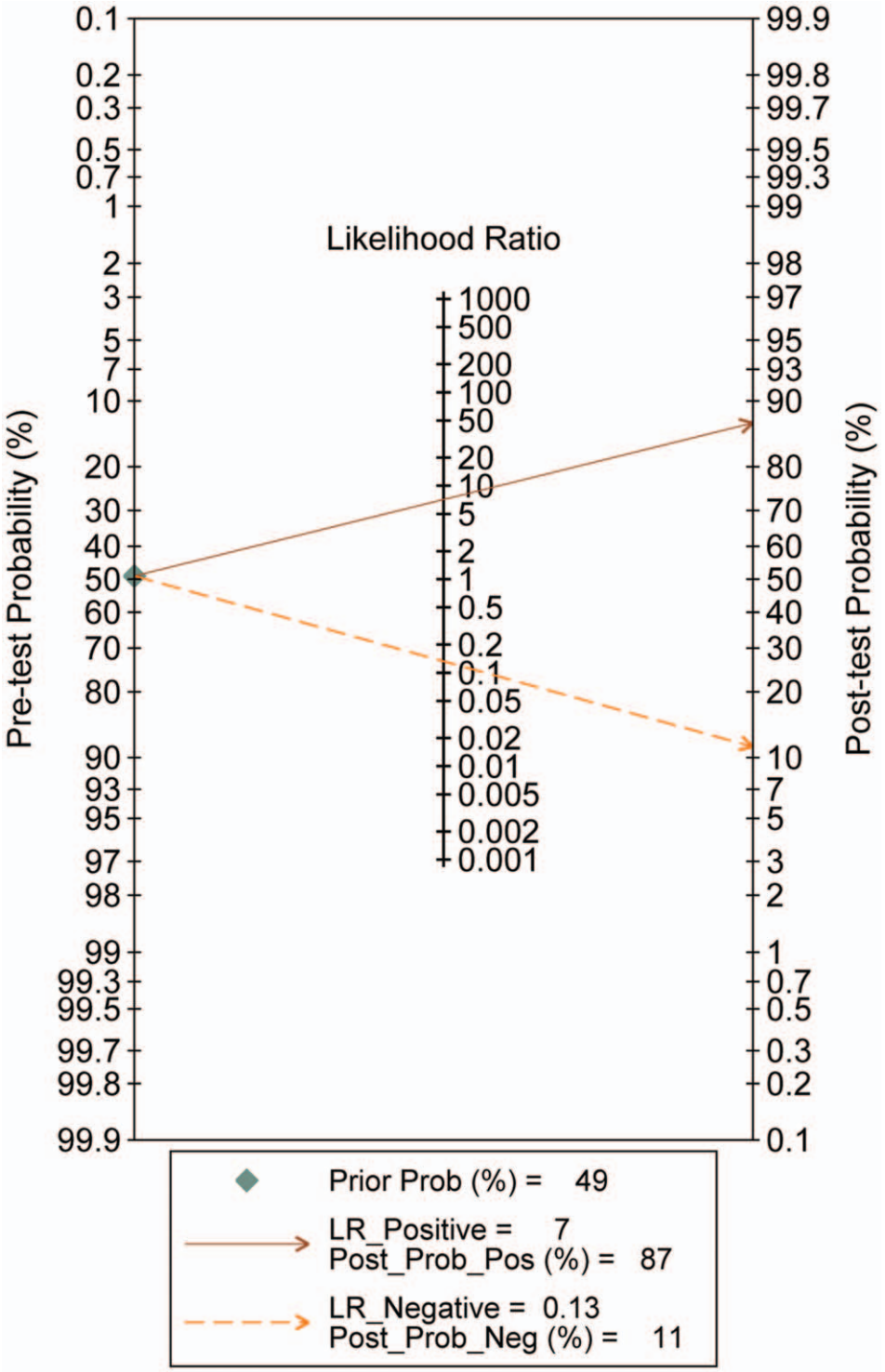

Figure 3. Fagan nomogram for the differentiation of thyroid nodules with CEUS. CEUS = contrast-enhanced ultrasound.

of the results of the reference standard, 2 studies were answered with "No". For the remaining items, all the studies included were answered with "yes".

3.3. Accuracy of CEUS in distinguish benign and malignant thyroid nodules

Using the bivariate model, it showed that the correlation coefficient was 0.18 with the ROC area 0.94 (95% CI 0.92–0.96), with relatively higher diagnostic values. The pooled sensitivity estimate was 0.88 with 95% confidence interval (CI) (0.85, 0.91) and the specificity estimate was 0.88 and 95% CI (0.83, 0.91). The pooled positive LR and the negative LR were 7.1% (5.2%, 9.8%) and 0.13% (0.10%, 0.18%), respectively. Furthermore, the DOR was 54 with the 95% CI (33, 89). Significant heterogeneity was found for sensitivity (I^2 = 79.78%, Q = 158.23) and for specificity (I^2 = 85.14%, Q = 215.41) (Fig. 2). The Fagan nomogram showed

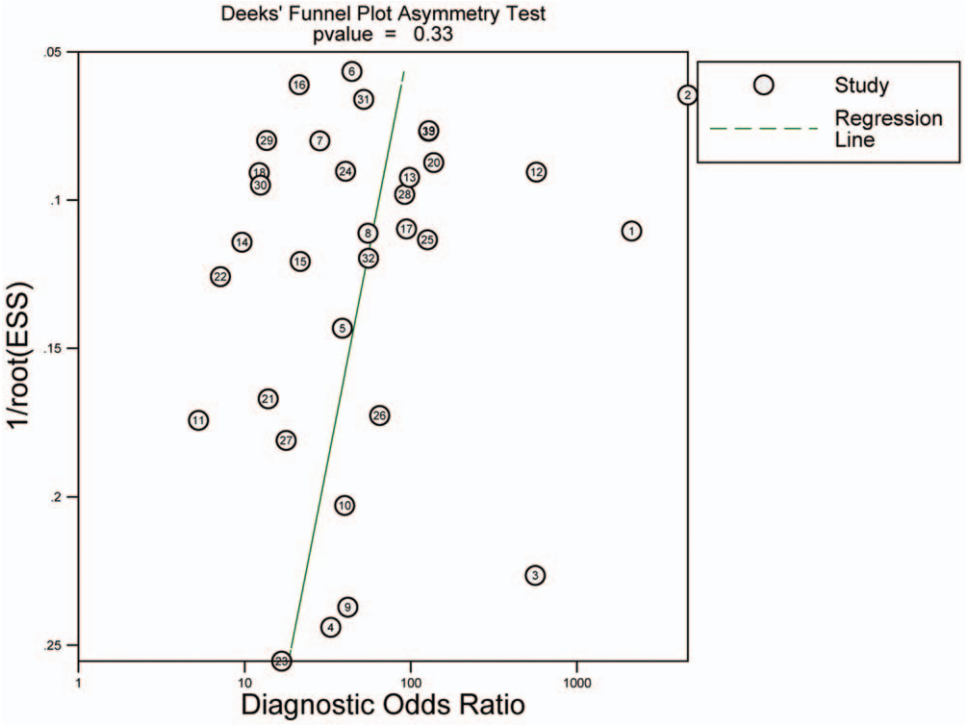

Figure 4. Deeks' funnel plot for the assessment of publication bias.

that the CEUS finding that was suspicious for malignant increased the pretest probability of cancer from 49% to 87%, whereas a normal CEUS finding decreased the pretest probability from 49% to 11% (Fig. 3). We did not observe significant publication bias using the Deek's funnel plot asymmetry test (Fig. 4).

For the HSROC model (Fig. 5), the pooled estimate and 95% CI of sensitivity, specificity, positive LR, negative LR, and the DOR were 0.88 (0.85, 0.91), 0.88 (0.83, 0.91), 7.13% (5.21%, 9.77%), 0.13% (0.10%, 0.18%), and 53.97 (32.63, 89.27), which were almost identical with the bivariate model.

4. Discussion

In this meta-analysis, we analyzed the diagnostic accuracy of CEUS on thyroid nodules by searching and including all the eligible diagnostic studies. We showed that sensitivity and specificity of CEUS on differentiation of thyroid nodules were 0.88 (0.85, 0.91) and 0.88 (0.83, 0.91), respectively. The DOR was 54 (33, 89), while the pooled positive LR and the negative LR were 7.1% (5.2%, 9.8%) and 0.13% (0.10%, 0.18%), respectively. Using SROC and HSROC model for further analysis, we got similar results and no significant publication bias using the Deek's funnel plot asymmetry test. Our study further improved the diagnostic values of CEUS on thyroid nodules, with previous reporting the sensitivity and specificity of 90% (95% CI, 88–93%) and 86% (95% CI, 83%, 89%) in the study of Ma et al[17], and the pooled sensitivity and specificity were 0.853 and 0.876 in the study of Yu et al.[16]

US is the most commonly used diagnostic tool in thyroid diseases. However, conventional US techniques could not differentiate the benign and malignant nodules accurately and efficiently.[23] Currently, several systems have been developed to help improve the diagnostic values of US in differentiation of the thyroid nodules, such as the Conventional color-Doppler ultrasound (CDUS), the quantitative-elastosonography, the acoustic radiation force impulse (ARFI)[25] and the thyroid image reporting and data system (TI-RADS). These diagnostic tools could be further divided into quantitative and qualitative methods and have both advantages and disadvantages. For example, the CDUS could not show the vessels clears in the thyroid nodules. The quantitative elastosonography has superior sensitivity compared with CEUS, which could provide additional information on the elastic properties of the tissue, but still, several variabilities existed in the diagnostic process.[4,23] Therefore, finding effective and special ways in the diagnosis of thyroid nodules is important.

CEUS has emerged as a useful tool in the field of medical US over the past decade. The diagnostic effects of CEUS have been studied for years in the examination of liver, uterus, prostate and other organs.[24] The advantage of CEUS is that it could exhibit the blood supply in the thyroid nodules, which is the character of malignant tumors. Meanwhile, CEUS could accurately evaluate the sequence and intensity of tumor perfusion and vascularity. In fact, CEUS is reported to provide both qualitative and quantitative evaluation of the contrast enhancement of thyroid nodules in previously published studies. Nevertheless, there are no unified standards for quantitative or qualitative studies, so no single feature of CEUS seems to be sensitive and specific enough for diagnosis of malignancy. Further studies are still needed to explore a reliable diagnostic standard for CEUS in differentiating thyroid nodules.[11] Furthermore, a recent meta-analysis of 7 eligible studies has found that the qualitative evaluation acquired better sensitivity and specificity for the differentiation of benign and malignant nodules, compared with the quantitative evaluation.[16] Even in our study, the studies included still have different methods in interpreting the results of CEUS, resulting in a relative high heterogeneity. Therefore, more advances and detailed methods needed to be further addressed in further studies.

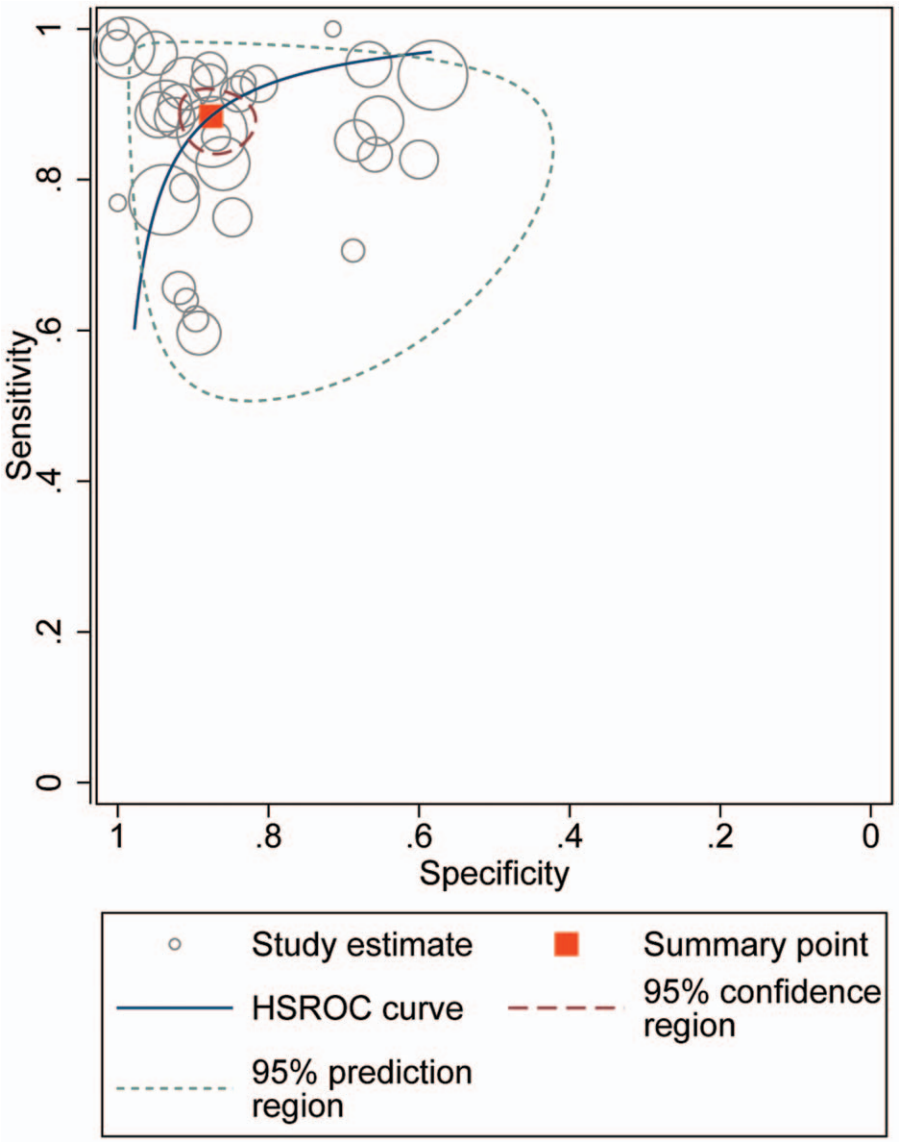

Figure 5. HSROC curve for CEUS on the diagnosis of thyroid nodules. CEUS = contrast-enhanced ultrasound, HSROC = hierarchical summary receiver operating characteristic.

This diagnostic meta-analysis has several limitations. First, a majority of studies were conducted in China, which might suitable for the patients in Chinese areas. Second, the procedures of performing CEUS in patients are complex and cost high in the examination. Third, the uniform standard of CEUS imaging is still not reached and more efforts need to be payed on the imaging of CEUS examination.

In conclusion, our meta-analysis is the one of the comprehensive and relatively new studies investigating the diagnostic accuracy of CEUS in differentiating of benign and malignant thyroid nodules. Our data showed that CEUS had good sensitivity and specificity and should be chosen with priority in thyroid diagnosis.

Author contributions

Conceptualization: Qinghua Liu, Hongbo Li, Jingjing Li.
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