Med Ultrason 2015, Vol. 17, no. 2, 192-199
DOI: 10.11152/mu.2013.2066.172.hyr

Acoustic Radiation Force Impulse imaging for detecting thyroid nodules: a systematic review and pooled meta-analysis.

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Abstract

Aim: To investigate the diagnostic performance of shear wave velocity (SWV) using virtual touch tissue quantification (VTQ) of acoustic radiation force impulse imaging (ARFI) technology in differentiating malignant and benign thyroid nodules by conducting a meta-analysis. **Material and methods:** The Cochrane library, Embase, Pubmed, and Web of Science were searched for relevant studies through December 2014. Studies evaluating the diagnostic accuracy of SWV in the identification of malignant and benign thyroid nodules by using VTQ of ARFI technology were selected. The cytology or histology was used as the reference standard. The pooled sensitivity, specificity, diagnostic odds ratio, likelihood ratio, and the area under the summary receiver operating characteristic (SROC) curve were used to examine the diagnostic accuracy of SWV. **Results**: A total of 13 cohort studies involving 1617 thyroid nodules from 1451 patients were identified. Of 13 studies, one was a retrospective study and others were prospective studies. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio of SWV in differentiating malignant and benign thyroid nodules were 86.3% (95%CI: 78.2–91.7), 89.5% (95%CI: 83.3–93.6), 7.04 (95%CI: 4.40–11.26), 0.17 (95%CI: 0.10–0.31), and 46.66 (95%CI:19.47–111.81), respectively. The area under the SROC curve was 94% (95% CI: 92–96). **Conclusions**: This meta-analysis indicates that VTQ is useful in evaluating the stiffness of thyroid nodules and differentiating between malignant and benign nodules. Due to the high sensitivity, specificity, and diagnostic odds ratio, SWV can be considered as a useful complement for conventional ultrasonography.

Keywords: acoustic radiation force impulse, virtual touch tissue quantification, ultrasound, thyroid nodules, meta-analysis.

Introduction

Thyroid nodules are a common finding in clinical practice. Approximately 5% of women and 1% of men have a palpable thyroid nodule in iodine-deficient areas of the world [1]. Thyroid lesions are found about 3-7% by palpation [2] and 19%–76% of randomly selected individuals by high-resolution ultrasound (US) [3,4]. Despite the majority of thyroid nodules are benign origin, about 5% to 15% account for the malignant nodules [5,6]. However, the incidence of thyroid nodules and thyroid carcinoma has increased over the last several decades [7]. Due to the similar characteristics of benign and malignant thyroid nodules and completely different treatment and prognosis, early identification of the property of the thyroid nodules is very important.

Fine-needle aspiration biopsy (FNAB) is considered to be the best approach in differentiating malignant from benign thyroid nodules [8]. However, its diagnostic accuracy is dependent on the nodules' numbers, sizes and locations, as well as on the operating skill of the clinician. Approximately 20%–25% cases of the FNAB diagnosis are reliable and the incidence of malignancy among

Received 01.02.2015 Accepted 20.04.2015
Med Ultrason
2015, Vol. 17, No 2, 192-199
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these uncertain cases may be up to 35.3% [9]. Acoustic Radiation Force Impulse imaging (ARFI) is a new elastographic imaging technique integrated into a conventional US system which can qualitatively and quantitatively analyze the stiffness of tissues. The principle of ARFI consists of the measurement of the average speed of the shear wave inside of a region of interest (ROI)[10] and the shear wave velocity (SWV) being measured in m/s [11]. Measurement value and depth of ARFI were also reported [12]. Several meta-analysis for differentiating between benign and malignant thyroid nodules [13-19] have been published in the recent years, but a systematic evaluation of the virtual touch tissue quantification (VTQ) is still lacking.

Here, we performed a systematic review and meta-analysis to investigate the diagnostic performance of SWV by using VTQ of ARFI technology in differentiating malignant and benign thyroid nodules.

Material and methods

Search strategy

We searched the Cochrane library, Embase, Pubmed, and Web of Science for relevant studies up to December 4, 2014. The medical subject heading terms were: ‘thyroid nodules’ OR ‘thyroid carcinoma’ OR ‘thyroid cancer’ OR ‘“thyroid neoplasm’ AND ‘Acoustic Radiation Force Impulse’ AND ‘shear wave velocity’ AND ‘virtual touch tissue quantification’ AND ‘sensitivity’ OR ‘specificity’. The literature search was performed without language restrictions. Moreover, the reference lists of the retrieved systematic and narrative reviews were also manually searched to identify additional relevant studies.

Study selection

The inclusion criteria were: prospective or retrospective cohort design; study population of at least 20 patients; evaluation of the malignant and benign thyroid nodules by using SWV by VTQ; use of histopathological examination (performed at surgery or biopsy) as the reference standard; providing the true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) number at per nodule level. If the studies did not provide data to directly construct 2×2 contingency tables, we calculated from the reported sensitivity, specificity, negative predictive value, and positive predictive value. Studies such as reviews, meta-analysis, letters, abstracts, case reports, or editorials were excluded. Two authors (L Zhang and Y Jiao) with a similar level of experience and expertise independently selected the eligible studies. Discrepancies between the two authors were resolved by a third author (JF Xu), who rechecked the search results and the assessment process.

Data extraction and quality assessment

The following information were independently extracted by two authors (L Zhang and Y Jiao) using a standardized form: the first author’s surname, year of publication, origin of the study, study design, number of patients, number of nodules available for analysis, mean diameter of nodules, inclusion criteria for nodule size, diagnosis criteria, reference standard, TP, FN, FP, and TN numbers, sensitivity, and specificity.

The methodological quality of eligible studies was assessed by using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [20]. The QUADAS-2 tool consists of 4 key domains and 3 applicability concerns. The key domains concern the patient selection, index test, reference standard, flow and timing. Applicability concerns are structured in a way similar to risk bias sections but not include flow and timing. For each item of the QUADAS-2 tool, if a study is judged as “low” on all domains relating to bias or applicability, then it is appropriate to have an overall judgment of “low risk of bias” or “low concern regarding applicability” for that study. If a study is judged “high” or “unclear” in one or more domains, then it may be judged “at risk of bias” or as having “concerns regarding applicability.”

Statistical analysis

All the analysis was performed by using the Midas module of Stata statistical software, version 12.0 (Stata Corp, College Station, TX, USA), RevMan software, version 5.3.5 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark),and Meta-DiSc software, Version 1.4 (Madrid, Spain) [21]. Stata and Meta-DiSc software were used to pool statistics indexes and draw statistical graphs. The area under the summary receiver operating characteristic (SROC) curve was used to examine the diagnostic accuracy of SWV. Meta-Disc software was used to pool the positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR) with corresponding 95% confidence intervals (CI). Meta-Disc was also used to test the threshold effect. If not, a meta-regression analysis was conducted according to the source of cases (Asian or No-Asian group), size of nodules (size>10 mm or<10 mm), and SWV records (2.60 m/s or <2.60 m/s), respectively. Threshold effect was tested with SROC space and Spearman correlation coefficient [26]. Representation of a typical ‘‘shoulder arm’’ pattern in a SROC space and a strong positive correlation between the log of sensitivity and log of 1- specificity would suggest presence of threshold effect. RevMan software was used to assess the methodological quality of the eligible studies.

Estimates of summary sensitivity and specificity for each nodule were calculated using the bivariate mixedeffects regression model developed by van Houwelingen, modified for the synthesis of diagnostic test data [22,23]. The pooled +LR and -LR were calculated based on the pooled sensitivity and specificity by assuming prior probabilities of 5 % and 10 % of thyroid nodules, depending on age, gender, radiation exposure history, family history, and other factors [3]. Studies providing SWV results were included simultaneously to calculate the summary sensitivity and specificity of SWV for further analysis.

The inconsistency index (I^2) and Cochrane Q statistic were used to estimate the heterogeneity across the included studies. If Cochran Q statistic value $p>0.1$ or $I^2<50\%$, we used a fixed-effect model; otherwise, a random effects model was selected [24]. Deek's funnel plot asymmetry test was used to test the potential publication bias, with $p<0.10$ for the slope coefficient indicating significant asymmetry [25].

The random effects model was applied to determine pooled estimates of SEN, SPE, positive likelihood ratio (+LR), and negative likelihood ratio with corresponding 95% confidence intervals (CI) of SWV in detection of malignant thyroid nodules.

Publication bias

The Deeks' funnel plot was used. It was conducted by a regression of diagnostic log odds ratio (lnDOR) versus the inverse of the square root (1/sqrt) of the effective sample size ($1/ESS^{1/2}$) and weighted by effective sample size. A p-value <0.10 for the slope coefficient indicating significant asymmetry [27]. Furthermore, groups would be divided into subgroups based on the heterogeneity between studies.

We found 5 studies were published by Xu et al from the same hospital; we confirmed via telephone that the samples patients in these studies were included by the examination time successively, so we accepted the study which had the largest time span [37]. Two studies from Zhang et al [38,39] had two separate periods.

Results

Literature searches

The initial search yielded 2437 papers. After screening the title or abstract and excluding the duplication, 19 full-text articles were assessed for eligibility. Six papers were further excluded because the authors analyzed the SWE but not SWV. Therefore, 13 studies [26-38] were ultimately included in the meta-analysis. Figure 1 lists the diagram of the study selection process.

Study characteristics

A total of 1617 thyroid nodules (mean diameters range from 7.8 mm to 39.7 mm) from 1451 patients were identified. Patients' age ranged from 15 to 93 years.

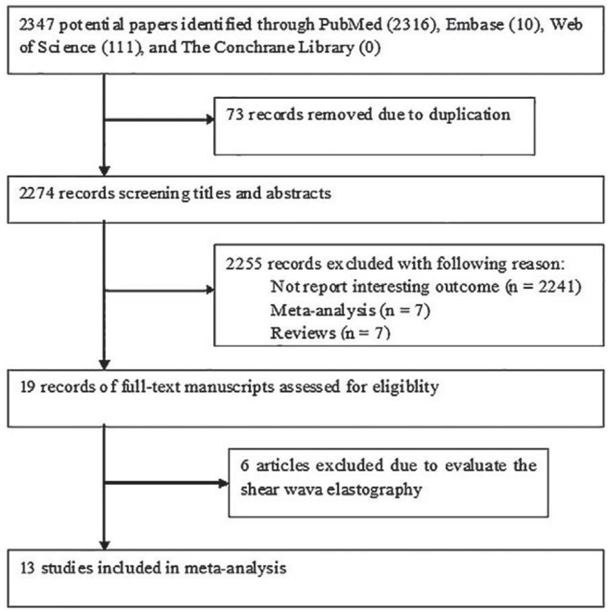

Fig 1. Flow chart of study selection process

All the 13 studies were diagnostic cohort studies (1 retrospective and 12 prospective studies). A total of 495 (30.6%) nodules were malignant. Approximately 24.5% of the patients were males, but two studies [35,36] did not mention the gender distribution. Table I summarizes the detailed characteristics of the included studies.

Methodology quality assessment

According to the methodological assessment of the QUADAS-2 checklist, the quality of the included studies was judged to be high (fig 2). All the quality assessment items of the included studies had a low risk of bias except for one study [38] did not describe the reason for the excluded patients.

Data synthesis and analysis

As shown in figure 3, significant heterogeneity in pooling the sensitivity (I^2=88.06%, p<0.01) and specificity (I^2=90.09%, p<0.01) was detected, so we pooled the sensitivity and specificity in the random effects model. The summary sensitivity and specificity were 86% (95% CI: 78%–92%) (fig 3A) and 90% (95 % CI: 83%–94%) (fig 3B), respectively. As shown in figure 4, the summary +LR, -LR and DOR were 7.04 (95%CI 4.40–11.26), 0.17(95%CI: 0.10–0.31), and 46.66 (95% CI: 19.47–111.81, respectively. As shown in figure 5, the area under the SROC was 94% (95%CI: 92%~96%). The pooled +LR and -LR values calculated by setting the prior probabilities of 5% and 10% were shown in figure 6.

Subgroup analysis

The threshold effect test showed that the Spearman correlation coefficient was –0.129, p=0.674, suggest-

Table I. Characteristics of the included studies

Author/ Year	Country	Design	N of patients (N of Men)	N of nodules (N of malignant nodules)	Mean diameter (mm)	Inclusion Criteria (nodule size) (mm)	Diagnosis criteria (m/s)	Reference standard (nodules%)	TP	FP	FN	TN	Se	Sp
Bojunga 2012 [26]	Germany	Prospective	138(39)	158(21)	20	>5	2.57	FNAB and/or H (100%)	12	20	9	117	57	85
Calvete 2014 [27]	Spain	Prospective	157(33)	157(28)	19.3	≥6	2.55	FNAB and/or H (100%)	27	23	1	106	86	96
Deng 2014 [28]	China	Prospective	146(42)	175(56)	18.2	>5	2.59	FNAB and/or H (100%)	45	19	11	100	80	84
Friedrich-R 2012 [29]	Germany	Prospective	55(19)	60(3)	24.1	≥10	4.30	FNAB and/or H (100%)	2	0	1	57	67	100
Fukuhara 2014 [30]	Japan	Prospective	101(32)	112(28)	20.3	≥10	2.01	FNAB and/or H (100%)	24	32	4	52	86	62
Grazhdani 2014 [31]	Italy	Prospective	74(22)	82(22)	NA	≥10	2.445	FNAB and/or H (100%)	20	15	2	45	91	75
Gu 2012 [32]	China	Prospective	72(21)	98(22)	21.8	NA	2.555	FNAB and/or H (100%)	19	5	3	71	86	93
Hou 2013 [33]	China	Prospective	77(17)	85(20)	23	NA	2.44	H (100%)	16	7	4	58	80	89
Zhan 2013 [34]	China	Prospective	30(7)	58(22)	20	NA	2.85	H (100%)	21	5	1	31	94	85
Zhang 2013 [35]	China	Prospective	155(NA)	155(62)	NA	NA	2.84	H (100%)	60	4	2	89	97	96
Zhang 2014 [36]	China	Prospective	107(NA)	113(46)	15	5-20	2.90	H (100%)	42	10	4	57	91	85
Zhang 2014 [37]	China	Retrospective	157(35)	173(96)	7.8	5-10	3.10	H (100%)	54	16	42	61	56	79
Zhuo 2014 [38]	China	Prospective	182(88)	191(69)	39.7	NA	2.545	FNAB and/or H (100%)	66	5	3	117	96	96

Note: N- number, FNAB=fine-needle aspiration biopsy, H- Histology, TP=true positive, FP=false positive, FN=false negative, TN=true negative, NA: not mentioned, Se-Sensitivity, Sp- Specificity

ing other factors besides threshold effect might result in heterogeneity between included studies. The meta-regression analysis indicated p-values were 0.64, 0.05, 0.26, respectively, suggesting the source of cases (Asian or No-Asian group), size of nodules (size>10 mm or<10 mm), and SWV records (2.60 m/s or <2.60 m/s) had nothing to do with heterogeneity.

Publication bias

The Deeks' funnel plot for testing publication bias showed that the studies were distributed symmetrically with a p-value of 0.88, indicating no clear evidence of publication bias (fig 7). Regression analysis of lnDOR against 1/Effective Sample Size $^{1/2}$ showed no obvious small-study bias in our meta-analysis.

Discussions

The aim of our meta-analysis was to evaluate the diagnostic value of SWV in differentiating between malignant and benign thyroid nodules. The findings demonstrated that SWV had high sensitivity and specificity, moderate LRs and DOR, high area under the SROC.

A recent meta-analysis by Lin P et al [15] reported 15 studies using the SWE, point-SWE or 2D-SWE to evaluate 1,867 thyroid nodules in 1,525 patients. The pooled sensitivity, specificity, and area under the SROC of SWE for detecting malignant thyroid nodules were 84% (95%CI:77–90), 88% (95%CI:84–92), and 93%

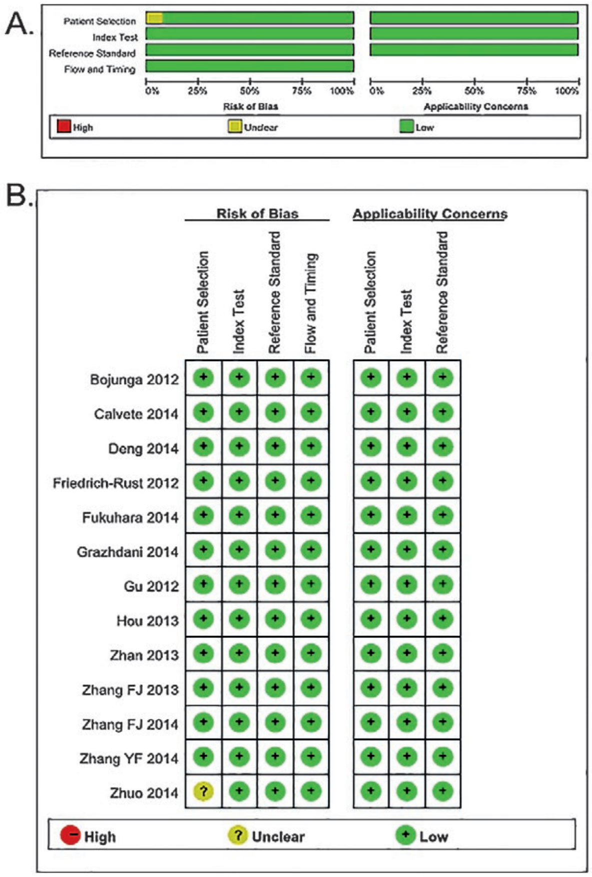

Fig 2. Quality assessment, by using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. A) Risk of bias and applicability concerns graph: review authors' judgments about each domain presented as percentages across included studies. B) Risk of bias and applicability concerns summary: review authors' judgments about each domain for each included study.

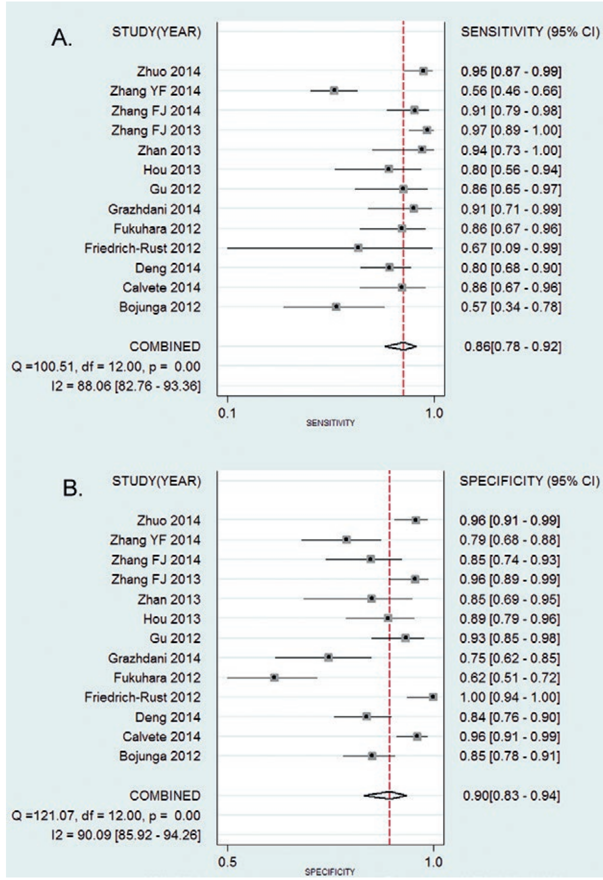

Fig 3. Forest plots for sensitivity (A) and specificity (B) of shear wave velocity for the differentiation of thyroid nodules.

(95%CI:90–95), respectively. However, this meta-analysis combined all the elastography images, including elastography, SWE and SWV, the included studies published only between 2012 and 2013. Our study was specially designed to evaluate the diagnostic value of SWV in differentiating benign and malignant thyroid nodules, and updated to December 4, 2014.

The overall malignancy rate in our meta-analysis was 30.6%, which was much higher than that in clinical practice, occurring in 5%~15% of cases of the discovered thyroid nodules [5,6]. One of the important contributing factors is surgery. Most patients underwent the conventional ultrasound examination, nodules with suspicious malignant signs received further examination. Otherwise, nodules with benign signs would have been excluded, which results in selection bias. Another important factor is the fact that some of the patients included in these studies were from community clinics or other health care centers [15].Therefore, selection bias cannot be excluded.

We used the bivariate model of stata 12.0 to pool statistics data, and this model could keep the two dimensional characteristic of the original data and take into consideration of the negative correlation between sensitivity and specificity. The included studies had significant heterogeneity. Meta-regression analyses showed that the source of cases, size of nodules, and SWV records did not explain the source of heterogeneity. Difference of sampling error or cut-off value in different studies occurred in most of the Diagnostic Accuracy Studies. Friedrich-R [31]'s cut-off value of SWV was 4.30 m/s, only included 3 TP nodules and 0 FP, and the specificity was 100%; while cut-off values of SWV in other studies ranged from 2.01 m/s to 3.10m/s, so this study could explain the part source of heterogeneity. When we excluded this study from the meta-analysis, the summary sensitivity and specificity was 86% (95%CI:78–92) and 88% (95%CI:82–92), respectively. These findings revealed that this study had little impact on our pooled re-

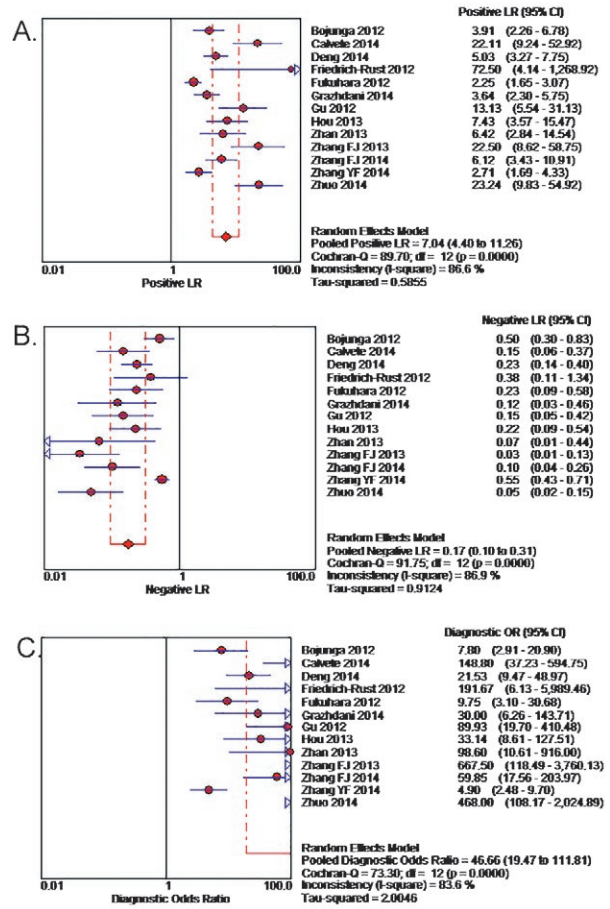

Fig 4. Forest plots for negative likelihood ratio (A), positive likelihood ratio (B), and diagnostic odds ratio (C) of shear wave velocity for the differentiation of thyroid nodules.

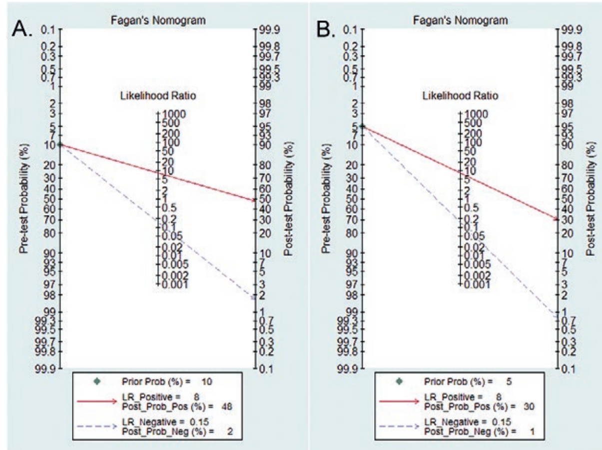

Fig 5. Hierarchical summary receiver operating characteristic curve (HSROC) of shear wave velocity for the differentiation of thyroid nodules.

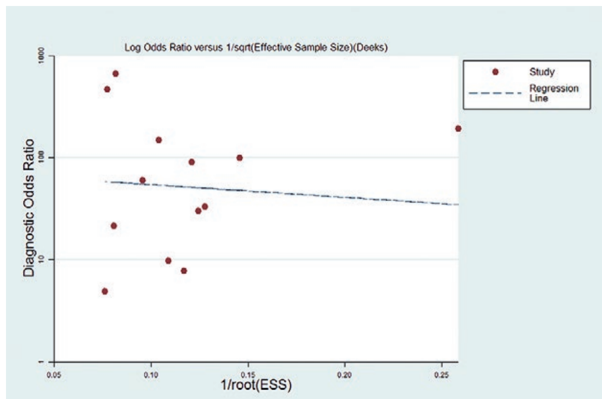

Fig 6. Fagan's Nomogram shows that virtual touch tissue quantification as a screening tool for malignant thyroid nodules needs to combine with other methods. A) pretest probability at 10%; B) pretest probability at 5%.

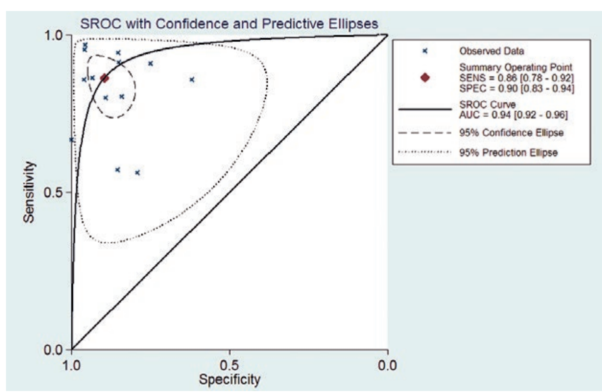

Fig 7. Deeks' funnel plot with superimposed regression line for identifying publication bias Log Odds Ratio versus 1sqrt (Effective Sample Size) (Deeks) indicated that no significant bias was found. ESS=effective sample size.

sults. It should be noted that eight (8/13) studies were from China, nine (9/13) studies were from Asia, and only four (4/13) studies were conducted in Non-Asian countries. Therefore, more well-designed multicenter studies particularly in non-Asia countries are needed to generalize these findings.

Conclusions

Our meta-analysis suggests that VTQ is a useful technique in evaluating the hardness of thyroid nodules and differentiating between malignant and benign nodules. Due to the high sensitivity, specificity, and diagnostic accuracy, and moderate LRs of SWV method, it can be considered as a useful complement for conventional ultrasonography.

Conflicts of interest: none

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