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Diagnostic value of endobronchial ultrasound elastography for differentiating benign and malignant hilar and mediastinal lymph nodes: a systematic review and meta-analysis

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Abstract

Aims: In the present study, a meta-analysis was performed to evaluate the diagnostic value of endobronchial ultrasound (EBUS) elastography for differentiating benign and malignant hilar and mediastinal lymph nodes (LNs). **Material and methods:** A comprehensive literature search was carried out through PubMed, Embase, and Cochrane Library. Two authors screened the papers and extracted the data independently and any discrepancies were resolved by discussion. The methodological quality of each included study was assessed by the Quality Assessment of Diagnostic Accuracy Studies 2 tool. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and area under the curve were calculated to evaluate the value of EBUS elastography for hilar and mediastinal LNs. **Results:** Seventeen studies with the number of 2307 LNs were included. There was significant heterogeneity across the included studies. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio for the diagnosis of hilar and mediastinal LNs by EBUS elastography were 0.90 (95% confidence interval [CI], 0.84-0.94), 0.78 (95% CI, 0.74-0.81), 4.1 (95% CI, 3.4-4.9), 0.12 (95% CI, 0.07-0.21) and 33 (95% CI, 17-64), respectively. Furthermore, area under the curve was calculated to be 0.86 (95% CI, 0.82-0.88). **Conclusion:** EBUS elastography is a valuable technology in the differentiation of benign and malignant hilar and mediastinal LNs and could provide supplementary diagnostic information during endobronchial ultrasound-guided transbronchial needle aspiration. The combination of EBUS elastography and B-mode EBUS could improve the diagnostic accuracy for hilar and mediastinal LNs.

Keywords: endobronchial ultrasound; elastography; lymph nodes; diagnosis; meta-analysis

Introduction

Lung cancer is among the most common diagnosed malignant tumours with a high mortality rate worldwide and poor 5-year survival rate of only 16%, despite the significant advances in diagnostic and therapeutic approaches [1,2]. The adequate treatment and prognosis of lung cancer is determined by a proper diagnosis and staging of the disease [2,3].

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is considered as a highly sensitive, specific, safe and minimally invasive technology, which has developed into the most widely used standard sampling technique in the diagnosis of hilar and mediastinal lymph nodes (LNs) [4,5]. Current international guidelines recommend that EBUS-TBNA should be carried out before mediastinoscopy, especially for the pathological diagnosis and staging of LNs in patients with lung cancer [4-6]. Compared with conventional mediastinoscopy, which is relevant to a surgical operation under general anaesthesia, EBUS-TBNA has a comparable diagnostic accuracy, has a relatively lower risk of

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adverse events and is much more cost-efficient [5-8]. The evaluation of the LNs during endobronchial ultrasound (EBUS) according to conventional B-mode features such as size, shape, echogenicity, distinct border, central hilar structure and coagulation necrosis sign, has been found helpful in the detection of LNs metastasis [9]. Furthermore, studies demonstrated that vascular pattern on power Doppler mode during EBUS can also predict nodal metastasis in patients with lung cancer. However, it is still difficult for certain cases to predict LNs metastasis only by conventional B-mode features [10,11].

Ultrasound elastography exhibits potential application to the differential diagnosis of benign and malignant LNs [12,13]. In recent years, EBUS elastography has been introduced as a novel modality in the evaluation of hilar and mediastinal LNs [14-17]. However, the diagnostic performance of EBUS elastography for the differentiation of benign and malignant hilar and mediastinal LNs is variable across previous studies, with the sensitivity ranging from 64% to 100% and the specificity ranging from 65% to 92% [14-16].

Whether EBUS elastography can be considered as a valuable scanning modality is still a controversial issue. Therefore, we performed a meta-analysis to assess the diagnostic performance of EBUS elastography in the noninvasive discrimination between benign and malignant hilar and mediastinal LNs.

Material and methods

Meta-analysis principles

The present meta-analysis was carried out on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which include 27 items and provide specific guidance for the reporting of systematic reviews [18]. We registered our protocol with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLAY) (registration number: INPLASY2020110117).

Search strategy

The Pubmed, EMBASE and Cochrane Library were systematically searched from inception to November 2020, to identify English-language studies on EBUS elastography for differentiating benign and malignant LNs. The search terms were as follows: "elasticity", "elastograms", "elastography", "elastosonography", "elasticity imaging", "endobronchial ultrasound", "EBUS", "EBUS elastography", "lymph node", "lymph nodes", "lymphadenopathy", and "lymphaden". Detailed search terms are provided in supplementary file 1. Reference lists of the included studies and relevant reviews were also screened to find additional relevant studies.

Inclusion and exclusion criteria

Two reviewers (JW and YS) screened the titles and the abstracts of retrieved studies independently. Before identifying the literature, they established the inclusion and exclusion criteria together to increase validity and reproducibility. Inconsistencies between the reviewers were resolved through discussion.

The inclusion criteria were as follows: (1) diagnostic studies were included; (2) studies evaluating the diagnostic accuracy of EBUS elastography in distinguishing malignant and benign hilar and mediastinal LNs were included; (3) a reference standard was adopted to confirm malignant intrathoracic LNs, such as cytology obtained by EBUS-TBNA or other method, histology of surgical resection, or more than 6 months of follow-up; (4) if several diagnostic methods were used in a study, only the best result was chosen.

The exclusion criteria were as follows: (1) case reports, letters, consensus statements, and unpublished articles; (2) studies without sufficient data to construct diagnostic 2x2 tables; (3) studies that contained an overlapped population.

Data extraction

Two reviewers (JW and YS) independently extracted the relevant data from the eligible studies using a predesigned data collection form. Any discrepancies were resolved by discussion with the senior author. For eligible studies, the following items were extracted: last name of the first author, year of publication, country, study type, sample method, malignancy prevalence, diagnostic method, blinding method, cut off, ultrasound equipment, probe frequency, sample size, lymph node, short-axis diameter, mean age, gender, standard reference, time between EBUS elastography and the standard reference.

Study quality assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [19] was used to assess the risk of bias and methodological quality. The quality of each eligible study was assessed by an appraisal of the risk of bias of four domains and clinical applicability of three domains of the study characteristics. Four domains included patient selection, index test, reference standard and flow and timing. Every domain was assessed for risk of bias, and the first three domains were assessed for applicability. The quality assessment was carried out using RevMan 5.3 software (Nordic Cochrane Centre, Copenhagen, Denmark).

Statistical analysis

This meta-analysis was performed by StataSE 15 (Stata Corporation, College Station, Texas). All statistical analyses were performed by one author (JW), who has experience in performing meta-analysis. The pooled

estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) with corresponding 95% confidence intervals (CIs) were calculated by a bivariate random effect model in this study, which indicated the accuracy of EBUS elastography in the differentiation of benign and malignant hilar and mediastinal LNs. Furthermore, the summary receiver operator curve (SROC) was constructed and the area under the curve (AUC) was calculated. An AUC close to 0.5 reveals a poor test, while an AUC close to 1.0 shows a perfect diagnostic test [20]. The inconsistency index (I^2) and the Cochrane Q test were utilized to evaluate the heterogeneity among included studies with a p-value <0.1 or I^2 >50% indicating significant heterogeneity [21]. The Deeks' funnel plot asymmetry test was applied to evaluate publication bias [22], through a p-value >0.05 showing no significant publication bias.

Meta-regression analyses utilizing several covariates were performed to investigate the potential causes of heterogeneity: study design (prospective versus other), year published (2014-2017 versus 2019-2020), reference standard (pathology versus pathology or follow-up), diagnostic method (quantitative versus qualitative) and sampling (consecutive versus others).

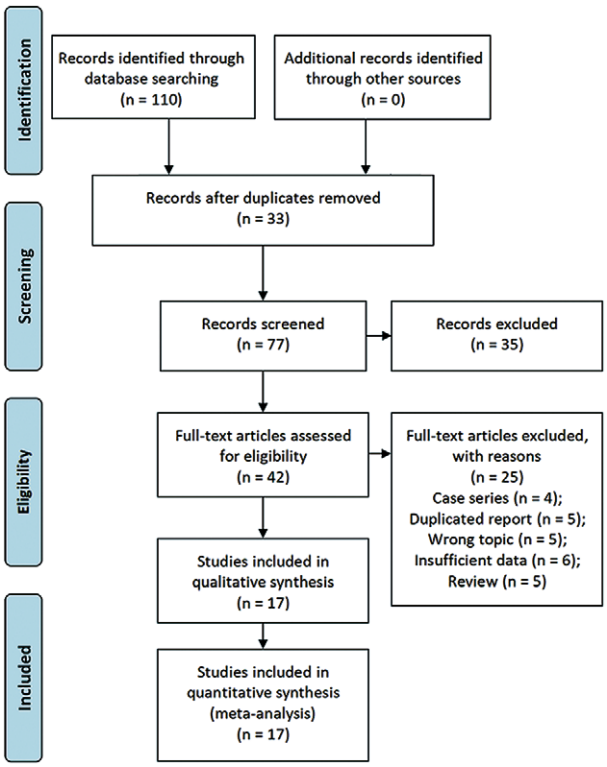

Fig 1. Flowchart of study selection

Results

Study selection

In the three databases, our literature search yielded 110 publications for consideration. Figure 1 shows the flow chart of the study selection. Finally, 17 publications were included in this meta-analysis [14-16,23-36].

Characteristics of the included studies

The 17 enrolled studies were published between 2014-2020 and written in English [14-16,23-36]. A total of 1360 patients with 2307 hilar and mediastinal LNs were included in these studies. Five studies were performed in China [15,23,27-29], 3 in Japan [14,24,35], 2 in Netherlands [16,33], 1 in Slovenia [25], 1 in Thailand [26], 1 in Taiwan [30], 1 in Spain [31], 1 in France [32], 1 in Turkey [34] and 1 in Germany [36]. There were 10 prospective [15,16,25,26,29,31-34,36] and six retrospective [14,24,27,28,30,35] studies and one study did not depict the study design [23]. Double blinding between the index test and standard reference was found in ten studies [15,24,25,27,28,31,32,34-36] and single blinding in four studies [14,23,29,33]. Three studies [16,26,30] did not report a blinding method. The patients were consecutively enrolled in eight studies [14,15,24,25,29,32,34,35] and eight studies did not report the sample method [16,23,26-28,30,31,33]. One study did not consecutively enroll patients [36]. The sample size of the enrolled studies ranged from 21 to 327 and the mean age ranged from 56 to 68 years. The malignancy prevalence of LNs ranged from 33% to 80% across different studies. The mean size of short-axis diameter of LNs ranged from 8 to 20 mm. Nine studies [16,23-26,29,33-35] used quantitative diagnostic methods (strain ratio, stiff area ratio, blue colour proportion, or strain histogram) while eight studies used qualitative diagnostic methods (3, 4 or 5 colour classifications) [14,15,27,28,30-32,36]. Table I and II epitomizes the data extracted from the enrolled studies. More details are showed in supplementary file 2.

Quality assessment

The quality assessment results of the risk of bias and applicability concerns of the enrolled studies were shown graphically in figure 2. With respect to the patient selection domain, eight studies were considered as "unknown" [16,23,26-28,30,31,33], because they did not report the sample method. One was considered as having high bias because the patients were not enrolled consecutively [36]. Six studies were considered as having high bias because part of the patients were excluded inappropriately [14,15,28,30,32,36]. Concerning the index test domain, 6 studies [14,16,23,26,29,30] were considered as "unknown" because the blinded status of the golden standard was not explicitly reported. Concerning the ref-

Table I. Primary data extracted from included studies for meta-analysis

Author	Country	Study type	Blind method	Sample method	Patient (n)	Male/ female	Age (year)	Lymph node (n)	Malignant node (n)	Malignancy prevalence (%)
Izumo [14], 2014	Japan	Retro	Single blinded	Consecutive	30	17/13	67.1±15.5	75	42	56
He [23], 2015	China	NR	Single blinded	NR	40	26/14	65 (median)	68	42	62
Nakajima [24], 2015	Japan	Retro	Double blinded	Consecutive	21	15/6	63 (30–80)	49	16	33
Rozman [25], 2015	Slovenia	Pro	Double blinded	Consecutive	33	25/8	67.5±8.2	80	34	43
Korrungruang [26], 2017	Thailand	Pro	NR	NR	72	41/31	58.3±12.5	120	96	80
Sun [27], 2017	China	Retro	Double blinded	NR	56	32/24	56	68	35	51
Gu [15], 2017	China	Pro	Double blinded	Consecutive	60	49/11	62 (26-82)	133	89	67
Huang [28], 2017	China	Retro	Double blinded	NR	47	29/18	60.19±11.03	78	33	42
Ma [29], 2018	China	Pro	Single blinded	Consecutive	60	40/20	61.6	79	39	49
Lin [30], 2019	Taiwan	Retro	NR	NR	94	65/29	62.8 (20-97)	206	74	36
Roca [31], 2019	Spain	Pro	Double blinded	NR	27	16/11	68±10	42	18	43
Fournier [32], 2019	France	Pro	Double blinded	Consecutive	114	80/34	60.2±12.2	217	120	55
Verhoeven [33], 2019	Netherlands	Pro	Single blinded	NR	63	39/24	64.3 (41–83)	120	45	38
Çağlayan [34], 2020	Turkey	Pro	Double blinded	Consecutive	119	69/50	63.2±12.4	221	93	42
Uchimura [35], 2020	Japan	Retro	Double blinded	Consecutive	132	91/41	71 (median)	149	68	46
Gompelmann [36], 2020	Germany	Pro	Double blinded	Not consecutive	65	34/31	63 (52-82)	77	55	71
Verhoeven [16], 2020	Netherlands	Pro	NR	NR	327	200/127	66 (26-90)	525	253	48

Pro, prospective; Retro, retrospective; NR, not reported

erence standard domain, 4 studies [16,26,30,33] were considered as "unknown" because the blinded status of index test was not definitely reported. With regard to the flow and timing domain, 6 studies were considered as having high bias because they did not enroll all the patients for analysis [14,15,28,30,32,36]. Regarding applicability, for patient selection, index test and reference standard domains, all studies were considered to have low concerns.

Data synthesis and publication bias

Summaries of diagnostic sensitivity and specificity of EBUS elastography for differentiating malignant and benign hilar and mediastinal LNs were analysed by the random effects method on the basis of significant statistical heterogeneity (I^2=89.56% for sensitivity; I^2=69.31% for specificity). Overall, the pooled sensitivity and specificity of EBUS elastography were 0.90 (95% CI, 0.84-0.94) and 0.78 (95% CI, 0.74-0.81; fig 3). The pooled PLR, NLR, and DOR of EBUS elastography were 4.1 (95% CI, 3.4-4.9), 0.12 (95% CI, 0.07-0.21), and 33 (95% CI, 17-64), respectively and the post-test probability was 50% and 3% (fig 4). The AUC under the SROC curve for the value of EBUS elastography in the diagnosis of LNs was 0.86 (95% CI, 0.82-0.88; fig 5).

The Deeks' funnel plot was carried out to evaluate the publication bias of the eligible studies. However, as

Table II. Characteristics of the included studies

Author	Diagnostic method	Cut-off value	Short-axis diameter (mm)	Reference standard	Time between reference and index test	US equipment	Sen (%)	Spe (%)
Izumo [14]	3 classifications	Predominantly blue	15.0 median (5.0–50.0)	Pathology	After EBUS	BF-UC260FW	100	92
He [23]	Strain ratio	32.07	17 median	Pathology	After EBUS	EB-1970UK	88	81
Nakajima [24]	Stiff area ratio	0.311	8.44 (5.0–21.7)	Pathology or follow-up	After EBUS	BF-UC260FW	81	85
Rozman [25]	Strain ratio	8	11.1±4.5	Pathology or follow-up	After EBUS	BF-UC180F	88	85
Korrungruang [26]	Strain ratio	2.5	18.8±7.9	Pathology or follow-up	After EBUS	BF-UC180F	100	71
Sun [27]	5 classifications	Score: 4-5	19.92±9.09	Pathology or follow-up	After EBUS	EB1970, Pentax, Japan	86	82
Gu [15]	3 classifications	Predominantly blue	NR	Pathology	After EBUS	BF-UC260FOL8 and EU-C2000	100	65
Huang [28]	3 classifications	Predominantly blue	NR	Pathology	After EBUS	BF-UC260F and NA-201SX-4022	96	87
Ma [29]	Blue color proportion	36.70%	NR	Pathology	After EBUS	BF-UC260FW	92	68
Lin [30]	3 classifications	Predominantly blue	13.6 (2.0-56.3)	Pathology or follow-up	After EBUS	EU-ME2 PREMIER PLUS	91	83
Roca [31]	3 classifications	Predominantly blue	15 ± 6	Pathology or follow-up	After EBUS	PENTAX, EB 1970 UK	72	92
Fournier [32]	3 classifications	Predominantly blue	16.2 ± 8.5	Pathology	After EBUS	OlympusBF UC 180F and OlympusEU-ME2	87	68
Verhoeven [33]	Strain histogram	78	9.95 (4–26)	Pathology or follow-up	After EBUS	Pentax EB-1970UK echo-endoscopes	93	75
Çağlayan [34]	Strain ratio	2.47	16.2±11.1	Pathology	After EBUS	BF-UC180F	75	65
Uchimura [35]	Stiffness area ratio	0.41	8	Pathology or follow-up	After EBUS	BF-UC260FW	88	80
Gompelmann [36]	3 classifications	Predominantly blue	NR	Pathology	After EBUS	NR	71	67
Verhoeven [16]	Strain histogram	78	12.3 (3-50)	Pathology or follow-up	After EBUS	Pentax EB1970UK and EB19-J10U	64	76

Sen, sensitivity; Spe, specificity; NR,not reported; US, ultrasound; EBUS, endobronchial ultrasound

shown in figure 6, which indicated the publication bias existed (p=0.00). This indicated publication bias might be part of source of heterogeneity.

Meta-regression and subgroup analyses

Due to the significant heterogeneity among studies, a meta-regression analysis was performed to explore other potential sources of heterogeneity. The covariables included study design (prospective versus others), year of publication (2014-2017 versus 2018-2020), reference standard (pathology versus pathology or follow-up), diagnostic method (quantitative versus qualitative), and sampling (consecutive versus others). Among the various potential covariates, study design and year of publication were associated with the heterogeneity of the sensitivity, while study design, year of publication, reference standard, diagnostic method, and sampling were associated with the heterogeneity of the specificity (fig 7).

The subgroups with respect to study design, prospective studies had a lower diagnostic performance to others (sensitivity: 0.89 and 0.92, p=0.04; specificity: 0.73 and 0.83, p=0.00). The subgroups with regard to year of publication, studies published between 2018 and 2020 had a

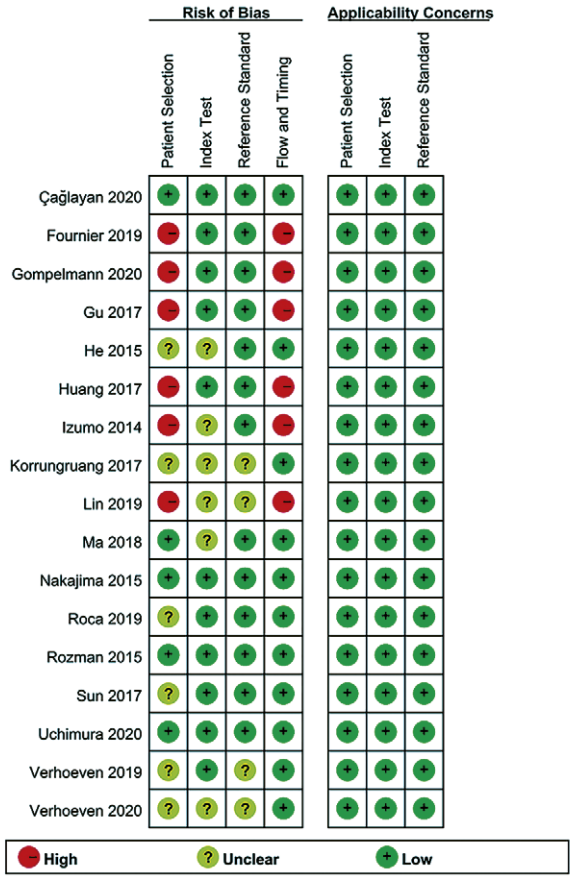

Fig 2. Quality assessment of the included studies using QUADAS-2 tool

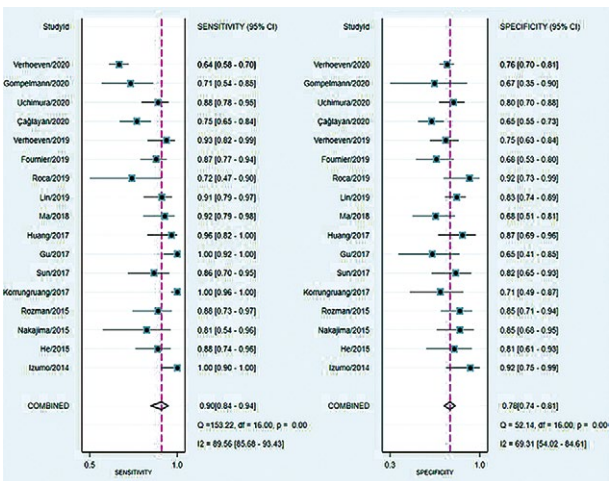

Fig 3. Forest diagrams of EBUS elastography for differentiating hilar and mediastinal LNs

lower diagnostic performance to studies between 2014 and 2017 (sensitivity: 0.84 and 0.95, p=0.00; specificity: 0.75 and 0.82, p=0.00). The subgroups concerning reference standard, the sensitivity between pathology and

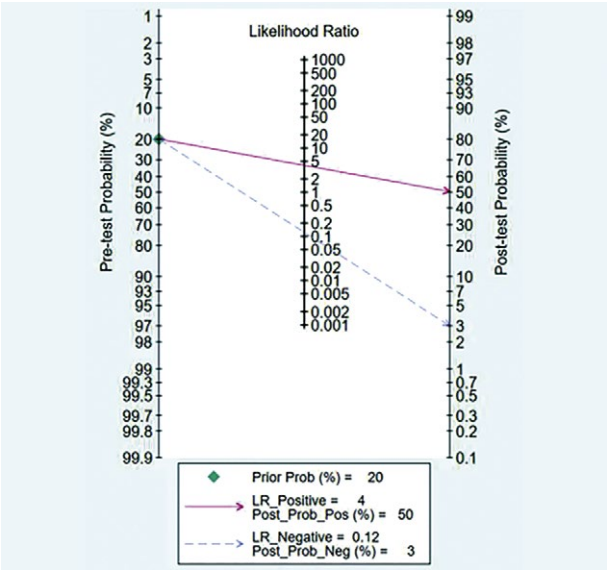

Fig 4. Fagan nomogram for detecting malignant hilar and mediastinal LNs

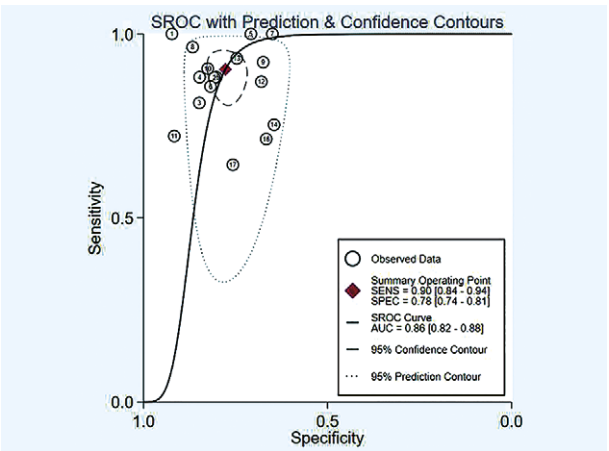

Fig 5. Summary receiver operating characteristics curve of EBUS elastography for malignant hilar and mediastinal LNs

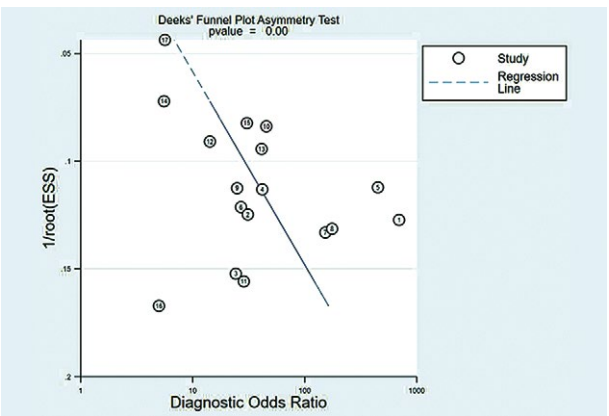

Fig 6. Funnel plot of EBUS elastography for malignant hilar and mediastinal LNs

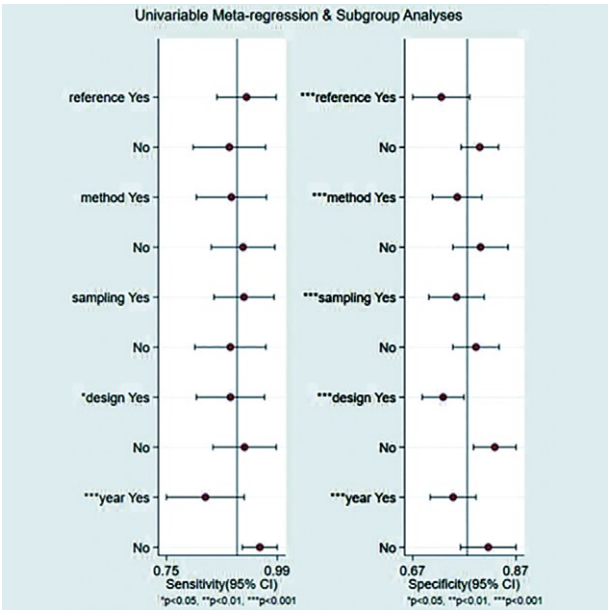

Fig 7. Meta-regression and subgroup analyses

pathology or follow-up was similar (sensitivity: 0.92 and 0.89, p=0.33), but the specificity of subgroup of pathology or follow-up was higher (specificity: 0.80 and 0.73, p=0.00). The sensitivity between quantitative method and qualitative method was similar (sensitivity: 0.89 and 0.92, p=0.05), while the specificity of qualitative method was higher (specificity: 0.80 and 0.76, p=0.00). Finally, a similar sensitivity was detected between consecutive sampling and others (sensitivity: 0.92 and 0.89, p=0.24), while the specificity of other sampling methods was higher (specificity: 0.79 and 0.76, p=0.00) (Table III).

Discussion

In this meta-analysis, including 17 studies and 2307 hilar and mediastinal LNs, we have evaluated the diagnostic accuracy of EBUS elastography for the identification of hilar and mediastinal LNs. We found that the pooled sensitivity, specificity and DOR of EBUS elastography for identifying hilar and mediastinal LNs were 0.90 (95% CI, 0.84-0.94), 0.78 (95% CI, 0.74-0.81), and 33 (95% CI, 17-64), respectively. The PLR, NLR, and SROC AUC were 4.1 (95% CI, 3.4-4.9), 0.12 (95% CI, 0.07-0.21), and 0.86 (95% CI, 0.82-0.88), respectively. The findings of this meta-analysis show that EBUS elastography has a well diagnostic performance for hilar and mediastinal LNs.

A previous meta-analysis in 2018 [37], which comprised a total of 504 patients, depicted 7 studies, published between 2014 and 2017, evaluating the diagnostic accuracy of EBUS elastography in the diagnosis of hilar and mediastinal LNs. The 7 studies were also included in our meta-analysis. The pooled sensitivity, specificity, PLR, NLR, and DOR were 0.93 (95% CI, 0.85-0.97), 0.85 (95% CI, 0.78-0.90), 6.3 (95% CI, 4.2-9.2), 0.08 (95% CI, 0.04-0.18), and 74 (95% CI, 33-168), respectively. Compared to it, our meta-analysis comprising a total of 1206 patients reported 17 studies and the included studies were published between 2014 and 2020. Although our results are somewhat lower to the previous study, our meta-analysis includes more additional objective studies (17 studies versus 7 studies) to support clinical practice of EBUS elastography for the diagnosis of hilar and mediastinal LNs.

Table III. Meta-regression and subgroup analyses

Covariate	N	Sensitivity (95% CI)	p-value	Specificity (95% CI)	p-value
Study design			0.04*		0.00*
Prospective	10	0.89 (0.82 - 0.96)		0.73 (0.69 - 0.77)	
Others	7	0.92 (0.85 - 0.99)		0.83 (0.79 - 0.87)	
Year of publication			0.00*		0.00*
2018-2020	9	0.84 (0.75 - 0.92)		0.75 (0.70 - 0.80)	
2014-2017	8	0.95 (0.91 - 0.99)		0.82(0.76 - 0.87)	
Reference standard			0.33		0.00*
Pathology	8	0.92 (0.86 - 0.99)		0.73 (0.67 - 0.78)	
Pathology or follow-up	9	0.89 (0.81 - 0.96)		0.80 (0.77 - 0.84)	
Diagnostic method			0.05		0.00*
Quantitative	9	0.89 (0.82 - 0.97)		0.76 (0.71 - 0.81)	
Qualitative	8	0.92 (0.85 - 0.98)		0.80 (0.75 - 0.86)	
Sampling			0.24		0.00*
Consecutive	8	0.92 (0.85 - 0.98)		0.76 (0.70 - 0.81)	
Others	9	0.89 (0.81 - 0.96)		0.79 (0.75 - 0.84)	

N, number of studies; *, statistical significance (p<0.05); CI, confidence interval

EBUS elastography used qualitative diagnostic methods or quantitative diagnostic methods for diagnosing hilar and mediastinal LNs in eligible studies. Qualitative diagnostic methods in enrolled studies included the 3-, 4-, or 5-image pattern classifications and quantitative diagnostic methods included the stiffness area ratio, the strain histogram method, and the strain ratio. Generally, unlike qualitative diagnostic methods, quantitative diagnostic methods could avoid the disadvantage relative to subjective evaluations by using specific numerical values [16,33]. In the subgroup analysis, 9 studies [16,23-26,29,33-35] using quantitative diagnostic methods showed pooled sensitivity of 0.89 (95% CI, 0.81-0.96) and specificity of 0.76 (95% CI, 0.71-0.81); in comparison, the pooled sensitivity of the 8 studies [14,15,27,28,30-32,36] using qualitative diagnostic methods was 0.92 (95% CI, 0.85-0.98) and the specificity was 0.80 (95% CI, 0.75-0.86). A higher specificity of qualitative diagnostic methods was observed (p=0.00); in contrast, the sensitivities were comparative (p=0.05). However, in three studies using qualitative diagnostic methods [14,15,28,30,32,36], the comparative analysis was performed between LNs with colour type 1 (not predominantly blue) and 3 (predominantly blue) and LNs with a mixed colour (type 2) were excluded. This might have resulted in patient selection bias. On the other hand, qualitative methods are operator dependent and may not provide an objective diagnosis. Therefore, the result should be interpreted with caution and large prospective studies are still required to verify the present result.

Ultrasound elastography is mainly used to detect the tissue stiffness [38,39]. Several previous studies found out that some malignant LNs were very soft, while some benign LNs appeared quite hard [26,32,40,41]. Possible explanations for the findings may lie in the high vascular invasion or necrotic structure of malignant LNs that appear soft under elastographic evaluation. By comparison, nonspecific inflammation, having areas of hard fibrotic or anthracotic tissues frequently occur in benign LNs and, therefore, the strain within the node may increase as the "stiffer" components of the node are assessed, ultimately influencing the application of elastography techniques. This confirms again that EBUS elastography reveals tissue stiffness and not malignancy or benignity.

Studies that compared conventional EBUS imaging to EBUS elastography have shown that EBUS elastography is superior to imaging by EBUS alone [14,23,25,30]. However, a prospective study by Gu et al [15] showed that EBUS elastography in combination with conventional EBUS B-mode features could improve the specificity from 65% to 72.7%. The study by Fujiwara et al [17] also demonstrated that the sensitivity and specificity of the stiffer area comprised more than 31% of the entire lymph node area for diagnosing malignancy were 72.1% and 84%, and by adding sonographic features to the elastographic findings, the sensitivity and specificity improved to 93.7% and 89.4%. A retrospective study of 149 mediastinal and hilar LNs by Uchimura et al [35] reported that by adding B-mode sonography to EBUS elastography, the sensitivity increased to 98.3%. Therefore, the combination of EBUS elastography and B-mode EBUS may lead to a higher diagnostic accuracy than either technology alone for differentiating benign and malignant LNs. In clinical practice, the procedure of B-mode EBUS is always before EBUS elastography, so the combination of EBUS elastography and B-mode EBUS for assessing the LNs is more feasible.

As the significant heterogeneity in the present study (sensitivity: I^2=89.56%, p=0.00; specificity: I^2=69.31%, p=0.00), meta-regression analyses were carried out to explore the sources of heterogeneity. We found that study design and year of publication accounted for part of the significant sources of heterogeneity in terms of sensitivity and study design, year of publication, reference standard, diagnostic method and sampling in terms of specificity. Furthermore, the indicated publication bias might be another source of heterogeneity. On the other hand, there were other factors such as specialties of EBUS performers, different levels of experience and different equipment, which might also have played a role in significant heterogeneity among studies. Further meta-regression analyses was not carried out to explore the sources of heterogeneity on the basis of the factors referred above because of the insufficient information supplied in the eligible studies.

EBUS elastography cannot currently replace the more accurate EBUS-TBNA for differentiating hilar and mediastinal LNs, which has been considered as the first-line technology for hilar and mediastinal lymph node staging of lung cancer in many clinic guidelines [42,43]. However, EBUS elastography as a supplemental modality could be helpful for operators to perform EBUS-TBNA efficiently. It could help in selecting the most suspicious lymph node for biopsy in stations where multiple LNs are found and help operators to choose harder areas of LNs for fine needle aspiration (FNA) to avoid necrosis or blood vessels, then improving the quality of the specimens and decreasing the number of punctures [14,23,24].

It is important to consider several limitations regarding this study. First, only studies written in English were enrolled, which may result in potential selection bias. Second, only several included studies [16,26,27,32,36] evaluated the intra- or inter-observer variability. Therefore, further studies are needed to evaluate the variabil-

ity. Third, the diagnostic accuracy of EBUS elastography was acquired from enrolled studies which provided various elastic parameters with diverse threshold values, which may result in heterogeneity. Therefore, the classification of LNs by EBUS elastography still needs to be further explored, developed and improved because of the lack of uniform standards. Finally, most of the enrolled studies had methodological disadvantages, especially in domains such as patient selection, the index test, reference standard and flow and timing, so improvements in the future study design are needed to address the issue.

Conclusion

In summary, EBUS elastography is a valuable technology in the differentiation of benign and malignant hilar and mediastinal LNs with high sensitivity and moderate specificity, which may provide supplementary diagnostic information, increase the diagnostic yield, and reduce the number of unnecessary biopsies during EBUS-TBNA. Furthermore, the combination of EBUS elastography and B-mode EBUS could improve the diagnostic accuracy for hilar and mediastinal LNs. However, the conclusion of this study should be interpreted with caution because of the significant heterogeneity and the publication bias. Large prospective international multicentre studies are still required to support the present conclusion.

Conflict of interest: none

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