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Diagnostic yield of radial probe endobronchial ultrasonography-guided transbronchial biopsy without fluoroscopy in peripheral pulmonary lesions: A systematic review and meta-analysis

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Abstract

Purpose: Although radial probe endobronchial ultrasound (R-EBUS) has been used to investigate peripheral pulmonary lesions (PPLs), its diagnostic performance without fluoroscopy remains unclear. We sought to determine the diagnostic yield of R-EBUS-guided transbronchial biopsy (TBB) without fluoroscopy.

Methods: We performed a systematic literature review using Pubmed, Embase, and the Cochrane Central Register. Then, we performed a proportional meta-analysis to determine the diagnostic yield of this modality. Subgroup and meta-regression analyses were used to identify factors affecting the performance of R-EBUS-guided TBB without fluoroscopy.

Results: We identified 31 studies consisting of a total of 6491 patients. Pooled overall diagnostic yield of R-EBUS-guided TBB without fluoroscopy was 0.70 (95% confidence interval [CI], 0.67–0.74). There was significant heterogeneity across studies ($I^2 = 89.45\%$, $p < 0.001$). In subgroup and meta-regression analyses, air bronchus sign on chest computed tomography scans, larger size PPLs, probe location within lesions, and heterogeneous echogenicity were associated with significantly higher diagnostic yield. Diagnostic yield from the upper lobe was statistically lower than that from the middle and lower lobes. Pooled pneumothorax rate was 0.01 (95% CI, 0.01–0.01, $I^2 = 63.51\%$, $p < 0.001$).

Conclusions: R-EBUS-guided TBB without fluoroscopy appears to be a relatively useful tool with a low pneumothorax rate for the diagnosis of PPLs. Factors mentioned above may affect the diagnostic yield of this tool. Because of substantial between-study heterogeneity, our results should be interpreted with caution.

KEYWORDS
bronchoscopy, diagnostic imaging, lung neoplasms, solitary pulmonary nodules, ultrasonography

INTRODUCTION

Peripheral pulmonary lesions (PPLs) are focal radiological opacities characterized as nodules or masses. The widespread use of low-dose helical computed tomography (CT) for lung cancer screening has significantly increased the identification of PPLs.[1] Histological diagnosis of PPLs, especially small lesions and those adjacent to major vascular structures, remains challenging.

Various techniques including sputum cytology, percutaneous needle aspiration or biopsy, and fluoroscopic-guided transbronchial biopsy (TBB) are commonly used to diagnose PPLs.[2–4] Although the success rates of percutaneous needle techniques under fluoroscopic or CT guidance are high, ranging from 76% to 97%, there is the potential for spread of malignant cells from the tumor into the pleural cavity, increased risk of pneumothorax, and increased risk

Junghoo Lee and Jae-Uk Song contributed equally to this work.

of systemic arterial air embolism.[2,3] In contrast, the diagnostic yield of flexible fiber optic bronchoscopy (FFB) under fluoroscopic guidance using brushing, washing, and TBB is low, ranging from 14% to 71%.[4]

For over two decades, radial probe endobronchial ultrasound (R-EBUS) has been used as a complementary diagnostic modality to identify PPLs.[5] Once the location of the lesion is identified by R-EBUS; the small-caliber ultrasonographic probe is withdrawn to allow for other diagnostic tools to be used. This process is likely to cause false negative results, because unguided biopsy forceps can enter bronchial branches other than those originally identified by R-EBUS. Fluoroscopy can be used to overcome this weakness. However, fluoroscopy has the disadvantages of radiation exposure, space constraints in the bronchoscopy suite, and high cost.[6]

Several studies have examined the role of R-EBUS in diagnosing PPLs. Four previous meta-analyses of the use of R-EBUS to diagnose PPLs have been published.[7–10] However, these meta-analyses included all studies that performed R-EBUS regardless of whether fluoroscopy was used or not. Our aim in the present study was to evaluate the diagnostic yield of R-EBUS-guided TBB without fluoroscopy to diagnose PPLs through systematic review and meta-analysis. We also investigated factors affecting the diagnostic performance of R-EBUS-guided TBB.

METHODS

Data sources and search strategy

We searched three electronic databases (Pubmed, Embase, and the Cochrane Central Register) for relevant articles published before February 1, 2022. References listed in all considered articles were manually searched for additional relevant records. We used the following terms: ("endobronchial ultrasound" OR "endobronchial ultrasonography" OR "EBUS") and ("radial" OR "guide sheath") and ("lung" OR "peripheral" OR "pulmonary"). As this study was a systematic review of published articles, neither informed consent nor ethics approval was required.

Inclusion criteria

This meta-analysis included all studies that performed R-EBUS-guided TBB without fluoroscopy to diagnose PPLs and provided data regarding the diagnostic yield of the index tool. We included trials that compared R-EBUS with other tools as well as trials with R-EBUS-only arms. Diagnosis was confirmed either histologically or through follow-up for at least 6 months. Both retrospective and prospective studies were included and full-length studies or letters published in peer-reviewed English language journals were considered eligible for inclusion in the study. Review articles, case reports, commentaries, and extension or post hoc studies were excluded.

Data screening, extraction, and outcomes

Two authors independently screened those studies that met the predefined criteria for eligibility based on title and abstract. After review at the full-text level, we extracted potentially relevant studies. Any disagreements in the process of study selection or data extraction were resolved by

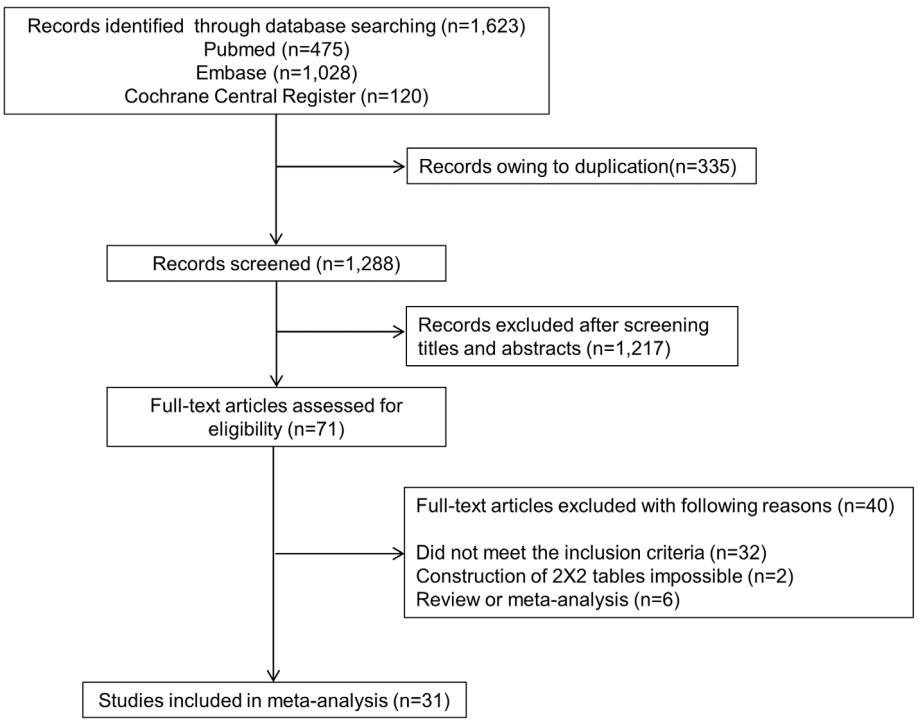

FIGURE 1 Flow diagram demonstrating how eligible studies were identified.

TABLE 1 Characteristics of the studies included in the meta-analysis

Study, yr	Design	Country	Total subjects (no.)	Age (mean, yr)	Male (%)	Use of a GS	Use of rapid on-site examination	Nodule size (mean, mm)	Incidence of pneumothorax (%)	Incidence of significant bleeding (%)	Histological procedures	Study objectives
Chao et al. (2009)[14]	Prospective	Taiwan	182	62.3	61	No	No	34.9	2.20	3.30	BW, TBB, and TBNA	To investigate the diagnostic yield of R-EBUS-guided TBNA
Chen et al. (2015)[15]	Retrospective	Taiwan	815	65.7	64.5	No	Yes	NA	NA	NA	Brushing and TBB	To evaluate the impact of ROSE on the diagnostic yield of R-EBUS
Chung et al. (2007)[16]	Prospective	Taiwan	113	59.6	66.4	No	No	24.5	0.90%	4.40%	TBB	To investigate the diagnostic yield of R-EBUS-guided TBB
Dooms et al. (2007)[17]	Prospective	Germany	50	69	68	No	No	36.6	0%	2%	BAL and TBB	To investigate the diagnostic yield of R-EBUS-guided TBB
Durakovic et al. (2015)[18]	Retrospective	Denmark	147	67.8	45.6	No	No	40	2.00%	0%	BW, brushing, and TBB	To determine the sensitivity and complication rate of R-EBUS without the use of GS and fluoroscopy
Eberhardt et al. (2007)[19]	Prospective	Germany	39	54	59	No	No	25	5.12%	0%	TBB	To investigate the diagnostic yield of R-EBUS combined with electromagnetic navigation bronchoscopy
Eberhardt et al. (2009)[20]	Prospective	Germany	100	51.7	56	Yes	No	15.3	3%	NA	TBB	To assess the ability of R-EBUS-guided TBB to sample SPNs less than 20 mm in diameter
Evison et al. (2014)[21]	Retrospective	United kingdom	117	69.5	53	No	No	36.6	0.90%	0%	TBB	To investigate whether CT characteristics could predict the success of R-EBUS-guided sampling
Fuso et al. (2013)[22]	Retrospective	Italy	447	NA	NA	No	No	36	1.70%	NA	TBB	To investigate the diagnostic yield of R-EBUS-guided TBB
Guvenc et al. (2015)[23]	Retrospective	Belgium	760	NA	NA	No	No	NA	1.20%	NA	TBB	To identify computed tomography characteristics affecting the success rate of R-EBUS-mini probe diagnosis
Herth et al. (2002)[5]	Prospective	USA	50	62.5	74	No	No	33.1	2%	0%	TBB	To assess the ability of R-EBUS to provide imaging guidance for TBB
Herth et al. (2006)[24]	Prospective	USA	54	46.3	66.7	Yes	No	22	2%	0%	TBB	To investigate the diagnostic yield of R-EBUS-guided TBB
Hong et al. (2021)[25]	Retrospective	South Korea	607	67.8	65.1	Yes	No	31	2%	NA	Brushing and TBB	To investigate the use of R-EBUS-TBB using GS without fluoroscopy
Huang et al. (2009)[26]	Retrospective	Taiwan	83	60	71.1	No	No	24	2.40%	3.61%	BW, brushing, and TBB	To investigate the diagnostic yield of R-EBUS-guided TBB
Huang et al. (2012)[27]	Retrospective	Taiwan	384	64.7	57.3	No	No	38	1.82%	0.52%	BW, brushing, and TBB	To determine the association between the number of biopsy specimens and the diagnostic yield of R-EBUS-guided TBB

(Continues)

TABLE 1 (Continued)

Study, yr	Design	Country	Total subjects (no.)	Age (mean, yr)	Male (%)	Use of a GS	Use of rapid on-site examination	Nodule size (mean, mm)	Incidence of pneumothorax (%)	Incidence of significant bleeding (%)	Histological procedures	Study objectives
Huang et al. (2019)[28]	Retrospective	Taiwan	438	66	54.6	No	No	37	1.40%	0%	Brushing and TBB	To investigate whether a biopsy-first or brushing-first strategy confers a better diagnostic yield and safety for R-EBUS-guided procedures
Kokkonouzis et al. (2013)[29]	Retrospective	Greece	20	NA	NA	No	No	30.2	5.00%	NA	Brushing and TBB	To compare the diagnostic yield between R-EBUS-guided TBB and TBB
Kuo et al. (2011)[30]	Prospective	Taiwan	408	NA	NA	No	No	34	NA	NA	BW and TBB	To assess the feasibility of R-EBUS echoic features as predictors of the diagnostic yield of TBB
Kuo et al. (2014)[31]	Retrospective	Taiwan	271	60	64.2	No	No	34.6	2.58%	8.12%	BW, brushing, and TBB	To compare yields of TBB and BW with those of BW plus bronchial brushing
Lin et al. (2012)[32]	Retrospective	Taiwan	39	65	48.7	No	No	29.1	NA	NA	TBB	To investigate the diagnostic yield of R-EBUS-guided TBB
Minami et al. (2015)[33]	Retrospective	Japan	60	69	58.3	Yes	Yes	28.9	NA	NA	TBB	To assess the diagnostic accuracy of TBB with R-EBUS-GS
Minezawa et al. (2015)[34]	Retrospective	Japan	149	70	57.7	Yes	No	All nodules ≤30 mm	3.40%	0%	Brushing and TBB	To predict the diagnostic accuracy of TBB with R-EBUS-GS
Moon et al. (2019)[35]	Retrospective	South Korea	184	65	50.5	No	No	32	4.80%	NA	TBB	To investigate the diagnostic performance of R-EBUS without GS and fluoroscopy
Paone et al. (2005)[36]	Prospective	Italy	87	65	71.3	No	No	NA	0%	0%	TBB	To compare the diagnostic yields of R-EBUS-guided TBB and TBB
Wang et al. (2018)[37]	Prospective	China	80	58.7	40	No	No	21.7	1.25%	5%	BAL, brushing and TBB	To compare the diagnostic yield, complications, and influencing factors between R-EBUS and CT-guided needle biopsy
Yang et al. (2004)[38]	Retrospective	Taiwan	122	66	65.6	No	No	NA	0%	0%	TBB	To investigate the diagnostic yield of TBB with or without R-EBUS-guidance
Yoshikawa et al. (2007)[39]	Prospective	Japan	123	66.2	59.5	Yes	No	31	0.80%	NA	Brushing and TBB	To assess the diagnostic accuracy of TBB with R-EBUS-GS
Zaric et al. (2016)[40]	Prospective	Serbia	168	62	69.6	No	No	NA	0.60%	0.60%	Suction catheter biopsy and TBB	To assess the safety and feasibility of R-EBUS guided suction catheter biopsy
Zhang et al. (2016)[41]	Prospective	China	54	60.9	64.8	Yes	No	30.2	0%	NA		

(Continues)

TABLE 1 (Continued)

Study, yr	Design	Country	Total subjects (no.)	Age (mean, yr)	Male (%)	Use of a GS	Use of rapid on-site examination	Nodule size (mean, mm)	Incidence of pneumothorax (%)	Incidence of significant bleeding (%)	Histological procedures	Study objectives
											Brushing and TBB	To compare the diagnostic yield of R-EBUS-GS and R-EBUS with distance
Zhang et al. (2018)[42]	Retrospective	China	328	61.6	61	No	No	30.9	0%	3.96%	TBB	To investigate the efficiency, safety, and influencing factors of R-EBUS with distance
Zhu et al. (2018)[43]	Prospective	China	150	59.5	54.4	Yes	No	NA	0.70%	0.70%	TBB	To analyze the applicability of R-EBUS-GS and CT-guided needle aspiration

Abbreviations: BAL, bronchoalveolar lavage; BW, bronchial washing; CT, computed tomography; GS, guided sheath; R-EBUS, radial endobronchial ultrasound; ROSE, rapid on-site examination; TBB, transbronchial biopsy; TBNA, transbronchial needle aspiration.

consensus-based discussion. A predefined form was used to extract data from each study. Extracted information included the following: first author's last name, published year, design, study country, study type, total number of subjects, subject demographic characteristics, objectives, effect size, and 95% confidence intervals (CI). The outcome of interest in this meta-analysis was the diagnostic yield of R-EBUS-guided TBB without fluoroscopy for diagnosis of PPLs.

Bias assessment

As recommended by the Cochrane Collaboration, the quality and risk of bias in diagnostic test accuracy were evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[11] This scale has four main components: patient selection, index test, reference standard, and flow and timing. Each component was examined for risk of bias, and the first three components were assessed for applicability. Discrepancies were resolved by consensus. Publication bias was evaluated using a funnel plot, and statistical significance was assessed using Egger's regression test.[12]

Data synthesis and statistical analysis

For diagnostic meta-analysis, we extracted the number of successful diagnoses either directly or through recalculation based on the reported measures of effect size in combination with the prevalence and sample sizes of the included studies. A proportional meta-analysis was performed to calculate the pooled diagnostic yield and pneumothorax rate of R-EBUS-guided TBB without fluoroscopy. Diagnostic yield was calculated as the number of successfully confirmed diagnoses using the index tool divided by the total number of PPLs. Pooled proportions with 95% CIs were calculated and are reported.

Between-study statistical heterogeneity was assessed using I^2 statistics and the Cochrane Q test.[13] Heterogeneity was assessed using I^2 statistics on a scale of 0%–100%. For $I^2 > 50\%$, a random-effects model was used, otherwise a fixed-effects model was used.[13] $I^2 > 50\%$ indicates a substantial level of between-study heterogeneity.[13] Subgroup and meta-regression analyses were performed to identify factors affecting diagnostic yield and potential sources of bias for the following input variables: study region, number of patients, use of a guided sheath, air bronchus sign on chest CT, lesion location, lesion size, CT findings, position of the probe lesion margin, and echogenicity.

A p value <0.05 was considered statistically significant. All analyses were performed using Stata statistical software (Version 14.2, Stata Corp LP) and Review Manager (Version 5.3, Nordic Cochrane Center, The Cochrane Collaboration).

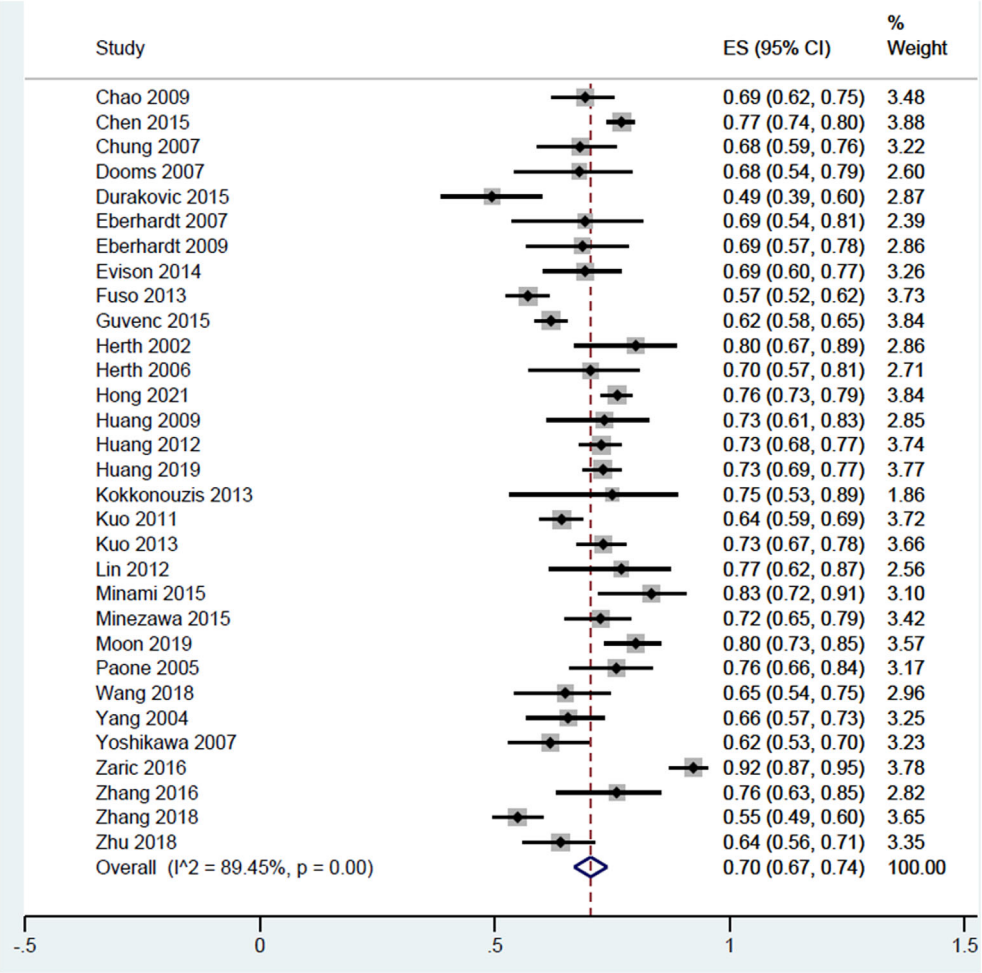

FIGURE 2 Forest plot of diagnostic yields for R-EBUS-guided TBB without fluoroscopy. R-EBUS, radial probe endobronchial ultrasound; TBB, transbronchial biopsy.

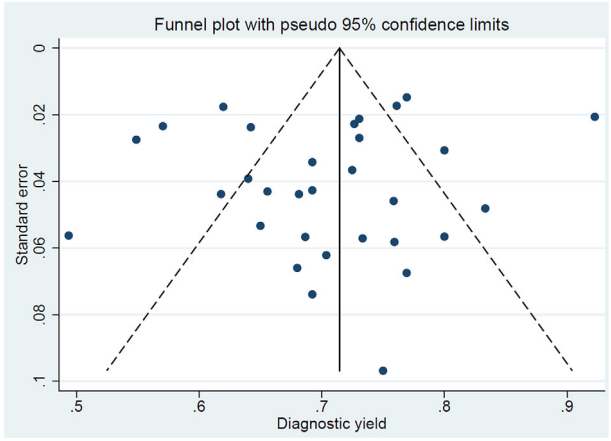

FIGURE 3 Funnel plot to assess publication bias.

RESULTS

Study search

A flow diagram of the selection procedure is presented in Figure 1. We initially identified 1623 records. After removal of duplicates, 1288 articles were considered eligible for abstract review based on title. Subsequently, 71 articles were selected for full text review. Forty records were excluded for the reasons presented in Figure 1, and 31 articles that met the defined inclusion criteria were finally included.[5,14–43]

Baseline characteristics of the included studies are presented in the Table 1. A total of 6491 patients were included in this systematic review and meta-analysis, and all studies were published between 2002 and 2021. The number of patients in each trial ranged from 20 to 815. Mean age ranged from 46.3 to 70 years. Percentage of males ranged from 40 to 71.3. Mean diameter of PPLs ranged from 15.3 to 40 mm. A guide sheath was used in eight studies[20,24,25,33,34,39,41,43] and rapid on-site examination (ROSE) was performed in two studies.[15,33] The incidence of pneumothorax and significant bleeding ranged from 0.60 to 5.12 and 0 to 8.12, respectively.

In pooled estimates, overall diagnostic yield of R-EBUS-guided TBB without fluoroscopy was 0.70 (95% CI, 0.67–0.74). Diagnostic yield ranged from 0.49 to 0.92 across studies. There was significant heterogeneity across studies (I^2 = 89.45%, $p < 0.001$). The forest plot for the meta-analysis is presented in Figure 2.

To identify factors affecting diagnostic yield and potential sources of the substantial between-study heterogeneity,

TABLE 2 Subgroup analysis of the diagnostic yields of R-EBUS-guided TBB without fluoroscopy

Variables	No. of studies	No. of patients	Diagnostic yield (95% CI)	Likelihood ratio, I^2%	Heterogeneity, p value
Study design					
Prospective	17	4880	0.71 (0.64–0.78)	89.18	<0.001
Retrospective	14	1625	0.70 (0.67–0.74)	89.71	<0.001
No. of patients					
≥100	20	5912	0.69 (0.64–0.73)	93.00	<0.001
<100	11	293	0.74 (0.71–0.78)	0	0.46
Use of a guide sheath					
Yes	8	1264	0.72 (0.67–0.77)	66.13	<0.001
No	23	5241	0.70 (0.66–0.74)	91.58	<0.001
Air bronchus sign on chest CT					
Yes	9	2061	0.81 (0.75–0.86)	88.56	<0.001
Adjacent or none	9	926	0.46 (0.32–0.61)	95.26	<0.001
Lesion location					
Upper lobe	18	2048	0.71 (0.68–0.74)	46.28	0.02
Middle or lower lobe	18	1911	0.76 (0.71–0.81)	81.82	<0.001
Lesion size					
≥3 cm	14	2293	0.81 (0.77–0.86)	83.78	<0.001
<3 cm	14	1771	0.62 (0.56–0.67)	78.26	<0.001
≥2 cm	16	2598	0.75 (0.71–0.80)	83.16	<0.001
<2 cm	17	697	0.53 (0.45–0.61)	76.50	<0.001
CT findings					
Solid type	7	1518	0.75 (0.73–0.77)	0	0.51
Non-solid type	7	421	0.71 (0.67–0.75)	0	0.47
Position of the probe					
Within	11	2052	0.81 (0.77–0.85)	80.17	<0.001
Adjacent	11	858	0.47 (0.39–0.55)	79.61	<0.001
Lesion margin					
Continuous	2	320	0.64 (0.59–0.70)	22.62	0.26
Non-continuous	2	359	0.72 (0.67–0.76)	83.74	0.01
Echoic features					
Homogenous	2	305	0.55 (0.50–0.61)	57.3	0.13
Heterogeneous	2	374	0.78 (0.74–0.83)	0	0.39

Abbreviations: CI, confidence interval; CT, computed tomography; R-EBUS, radial endobronchial ultrasound; TBB, transbronchial biopsy.

additional subgroup and meta-regression analyses were performed (Tables 2 and 3). Lesions with an air bronchus sign on chest CT had a significantly higher diagnostic yield than those without an air bronchus sign (0.81, 95% CI, 0.75–0.86 vs. 0.46, 95% CI, 0.32–0.61; $p < 0.001$). Regarding location, the diagnostic yield from the upper lobe was significantly lower than that from the middle and lower lobes (0.71, 95% CI, 0.68–0.74 vs. 0.76, 95% CI, 0.71–0.81; $p = 0.046$). Larger PPLs had a significantly higher diagnostic yield (0.81, 95% CI, 0.77–0.86 vs. 0.62, 95% CI, 0.56–0.67; $p < 0.001$ for cutoff 3 cm, and 0.75, 95% CI, 0.71–0.80 vs. 0.53, 95% CI, 0.45–0.61; $p < 0.001$ for cutoff 2 cm, respectively) than smaller PPLs. Subjects in which the probe was located within the lesions had a statistically high diagnostic yield (0.81, 95% CI, 0.77–0.85). If the probe was placed adjacent to the lesion rather than within the lesion, the diagnostic yield of TBB decreased substantially (0.47, 95% CI, 0.39–0.55; $p < 0.001$). Homogenous echogenicity was associated with a significantly lower diagnostic yield than heterogeneous echogenicity (0.55, 95% CI, 0.50–0.61 vs. 0.78, 95% CI, 0.74–0.83, respectively; $p = 0.037$). Meta-regression analysis failed to prove a relationship between the diagnostic yield of this modality and study design ($p = 0.719$), number of patients ($p = 0.163$), use of a guide sheath ($p = 0.680$), presence of a solid pattern on chest CT findings ($p = 0.118$), or lesion margin ($p = 0.398$) (Table 3).

QUADAS-2 assessment results are summarized in Figure S1. Overall, the quality of the studies was deemed satisfactory. However, the QUADAS-2 tool showed that unclear consecutive or random sampling of enrolled patients

TABLE 3 Univariate meta-regression analysis to identify potential sources of heterogeneity among studies

Covariates	Regression coefficient	Standard error	95% CI for coefficient	*p* value
Study design (prospective vs. retrospective)	0.012	0.034	−0.057–0.081	0.719
No. of patients (≥100 vs. <100)	−0.51	0.036	−0.125–0.022	0.163
Use of a guide sheath	0.016	0.038	−0.062–0.094	0.680
Air bronchus sign on chest CT	0.347	0.074	0.189–0.504	<0.001
Lesion location (upper vs. middle or lower lobes)	−0.056	0.019	0.723–0.799	0.046
Lesion size (≥3 vs. <3 cm)	0.195	0.035	0.124–0.266	<0.001
Lesion size (≥2 vs. <2 cm)	0.222	0.046	0.130–0.315	<0.001
CT findings (solid vs. non-solid type)	0.042	0.025	−0.012–0.096	0.118
Position of the probe (within vs. adjacent)	0.337	0.039	0.255–0.419	<0.001
Lesion margin (continuous vs. non-continuous)	−0.074	0.069	−0.372–0.224	0.398
Echoic features (homogenous vs. heterogeneous)	−0.230	0.046	−0.426 to −0.034	0.037

Abbreviations: CI, confidence interval; CT, computed tomography.

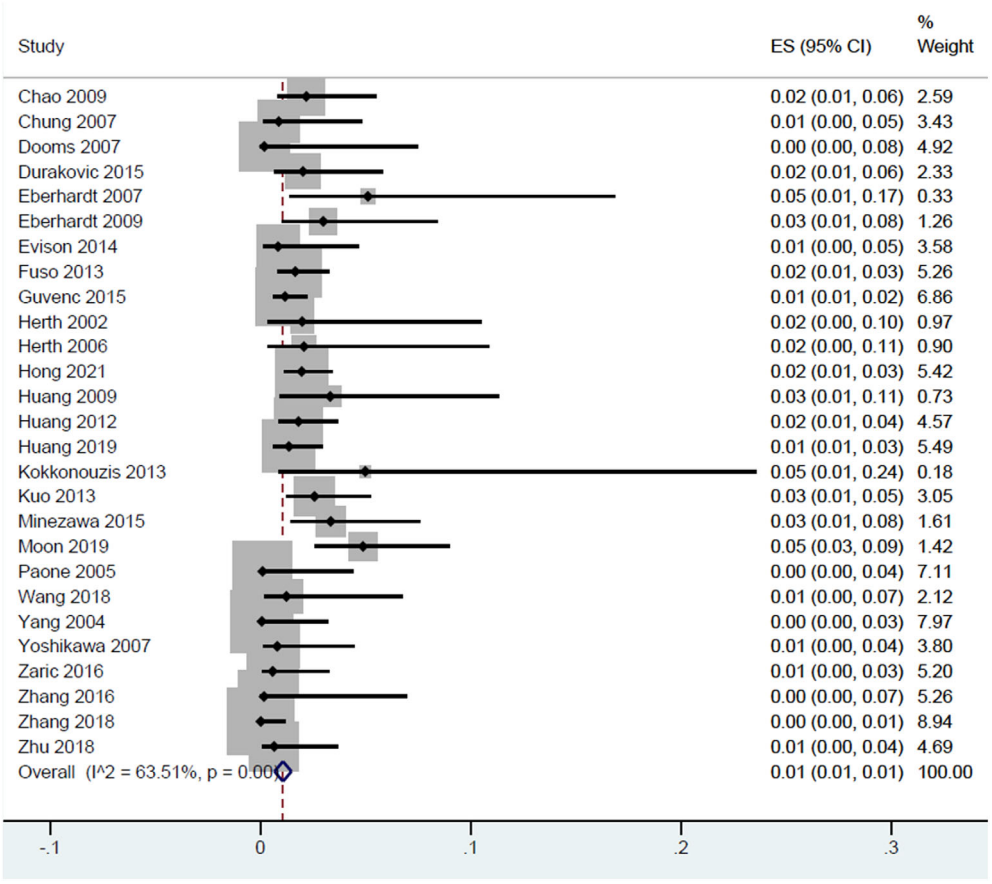

FIGURE 4 Forest plot of pneumothorax rates for R-EBUS-guided TBB without fluoroscopy. R-EBUS, radial probe endobronchial ultrasound; TBB, transbronchial biopsy.

and uncertainty regarding if data from all patients were included in the analysis may be potential sources of bias. As shown in Figure 3, the funnel plot did not reveal any evidence of obvious asymmetry, suggesting the absence of publication bias. Egger's test also did not provide any evidence of publication bias ($p = 0.450$).

To assess the safety of R-EBUS-guided TBB without fluoroscopy, we extracted data on post-procedural pneumothorax from 27 studies.[5,14,16–29,31,34–43] The pooled pneumothorax rate was 0.01 (95% CI, 0.01–0.01) with significant heterogeneity among studies ($I^2 = 63.51\%$, $p < 0.001$) (Figure 4).

DISCUSSION

The overall diagnostic yield of R-EBUS-guided TBB without fluoroscopy was 0.70 based on a pooled estimate. The previous four meta-analyses that assessed the diagnostic

performance of R-EBUS regardless of whether fluoroscopy or not was used to diagnose PPLs reported a pooled sensitivity ranging from 0.69 to 0.73.[7,8,10] Another meta-analysis that evaluated the diagnostic yield of R-EBUS reported a value of 0.71.[9] These findings indicate that regardless of whether fluoroscopy is used or not, the overall diagnostic yield of R-EBUS is similar.[7–10] Considering that the diagnostic yields of FFB alone without R-EBUS ranged from 0.19 to 0.62 based on seven studies,[4] R-EBUS without fluoroscopy could be a comparatively useful tool for diagnosing PPLs.

Substantial heterogeneity in pooled estimates was observed among the included studies. We investigated factors affecting diagnostic yield and potential sources of bias. In subgroup and meta-regression analyses, the presence of an air bronchus sign in chest CT findings, lesion location, lesion size, the position of the probe, and echogenicity affected the diagnostic yields of R-EBUS without fluoroscopy guidance. In particular, the air bronchus sign on chest CT, a PPL larger than 3 cm, and positioning of the R-EBUS probe within the lesion were associated with a diagnostic yield of 0.8 or more. These findings appear to be expanded as valuable factors affecting diagnostic yields of R-EBUS itself regardless of whether fluoroscopy is applied.

The pooled overall diagnostic yield of R-EBUS without fluoroscopy is lower than that of percutaneous needle techniques (0.76 to 0.97).[2,3] This suboptimal yield could be because of superficial or crushing sampling, and these specimens may be inappropriate for immunohistochemistry or molecular assays.[44] Combined modalities using guide-sheath guidance and ROSE may enhance the ability of R-EBUS to diagnose PPLs. We first compared the diagnostic yields of R-EBUS without fluoroscopy guidance according to whether a guided sheath was used. We found eight studies that used a guided sheath.[20,24,25,33,34,39,41,43] The diagnostic yield of R-EBUS with a guided sheath was similar to that of studies that did not use a guided sheath. We identified two studies that performed ROSE examination.[15,33] A retrospective study reported that the combination of R-EBUS with ROSE increased diagnostic yield, particularly for difficult PPLs (i.e., lesions <3 cm in size with a negative air bronchus sign), lesions located in the right apical and left apical-posterior segments, positioning of the probe adjacent to the lesions, and lesions with pleural effusion.[15] The other study did not find ROSE to be effective when used in combination with R-EBUS.[33]

There are several reasons why it is difficult to combine fluoroscopic guidance with R-EBUS. First, when target lesions are small they are difficult to visualize on fluoroscopy, and therefore, fluoroscopy would not be helpful for the diagnosis of PPLs.[24] The other disadvantages of fluoroscopy are radiation exposure, the requirement for a shield room, and its high costs.[6] Safety is generally one of the most important concerns when choosing a diagnostic procedure for PPLs. Pneumothorax is a well-known complication of TBB.[45] Previous studies have reported that fluoroscopy did not reduce the rate of iatrogenic pneumothorax after TBB using FFB.[46,47] In our pooled estimates, the risk of pneumothorax from R-EBUS without fluoroscopy were very low at ~1%. Given than an incidence rate of pneumothorax of 15% for post-procedure pneumothorax after percutaneous CT-guided biopsy was reported, our findings indicate that R-EBUS-guided TBB without fluoroscopy is safe.[45,48,49]

To the best of our knowledge, this is the first meta-analysis to report the diagnostic yield of R-EBUS without fluoroscopy. A strength of our study is that we provided reliable estimates through a rigorous literature search that included updated reports. We also evaluated several factors affecting the diagnostic yield of this technique by adding covariates to the bivariate model used in the meta-regression analysis. Our findings will hopefully inform the use of EBUS-guided TBB without fluoroscopy for diagnosis of PPLs in clinical practice.

One limitation of our study is the substantial heterogeneity among the included studies, although heterogeneity is frequently observed in systematic reviews of diagnostic test accuracy studies.[50] Heterogeneous patient populations are one potential source of this heterogeneity. Second, because many studies included in our analysis were observational in nature, our results should be interpreted with caution. Further large-scale randomized controlled trials need to be conducted to overcome this limitation. Third, although we performed detailed subgroup analyses, there were missing data for some variables.

CONCLUSIONS

Our meta-analysis revealed that R-EBUS-guided TBB without fluoroscopy is a relatively useful tool for diagnosis of PPLs with low risk of iatrogenic pneumothorax. Air bronchus sign on chest CT findings, lesion location in non-upper lobes, large PPL size, positioning of the probe within the lesion, and heterogeneous echogenicity have a significant impact on the diagnostic yield of this modality. Physicians could take these factors into consideration when selecting the optimal subjects for this diagnostic procedure. Because between-study heterogeneity was high in the present study, our findings should be interpreted with caution.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHOR CONTRIBUTIONS

Conceived and designed the analysis: Junghoo Lee. *Collected the data*: Junghoo Lee and Jae-Uk Song. *Contributed data or analysis tools*: Junghoo Lee and Jae-Uk Song. *Performed the analysis*: Junghoo Lee and Jae-Uk Song. *Wrote the paper*: Junghoo Lee and Jae-Uk Song.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DISCLAIMER

The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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