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Research article

Radial endobronchial ultrasound - guided bronchoscopy for the diagnosis of peripheral pulmonary lesions: A systematic review and meta-analysis of prospective trials

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ABSTRACT

Background: The diagnostic yield of radial endobronchial ultrasound (r-EBUS) for the diagnosis of peripheral pulmonary lesions (PPLs) varies between studies and is affected by multiple factors. We aimed to evaluate the efficacy and safety of r-EBUS, and to explore the factors influencing the diagnostic yield of r-EBUS in patients with PPLs.

Methods: The PubMed, Web of Science, and EMBASE databases were searched to identify relevant studies that used r-EBUS for diagnosing PPLs from the date of inception to Dec 2022. Meta-analysis was conducted using Review Manager 5.4 and Stata 15.1.

Results: An analysis of 46 studies with a total of 7252 PPLs was performed. The pooled diagnostic yield of r-EBUS was 73.4 % (95 % CI: 69.9%–76.7 %), with significant heterogeneity detected among studies ($I^2 = 90$ %, $P < 0.001$). Further analysis demonstrated PPLs located in the middle or lower lobe, >2 cm in size, malignant in type, solid in appearance on computerized tomography (CT), present in bronchus sign, the within probe location, and the addition of rapid on-site evaluation (ROSE) were associated with increased diagnostic yield, whereas use of a guide sheath (GS), bronchoscopy type, and a multimodality approach failed to influence the outcome. The pooled incidence rates of overall complications, pneumothorax and moderate and severe bleeding were 3.1 % (95 % CI: 2.1%–4.3 %), 0.4 % (95 % CI: 0.1%–0.7 %) and 1.1 % (95 % CI: 0.5%–2.0 %), respectively.

Conclusions: r-EBUS has an appreciable diagnostic yield and an excellent safety manifestation when used to deal with PPLs.

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1. Introduction

Lung cancer remains the most frequently malignant tumor worldwide and the leading cause of cancer related deaths in men [1]. The use of low-dose computerized tomography (CT) screening for persons with a high risk of lung cancer serves as an effective mean by which lung-cancer mortality can be decreased [2]. The further generalization of CT imaging has been accompanied by an increasing number of peripheral pulmonary lesions (PPLs); rapid and accurate identification of such lesions remains challenging. Although a transthoracic CT-guided percutaneous approach has an excellent diagnostic accuracy [3], its clinical implementation is suboptimal since this accuracy comes at the cost of a considerable complications including pneumothorax and bleeding [4,5], and it fails to perform mediastinal staging at the time of the same procedure.

Flexible bronchoscopy with a safer profile provides another available modality for the diagnosis of PPLs, however, the yield of conventional transbronchial biopsy is suboptimal [6]. This has led to the advancement of novel bronchoscopic techniques such as radial endobronchial ultrasound (r-EBUS), electromagnetic navigation bronchoscopy (ENB) and virtual bronchoscopic navigation (VBN) [7–16]. Among these bronchoscopic navigation techniques, r-EBUS, as a common and powerful tool, has been recommended for the diagnosis of PPLs by the American College of Chest Physicians and European Society for Medical Oncology [17,18]. r-EBUS for the diagnosis of PPLs was first reported by Herth et al. [19] in 2002, with a wide range of reported diagnostic yield between 50.0 % and 97.6 %, and complication rates between 0 % and 18.4 % [7–54]. Accurate estimates of diagnostic yield and complication rates of r-EBUS are critical for clinicians in the management of PPLs. Currently, there have been only one meta-analysis specifically evaluating the diagnostic yield of r-EBUS for diagnosing PPLs and reporting an overall weighted diagnostic yield of 70.6 % (95 % CI: 68%–73.1 %) [55]. This meta-analysis published by Ali et al. [55] in 2017 identified 57 studies with a total of 7872 lesions, however, more than half of the publications included in their meta-analysis were retrospective with inherent risk of bias. Furthermore, they excluded studies that combined r-EBUS with VBN or ENB; it should be noted that this multimodality approach overcoming the limitations of any single technique has the potential to improve the diagnostic yield of PPLs [8,9,15,16].

We therefore undertook a meta-analysis of prospective trials using both old and multiple additional studies since 2017 to provide a clinical reference on how to better manage PPLs. In addition to a pooled estimate of r-EBUS diagnostic yield and complication rates, in particular we investigated factors associated with successful diagnosis using r-EBUS including lesion location, lesion size, probe location, lesion type, use of a guide sheath (GS), bronchus sign, lesion appearance on CT, bronchoscopy type, addition of rapid on-site evaluation (ROSE) and a multimodality approach.

2. Materials and methods

2.1. Literature search

We conducted this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) statement [56]. The protocol of the present study was registered at PROSPERO, with a registered number: CRD42022384295. The PubMed, Web of Science, and EMBASE databases were searched to identify relevant studies from the date of inception to Dec 2022 using the pre-determined search strategy (Supplementary File-Table S1). Manual screening of reference lists of the retrieved articles was also done and the above procedure was performed repeatedly until all relevant studies were captured.

2.2. Study selection

The detailed study selection was performed by two authors (S. Tian and X. Li) independently, with all discordance being indicated and solved by consensus and adjudication with the corresponding author (C. Bai). Full-text articles strictly assessed by for eligibility was followed by the preliminary examinations of titles and abstracts. Studies would be considered if they met the following criteria for inclusion: 1) r-EBUS employed for diagnosing PPLs; 2) sufficient data for calculating the diagnostic yield; 3) studies must be prospective; 4) at least 30 patients enrolled in the study; 5) diagnosis must be confirmed histopathologically or by close follow-up. Case reports, editorials, letters, conference abstracts, reviews, articles written other than in English and Chinese, studies in a human cadaver model were excluded.

2.3. Data extraction and quality assessment

All data was inspected and collected by two independent authors (S. Tian and J. Liu), and the conflicts were settled by consultation and input from the corresponding author (C. Bai). The following data was extracted: first author, publication year, study design, use of additional guidance modalities (i.e. GS, fluoroscopy, VBN and ENB), total number of PPLs, number of PPLs that were successfully diagnosed, and complications. Additionally, in cases where further stratified diagnostic information including lesion location, lesion size, probe location, lesion type (benign or malignant), use of a GS, bronchus sign, lesion appearance on CT [solid and part-solid and/or ground-glass opacity (GGO)], bronchoscopy type [ultrathin, external diameter (ED), $\leq$3.5 mm, and non-ultrathin, ED, >3.5 mm], addition of ROSE, and a multimodality approach was available these data were also recorded.

The quality of all included studies for risk of bias and applicability was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) instrument [57]. QUADAS-2 composed of four domains: patient selection, index test, reference standard, and flow and timing provided 14 signalling questions to assess each of these domains for risk of bias and the first three

domains for applicability. The quality examination of each eligible study was carried out by two investigators (S. Tian and X. Wang) independently. All discrepancies were resolved, and an agreement was reached after discussion with the corresponding author (C. Bai).

2.4. Definition of variables

Diagnostic yield was calculated as the number of PPLs achieving successful diagnosis by r-EBUS divided by the total number of PPLs. Incidence of complications was defined as the number of reported complications divided by the total number of patients. The criteria proposed by Ernst et al. [58] was used to grade the severity of bleeding. Bronchus sign was identified as the presence of a bronchus directly leading to PPLs on CT [59]. Probe location was classified into within, adjacent and outside according to the r-EBUS image based on the study of Kurimoto et al. [7].

2.5. Statistical analysis

Stata 15 and Review Manager 5.4 software were used to perform the present meta-analysis. A P-value of <0.05 was considered to indicate a statistically significant difference. For meta-analysis of diagnostic yield, collected data was pooled using inverse variance weighting.

Inter-study heterogeneity was assessed by I^2 statistic, which represents the percentage of total variation across studies attributing to heterogeneity rather than chance error [60]. $I^2 > 75\ \%$ was considered significant for high heterogeneity, in which case random-effects models would be used to perform the meta-analysis. Prespecified subgroup analysis and meta-regression for the diagnostic yield according to two continuous variables (publication year and sample size) and two categorical variables (single-center or multi-center; randomized or non-randomized) were performed to explore the possible causes of heterogeneity. Further, bubble charts presenting trends over time and sample size were utilized to describe the relations between publication year, sample size and the corresponding diagnostic yields. Moreover, correlation relationships between categorical characteristics of included studies and diagnostic yields, and residual heterogeneity within strata were investigated and assessed using stratified analysis.

We used sensitivity analysis to examine the influence of each individual study on the overall meta-analysis summary estimate. The risk of publication bias was identified with funnel plot [56] and Egger's test [61].

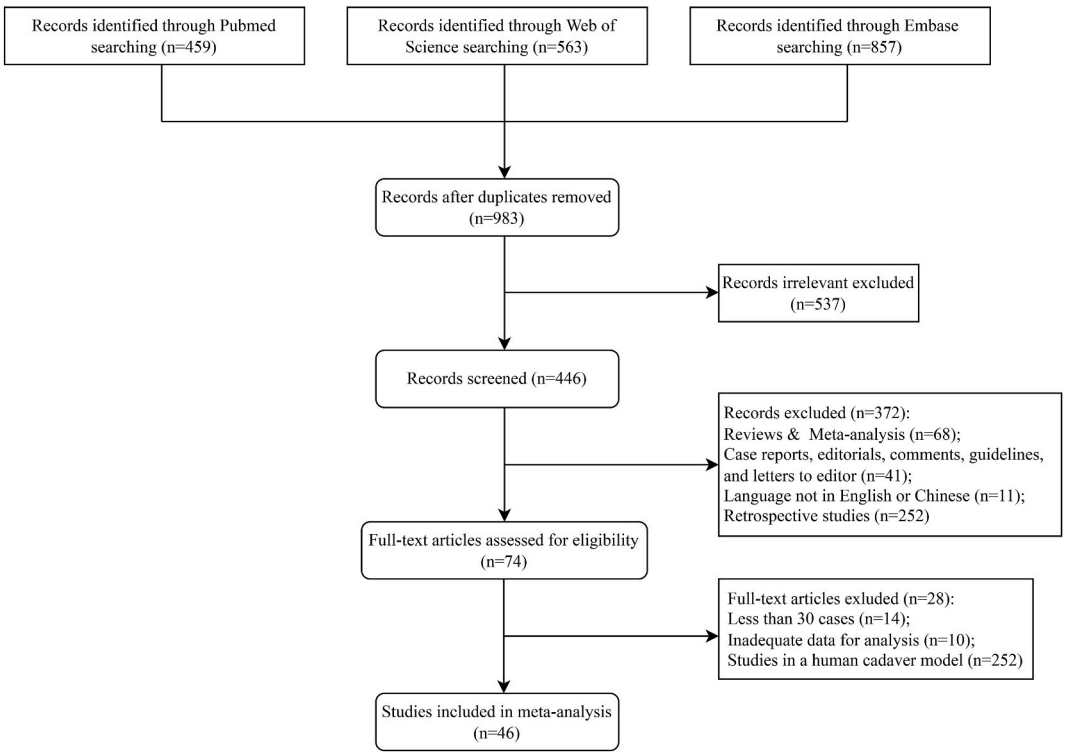

Fig. 1. The PRISMA flow diagram of the selected eligible studies.

3. Results

3.1. Literature search and study selection

Fig. 1 shows the PRISMA flow diagram of the selected eligible studies. The initial search across PubMed, Web of Science, and

Table 1
Details of included studies.

No.	Study ID	Design	Additional guidance[#]	Number diagnosed	Number of PPLs	Diagnostic yield (%)	Complications
1	Herth2002 [19]	S, R	None	40	50	80.0	2 bleeding, 1 PTX
2	Kurimoto2004 [7]	M, N	GS, Fluoro	116	150	77.3	2 bleeding
3	Paone2005 [20]	S, R	None	66	87	75.9	None Reported
4	Chung2007 [21]	S, R	None	77	113	68.1	5 bleeding, 1 PTX
5	Dooms2007 [22]	S, N	None	34	50	68.0	1 bleeding
6	Eberhardt2007 [8]	S, R	GS, ENB	62	79	78.5	5 PTX
7	Yoshikawa2007 [23]	S, N	GS, Fluoro	106	123	86.2	1 PTX
8	Fielding2008 [24]	S, N	GS, Fluoro	93	138	67.4	1 bleeding, 2 PTX
9	Chao2009 [25]	S, R	None	126	182	69.2	6 bleeding, 4 PTX
10	Oki2009 [26]	S, N	Fluoro	49	71	69.0	None Reported
11	Disayabutr2010 [27]	S, N	Fluoro	101	152	66.4	None Reported
12	Ishida2011 [9]	M, R	GS, Fluoro, VBN	144	194	74.2	1 PTX
13	Kuo2011 [28]	S, N	None	262	408	64.2	No Data
14	Steinfort2011 [29]	S, R	GS, Fluoro	25	32	78.1	1 PTX
15	Triller2011 [30]	S, N	None	89	116	76.7	None Reported
16	Fielding2012 [31]	S, R	GS, Fluoro	25	37	67.6	3 PTX, 1 pneumonia
17	Oki2012 [32]	S, R	GS, Fluoro	129	203	63.5	1 bleeding, 3 PTX, 3 pneumonia
18	Chee2013 [10]	S, N	GS, ENB	30	60	50.0	5 PTX
19	Sánchez-Font2014 [33]	S, R	GS, Fluoro	39	50	78.0	None Reported
20	Boonsarngsuk2015 [34]	S, N	GS, Fluoro	90	112	80.4	1 pneumonia
21	Chen2016 [11]	S, R	GS, VBN	130	184	70.7	12 bleeding
22	Ost2016 [35]	M, N	No Data	197	385	51.2	No Data
23	Wang2016 [36]	S, N	GS, Fluoro	44	54	81.5	1 hemoptysis
24	Zaric2016 [37]	S, N	None	164	168	97.6	1 bleeding, 1 PTX
25	Zhang2016 [38]	S, R	GS	80	108	74.1	5 bleeding
26	Asano2017 [39]	M, R	GS, Fluoro, VBN	105	129	81.4	2 bleeding, 1 pneumonia, 1 hyperventilation
27	Hibare2017 [40]	S, N	None	37	55	67.3	2 bleeding, 1 hypoxemia
28	Maekura2017 [41]	S, N	GS, Fluoro, VBN	35	45	77.8	2 bleeding
29	Fang2018 [12]	S, R	GS, VBN	103	134	76.9	10 bleeding
30	Tachihara2018 [42]	S, R	GS, Fluoro, VBN	24	31	77.4	1 PTX
31	Bo2019 [13]	M, R	GS, VBN	491	670	73.3	7 bleeding, 12 PTX
32	Oki2019 [43]	M, R	GS, Fluoro, VBN	229	356	64.3	3 bleeding, 4 PTX, 3 pneumonia, 3 others*
33	Bae2020 [14]	S, N	GS, Fluoro, VBN	90	118	76.3	1 bleeding, 3 PTX
34	Xu2020 [44]	S, R	GS	115	138	83.3	26 bleeding
35	Cicenia2021 [45]	M, N	Fluoro, VBN	43	57	75.4	None Reported
36	Jiang2021 [46]	S, R	GS	20	31	64.5	2 bleeding
37	Katsurada2021 [47]	S, N	GS, Fluoro, VBN	58	79	73.4	1 AAD, 1 lung abscess
38	Xu2021(1) [15]	S, R	VBN	74	105	70.5	16 bleeding
39	Xu2021(2) [48]	S, R	GS	119	152	78.3	28 bleeding
40	Zheng2021 [49]	S, R	Fluoro, VBN	93	120	77.5	None Reported
41	Liu2022 [50]	M, R	GS, VBN	49	71	69.0	67 bleeding, 2 PTX
42	Oki2022(1) [51]	S, N	Fluoro, VBN	27	50	54.0	No Data
43	Oki2022(2) [52]	M, R	GS, Fluoro, VBN	304	596	51.0	4 bleeding, 8 PTX, 7 pneumonia, 4 others[&]
44	Qi2022 [53]	S, R	GS, Fluoro, VBN	159	198	80.3	2 bleeding
45	Zheng2022(1) [54]	M, R	GS, Fluoro, VBN	359	426	84.3	7 bleeding
46	Zheng2022(2) [16]	M, R	GS, ENB	301	385	78.2	13 bleeding

PPLs: peripheral pulmonary lesions; S: single-center; M: multi-center; R: randomized; N: non-randomized; PTX: pneumothorax; GS: guide sheath; Fluoro: fluoroscopy; ENB: electromagnetic navigation bronchoscopy; VBN: virtual bronchoscopic navigation; AAD: acute aortic dissection.
Include GS, fluoroscopy, VBN and ENB; *Include 1 vomit, 1 nausea and 1 myocardial infarction; [&] Include 1 arrythmia, 2 transient hypoxemia and 1 broken GS.

EMBASE identified 1879 records. After removing duplicates and irrelevant citations, a total of 446 articles remained for consideration. Following the initial screening with examination of abstracts, 74 potentially relevant studies were assessed for eligibility via full-text review and after screening, 46 prospective studies were ultimately included in this meta-analysis, which involved 7252 PPLs undergoing r-EBUS guided diagnosis.

3.2. Study characteristics and quality assessment

Baseline study characteristics are summarized in Table 1. Among the 46 included studies, for language, two studies were published in Chinese [11,12] and others were in English; for design, 11 studies were multi-center and the rest of the studies were single-center; plus, randomized and non-randomized studies accounted for 58.7 % (27/46) and 41.3 % (19/46), respectively.

For an overview of QUADAS-2 tool application for the 46 studies, see Supplementary File-Fig. S1. The evaluation results showed

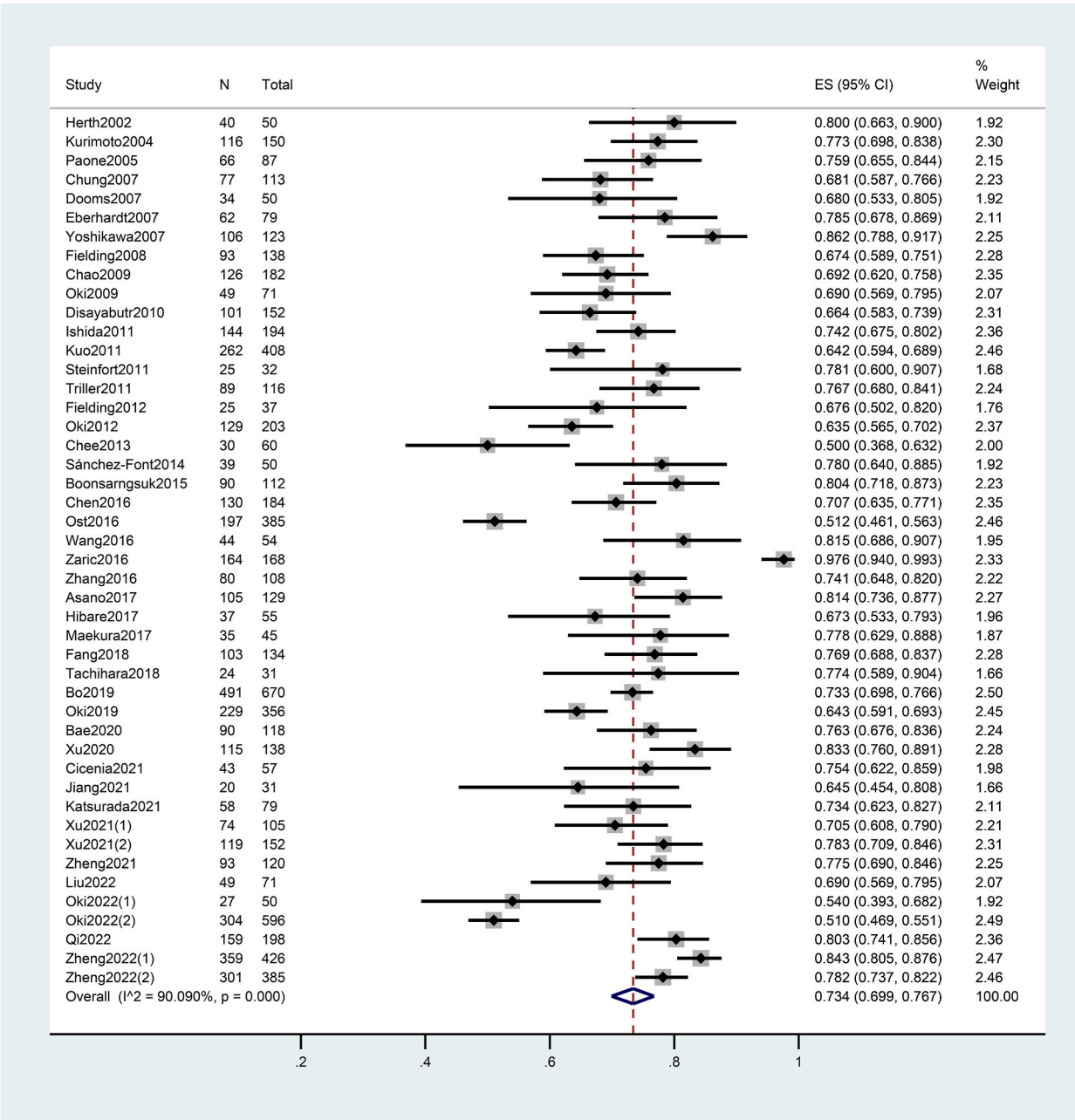

Fig. 2. Forest plot showing a summary of diagnostic yields for studies included in the meta-analysis.

that the patient selection and index test of included studies were good on the whole, with low risk of bias and excellent applicability concerns; while in the flow and timing domain, almost half of included studies had an undetermined risk of bias and applicability concerns. Furthermore, the reference standard to confirm the lesions with nonspecific inflammation varied between studies, potentially introducing probability for significant bias.

3.3. r-EBUS pooled diagnostic yield

Data pertaining to diagnostic yield was extracted from the 46 selected studies, demonstrating a pooled diagnostic yield of 73.4 % (95 % CI: 69.9%–76.7 %), with significant heterogeneity detected among studies ($I^2 = 90$ %, $P < 0.001$). Fig. 2 shows the forest plot with a summary of diagnostic yield for studies included in the meta-analysis.

Meta-regression analysis was subsequently carried out based on the following covariates: publication year, sample size and study designs (single-center or multi-center; randomized or non-randomized), to look for the possible causes of heterogeneity associated with diagnostic yield. As displayed in Table 2, no statistically significant results explaining the heterogeneity were observed. Also, we presented the relations between publication year, sample size and the corresponding diagnostic yields using bubble charts (Supplementary File-Fig. S2).

3.4. Stratified analysis

Stratification revealing various factors affecting the diagnostic yield of r-EBUS for PPLs suggested an association between reported diagnostic yield and lesion location ($P = 0.035$), lesion size ($P < 0.001$), probe location ($P< 0.001$), lesion type ($P< 0.001$), bronchus sign ($P = 0.001$), lesion appearance on CT ($P = 0.004$), and addition of ROSE ($P = 0.031$); however, this association failed to be found in the use of a GS ($P = 0.347$), bronchoscopy type ($P = 0.455$), and a multimodality approach ($P = 0.718$). Table 3 shows the results of these analyses.

More specifically, twenty-two studies reported diagnostic yields for different lesion locations. For 2550 lesions in the upper lobe, pooled diagnostic yield was 71.5 % (95 % CI: 67.1%–75.8 %), whereas for 369 lesions in the middle lobe and for 1393 lesions in the lower lobe, the diagnostic yields were 84.2 % (95 % CI: 77.5%–90.2 %) and 77.3 % (95 % CI: 72.9%–81.3 %), respectively. Twenty-five studies reported diagnostic yields according to lesion size. Pooled diagnostic yields for 1757 lesions (< 20 mm), for 1612 lesions (20–30 mm) and for 873 lesions (> 30 mm) were 64.1 % (95 % CI: 58.6%–69.6 %), 80.0 % (95 % CI: 73.4%–85.9 %) and 83.0 % (95 % CI: 76.2%–88.9 %), respectively. Sixteen studies reported the influence of probe location on the diagnostic yield of PPLs. The within position provided the highest pooled diagnostic yield of 82.6 % (95 % CI: 78.6%–86.2 %), followed by the adjacent position 56.8 % (95 % CI: 49.4%–64.0 %) and the outside position 17.3 % (95 % CI: 2.4%–38.8 %). As for lesion type, an superior pooled diagnostic yield was found in studies with malignant lesions when compared with benign lesions [77.8 % (95 % CI: 74.2%–81.3 %) vs. 60.8 % (95 % CI: 52.0%–69.3 %)]. Similarly, an inferior pooled diagnostic yield was observed in studies with lesions of negative bronchus sign relative to positive bronchus sign [55.3 % (95 % CI: 45.6%–64.7 %) vs. 74.9 % (95 % CI: 66.7%–82.4 %)]. Also, the pooled diagnostic yield of r-EBUS with the addition of ROSE (425 lesions) was 80.7 % (95 % CI, 74.6%–86.2 %), whereas that with the absence of ROSE (6827 lesions) was 72.9 % (95 % CI, 69.3%–76.4 %). While no statistical difference between diagnostic yield with studies that used and did not use a GS [74.3 % (95%CI: 71.1%–77.5 %) vs. 70.8 % (95%CI: 64.0%–77.2 %)], and used ultrathin and non-ultrathin bronchoscopy [70.8 % (95%CI: 65.7%–75.8 %) vs. 73.2 % (95%CI: 69.6%–76.8 %)] was detected. We were able to collect data pertaining to diagnostic yield for lesions with different appearances on CT scan from the 6 studies included in the meta-analysis [14,23,28,49,50,52], indicating solid lesions to be associated with higher diagnostic yield in relation to part-solid and/or GGO lesions [72.5 % (95%CI: 60.0%–83.5 %) vs. 51.7 % (95%CI: 44.7%–58.7 %)]. Moreover, many of the included studies focused on the effect of a multimodality approach on the diagnostic yield of PPLs. The overall outcomes demonstrated the diagnostic yields of none combined, only fluoroscopy combined, only VBN/EBN combined, and both fluoroscopy and VBN/EBN combined on a basis of r-EBUS were 71.9 % (95%CI: 66.7%–76.9 %) by pooling 22 studies with 2697 lesions, 75.5 % (95%CI: 71.0%–79.7 %) by pooling 14 studies with 1269 lesions, 75.6 % (95% CI: 70.4%–80.4 %) by pooling 12 studies with 1255 lesions, and 73.4 % (95%CI: 64.9%–81.2 %) by pooling 12 studies with 1829 lesions.

Table 2
Results of meta-regression analysis.

Covariates	Number of studies (%)	Diagnostic yield (%)	95 % CI (%)	P value
Sample size	NA	See Supplementary File-Fig. S2A	NA	0.118
Publish year	NA	See Supplementary File-Fig. S2B	NA	0.639
Multi-center				
Yes	11 (23.9)	71.2	63.3–78.5	0.948
No	35 (76.1)	74.2	70.6–77.6	
Randomized				
Yes	27 (58.7)	73.8	70.0–77.6	0.438
No	19 (41.3)	72.7	65.6–79.2	

CI: confidence interval; NA: not applicable.

Table 3
Summary results of the stratified analysis for r-EBUS in the diagnosis of PPLs.

Variables	Number of studies	Number diagnosed	Number of PPLs	Pooled yield (%)	95 % CI (%)	P value
Lesion location						0.035
Upper lobe	22	1790	2550	71.5	67.1–75.8	
Middle lobe	20	298	369	84.2	77.5–90.2	
Lower lobe	20	1055	1393	77.3	72.9–81.3	
Lesion size, mm						< 0.001
< 20	25	1086	1757	64.1	58.6–69.6	
20–30	16	1269	1612	80.0	73.4–85.9	
> 30	13	695	873	83.0	76.2–88.9	
Probe location						< 0.001
Within	16	1528	1854	82.6	78.6–86.2	
Adjacent	16	398	692	56.8	49.4–64.0	
Outside	6	14	72	17.3	2.4–38.8	
Lesion type						< 0.001
Malignant	27	2882	3767	77.8	74.2–81.3	
Benign	26	708	1271	60.8	52.0–69.3	
Use of a GS						0.347
Yes	30	3244	4354	74.3	71.1–77.5	
No	19	1570	2304	70.8	64.0–77.2	
Bronchus sign						0.001
Present	13	1272	1792	74.9	66.7–82.4	
Absent	10	277	517	55.3	45.6–64.7	
Appearance on CT						0.004
Solid	6	693	1079	72.5	60.0–83.5	
Others[#]	6	181	351	51.7	44.7–58.7	
Bronchoscopy type						0.455
Ultrathin	4	332	469	70.8	65.7–75.8	
Non-ultrathin	44	4841	6783	73.2	69.6–76.8	
Addition of ROSE						0.031
Yes	6	343	425	80.7	74.6–86.2	
No	43	4830	6827	72.9	69.3–76.4	
Multimodality approach						0.718
None	22	1938	2697	71.9	66.7–76.9	
Only fluoroscopy	14	941	1269	75.5	71.0–79.7	
Only VBN/EBN	12	958	1255	75.6	70.4–80.4	
Fluoroscopy and VBN/EBN	12	1221	1829	73.4	64.9–81.2	
Total	46	5173	7252	73.4	69.9–76.7	NA

r-EBUS: radial endobronchial ultrasound; PPLs: peripheral pulmonary lesions; CI: confidence interval; GS: guide sheath; CT: computed tomography; ROSE: rapid on-site evaluation; VBN: virtual bronchoscopic navigation; ENB: electromagnetic navigation bronchoscopy; NA: not applicable.
#: Part-solid and/or ground-glass opacity (GGO).

3.5. Sensitivity analysis

Fig. 3 and the corresponding table (see Supplementary File-Table S2) show the results of an influence analysis in which the pooled diagnostic yield of the remaining studies is reestimated by omitting each study in turn. It was found that the pooled estimates after excluding each study remained inside the confidence interval of the combined analyses, which demonstrated the stability of this meta-analysis.

3.6. Publication bias

As shown in Fig. 4, a symmetrical appearance for the pooled diagnostic yield in the funnel plot could be observed by visual inspection, and evidence of the absence of publication bias was also discovered by the Egger's test in the meta-analysis (P = 0.098).

3.7. Complication rates

A total of 314 complications in 6407 procedures were reported in 43 studies. The pooled complication rate was 4.2 % (95 % CI: 2.4%–6.5 %, Supplementary File-Fig. S3). After eliminating an outlier detected with an incidence rate of complication (97.2 %) from the study of Liu et al. [50], the pooled complication rate was 3.1 % (95 % CI: 2.1%–4.3 %, Fig. 5). To note, overall complication rate mentioned above included a considerable number of cases with mild bleeding and therefore, we investigated the incidence rate of pneumothorax and moderate and severe bleeding separately. For 58 patients with pneumothorax, pooled incidence rate was 0.4 % (95 % CI: 0.1%–0.7 %), whereas for 127 patients with moderate and severe bleeding, the incidence rate was 1.1 % (95 % CI: 0.5%–2.0 %) (Supplementary File-Fig. S4). This difference was statistically significant (P = 0.039).

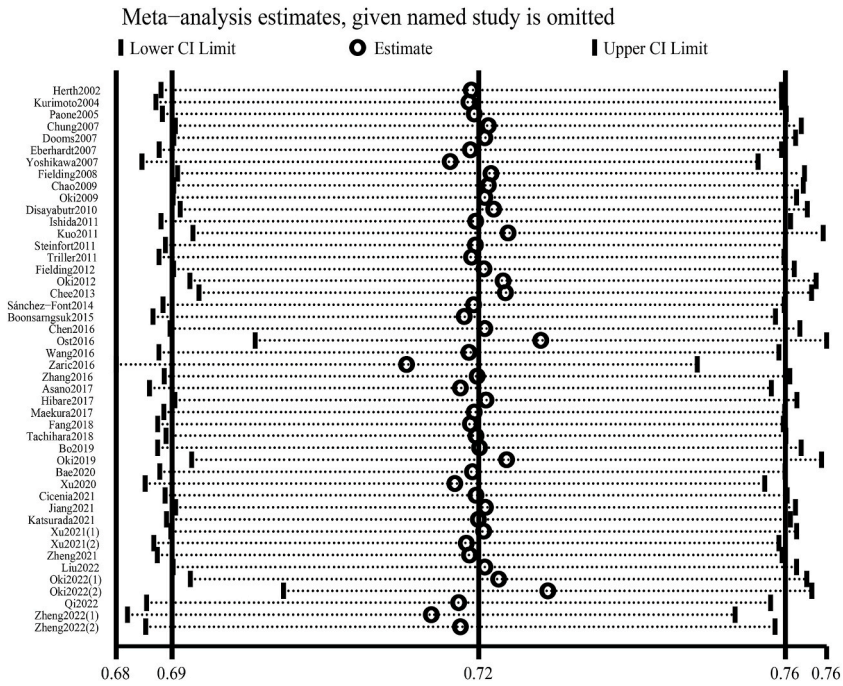

Fig. 3. Sensitivity analyses showing the influence of each individual study for the outcome of the meta-analysis.

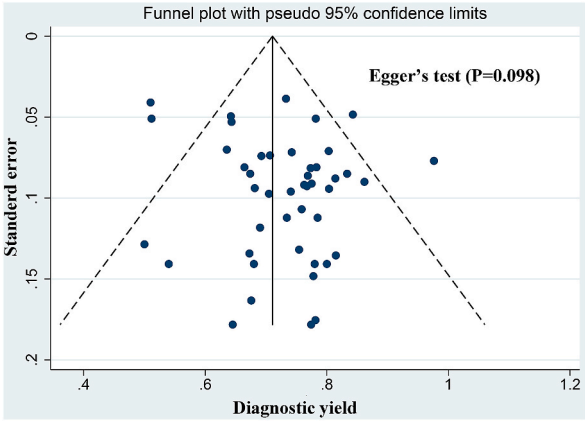

Fig. 4. The Funnel plot showing a symmetrical appearance.

4. Discussion

This meta-analysis performed from 46 prospective trials published from 2002 to 2022, including 7252 PPLs with lesions being the successful diagnosis in 5173 using r-EBUS, revealed a pooled diagnostic yield of 73.4 % (95 % CI: 69.9%–76.7 %), which was similar to the most recent prior meta-analysis that reported a pooled diagnostic yield of 70.6 % (95 % CI: 68%–73.1 %) [55]. Our study focuses on prospective trials published to date in order to avoid the inherent risk of bias and broadens the existing field of knowledge, building on the work of previous study [55] by systematically and comprehensively analyzing the factors affecting the performance of r-EBUS for diagnosing PPLs. This has great significance for the clinical field, since clinicians can provide the most suitable diagnostic approach to patients with PPLs at the initial evaluation. To the best of our knowledge, this is the first systematic review and meta-analysis of prospective trials comprehensively evaluating the diagnostic yield of r-EBUS for PPLs.

In recent years, in addition to r-EBUS, other advanced guided-bronchoscopy modalities such as VBN and ENB have entered the clinical settings in the diagnosis of PPLs. The pooled diagnostic yield of 73.4 % for r-EBUS in our analysis is comparable to VBN and ENB, which have been newly reported at 74.2 % by Giri et al. [62] and 72.9 % by Folch et al. [63]. Interestingly, VBN and ENB are significantly associated with higher costs by comparison of r-EBUS [64]. Furthermore, several groups have shown that a multimodality approach in which r-EBUS is combined with VBN/ENB performs better than r-EBUS alone for diagnosing PPLs, as the use of VBN or

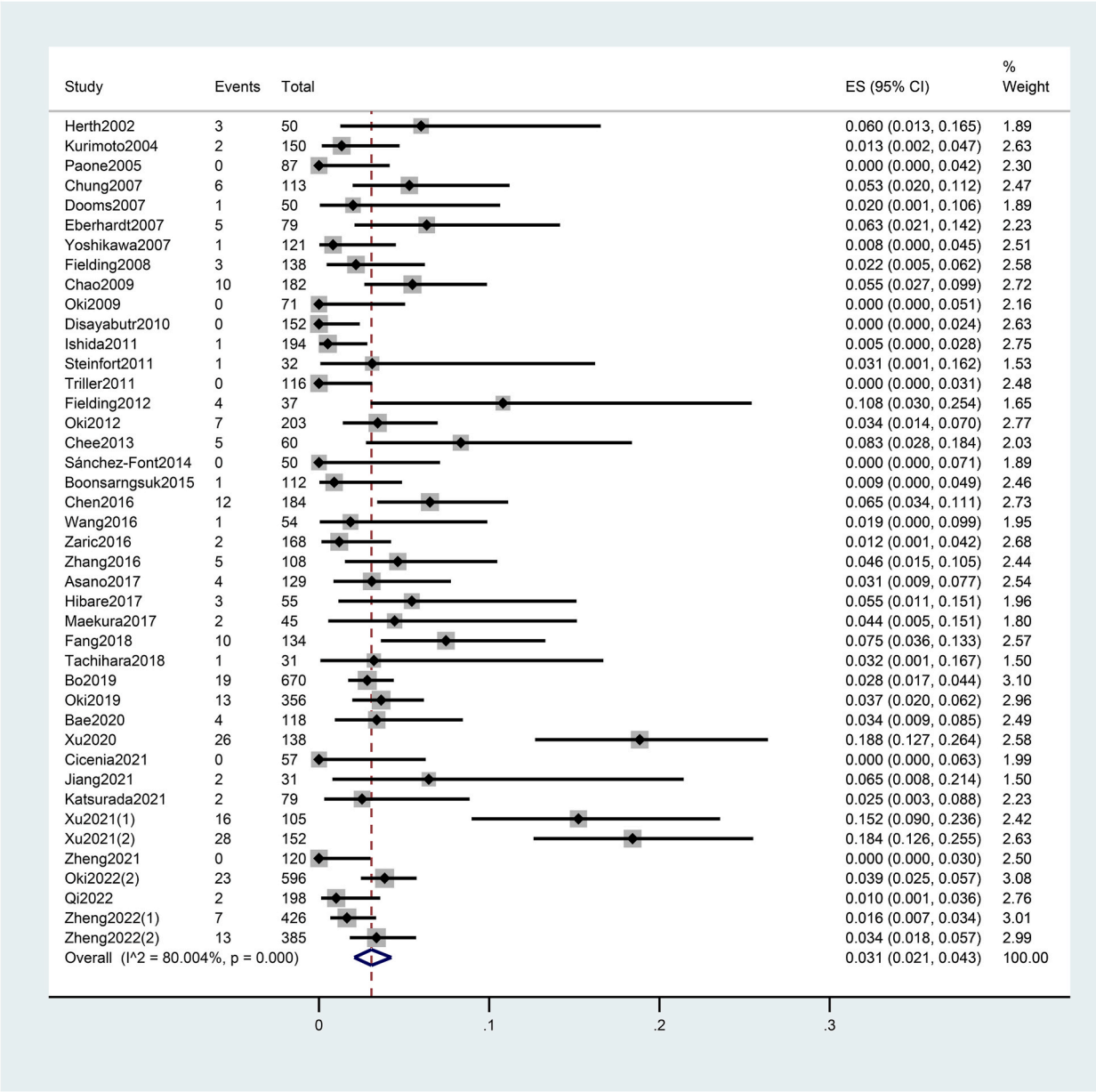

Fig. 5. Forest plot showing the incidence rates of overall complications.

ENB compensates for r-EBUS failing to navigate to the PPL [8,9,16]. But in the present study, the pooled diagnostic yield using r-EBUS combined with VBN/ENB was only 75.6 %, and superiority to the use of EBUS alone (71.9 %) cannot be validated, which was consistent with the findings of individual research included in our meta-analysis [10–15]. A possible explanation for this may be due to patient selection, with more difficult cases being selected for r-EBUS combined with VBN/ENB [35,65]. Plus, we could not evaluate the diagnostic yield according to each guidance system, especially for PPLs difficultly approached via r-EBUS, due to different combinations of guidance use and limited data among included studies. Therefore, more prospective randomized studies with larger data accrual are necessary to provide a more robust and broader view of the utilization of VBN/ENB. We also demonstrated that the concomitant use of fluoroscopy with the accompanying radiation exposure when diagnosing PPLs using r-EBUS alone or combined with VBN/ENB had little impact on the diagnostic yield. Our meta-analysis is therefore quite timely and provide useful information for the value of a multimodality approach in the diagnosis of PPLs.

Recently, ultrathin bronchoscope has been developed and demonstrated to be an excellent tool for the diagnosis of PPLs with a low complication rate [43,66]. Theoretically, the ultrathin bronchoscope with greater accessibility to peripheral bronchi with mobility has better applicability of r-EBUS compared with thin bronchoscope. However, this superiority was not demonstrated in our study. This

might be attributed to a limited sample size on ultrathin bronchoscope group. Notably, ultrathin bronchoscope might be a good option for selected PPLs, such as lesions in the superior segment of lower lobes with their acute angles and in the upper lobes [66]. Further investigation is warranted to better clarify these findings.

A major limitation of r-EBUS is that tissue sampling and r-EBUS scan cannot be carried out simultaneously due to the necessity to remove the probe from the working channel after localization. Apparently, it is challenging to advance the biopsy tool through pre-planned bronchial route and ultimately, to place the biopsy instrument into the same location as the r-EBUS probe. Hence, a GS providing access to PPLs for repeated sampling from the same region was introduced by Kurimoto et al. [7] to address this issue. Nevertheless, our study showed that use of a GS (74.3 %) had a similar pooled diagnostic yield compared with the non-GS method (70.8 %), which may be attributed to smaller specimens obtained from smaller size forceps with the use of a GS [67].

Seven factors were demonstrated to influence the diagnostic yield of r-EBUS for PPLs: lesion location, lesion size, probe location, lesion type (benign or malignant), bronchus sign, lesion appearance on CT, and addition of ROSE. In terms of lesion location, the diagnostic yield of the PPLs located in the upper lobe was significantly lower. Repeat biopsy for upper lobe lesions seems exceedingly difficult because the r-EBUS catheter with a relatively long and stiff tip fails to conform with sharply curved upper lobe bronchial route. The diagnostic yield of smaller PPLs (< 20 mm in lesion size) was suboptimal. On the contrary, bigger PPLs (> 20 mm in lesion size) were found to associated with the higher diagnostic yield. As for lesion type, malignant PPLs showed a statistically significant higher diagnostic yield than benign PPLs, this could be explained by the fact that benign PPLs seldom invading the bronchus mucosa cannot be detected easily. The diagnostic inferiority of r-EBUS was also evident for non-solid PPLs, possible reasons are listed as follows: although "blizzard sign" and "mixed blizzard sign" are useful to decide the location of GGOs during r-EBUS [68,69], the interpretation of the r-EBUS images remains challenging, especially for benign lesions. Plus, GGOs rarely penetrate the bronchus. Consequently, the use of transbronchial lung cryobiopsy (TBLC) that can yield larger samples with better cellular architecture preservation and fewer crush artifacts, thereby aiding in making histologic diagnosis, seems a promising diagnostic technique for GGOs [70–72]. Bronchus sign refers to the presentation of an air-filled bronchus leading to the PPLs, which was firstly described by Tsuboi and colleagues in 1967 [73]. Our study indicated that the diagnostic yield of PPLs with a bronchus sign was as high as 74.9 %, significantly higher than PPLs (55.3 %) without a bronchus sign. We note that this is aligned with prior reports [10,14,23,24,31,43,54]. With regard to probe location, it plays a significant role for improving the diagnostic yield. Similar to the results of previously published studies [7,10,12,14–16,21,25,27,28,34,49,50,54], in the current meta-analysis, the within position provided the highest diagnostic yield of 82.6 %, followed by the adjacent position 56.8 % and the outside position 17.3 %. The inferior diagnostic yield for the latter two conditions may be because r-EBUS-guided transbronchial biopsy only performs in one plane, resulting in the possibility of PPLs with adjacent and eccentric images being missed [74]. While for TBLC, tissues can be obtained in a 360-degree fashion with a larger contact area; thus, TBLC has the potential to improve the diagnostic yield of adjacent and eccentric PPLs [50,75]. Several studies showed that ROSE allowing rapid stain and real-time assessment for direct slides could improve the diagnostic yield for PPLs [44,48,53]. Our results were consistent with this. However, less than half of the surveyed hospitals were eligible for ROSE during bronchoscopic procedures according to a national cross-sectional study [76].

Regarding r-EBUS safety, our pooled incidence rates of overall complications (3.1 %), moderate and severe bleeding (1.1 %) requiring additional therapeutic interventions and pneumothorax (0.4 %) are consistent with the results of prior meta-analyses [55,77], which are significantly less than previous meta-analysis that reported the pooled overall complication rate of 38.8 %, bleeding rate of 18.0 % and pneumothorax rate of 25.3 % with respect to CT-guided transthoracic lung biopsy [4]. Given the fact that r-EBUS-guided transbronchial biopsy and CT-guided transthoracic lung biopsy have their own advantages and disadvantages, these two techniques should be complementary to each other for diagnosing PPLs, not fully replace one another.

The present meta-analysis has certain limitations that should be addressed. First, some data such as editorials and conference abstracts had to be excluded because of inadequate information available, which may inadvertently lead to the accentuation of publication bias. Second, although all included studies in our meta-analysis were prospective with almost devoid of a risk of bias and QUADAS-2 instrument was also used, the quality of the studies included still remained to be non-controlled as a result of multiple factors (e.g. the resistance of the probe to pass through the lesion [78], sampling tools [79], experience of operators, addition of confocal laser endomicroscopy [80]) potentially affecting the diagnostic yield of r-EBUS for PPLs being not described in detail. Third, the sample size of stratified analysis for some factors associated with successful diagnosis using r-EBUS was relatively small, so that the significance of these findings was limited and remained to be corroborated. Lastly, substantial heterogeneity was observed in the present study due to the diversity of diagnostic yield reported among studies. Though meta-regression and stratified analysis were performed to explore the possible causes of heterogeneity, and sensitivity analysis to investigate the influence of each individual study on the pooled estimates, these results still needed to be treated with caution.

5. Conclusion

Our results suggested that r-EBUS had a appreciable diagnostic yield and a considerably low complication rate when used to deal with PPLs. The diagnostic yields of r-EBUS differed significantly by lesion location, size, type, appearance on CT, bronchus sign, probe location, and addition of ROSE. However, use of a GS, bronchoscopy type, and a multimodality approach failed to further improve the diagnostic yield. Obviously, establishing a well-predictive system for the diagnostic yield is desired to help clinicians determine which procedure is optimal for individual patients, and thereby enabling patients to benefit most.

Ethical statement

An ethics statement is not applicable because this study is based exclusively on published literature.

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Data availability statement

Data included in article/supplementary material/referenced in article.

CRediT authorship contribution statement

Sen Tian: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Data curation, Conceptualization. **Xiang Li:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Jian Liu:** Writing – original draft, Software, Investigation, Data curation. **Xinyu Wang:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Hui Chen:** Writing – review & editing, Investigation, Data curation. **Zeyu Dai:** Writing – review & editing, Investigation. **Qian Chen:** Writing – review & editing, Software. **Hui Shi:** Writing – review & editing, Formal analysis. **Yonghua Li:** Writing – review & editing, Data curation. **Haidong Huang:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Chong Bai:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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Abbreviations

r-EBUS	Radial endobronchial ultrasound
PPLs	Peripheral pulmonary lesions
CT	Computerized tomography
ROSE	Rapid on-site evaluation
GS	Guide sheath
ENB	Electromagnetic navigation bronchoscopy
VBN	Virtual bronchoscopic navigation
CI	Confdence interval
PRISMA-DTA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy
GGO	Ground-glass opacity
ED	External diameter
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
TBLC	Transbronchial lung cryobiopsy

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