Systematic review and/or meta-analysis

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Diagnostic performance and safety for robotic-assisted bronchoscopy in pulmonary nodules: a systematic review and meta-analysis

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Background: Robotic-assisted bronchoscopy (RAB) is an emerging diagnostic tool that combines robotics and bronchoscopy. This meta-analysis aimed to comprehensively evaluate the performance and safety of RAB for pulmonary nodule diagnosis.
Methods: PubMed, Embase, Cochrane Library, and Web of Science were searched from their inception up to 4 November 2024. The quality of the studies was assessed by the Quality Assessment of Diagnostic Accuracy Studies-2. Random and fixed effects models were used to estimate the pooled diagnosis yield in strict or intermediate criteria, sensitivity for malignancy, and complication rate of RAB in pulmonary nodule diagnosis, with rates (%) and 95% confidence intervals (CIs).
Results: In total, 27 cohort studies were included. The pooled diagnostic yields of RAB for pulmonary nodules were 69.6% (95%CI: 61.8%–76.8%) for strict criteria and 86.6% (95%CI: 83.7%–89.2%) for intermediate criteria, with a sensitivity for malignancy of 85.4% (95%CI: 83.0%–87.7%). The pooled complication rate was estimated to be 3.0% (total pneumothorax, 2.0%; pneumothorax that required intervention, 0.5%; bleeding, 0.1%). The diagnostic yields were different ($P < 0.05$) among subgroups of patients based on total number of biopsies (≤100 vs. >100; 83.6% vs. 69.6%), prevalence for malignancy (<60% vs. ≥60%; 66.6% vs. 83.1%), radial endobronchial ultrasound view (concentric vs. eccentric vs. invisible; 88.6% vs. 84.5% vs. 46.0%). A difference ($P = 0.005$) in sensitivity for malignancy was observed between the group with average lesion sizes ≤20 mm and the group with sizes >20 mm (86.4% vs. 77.5%).
Conclusion: RAB may be effective and safe in pulmonary nodule diagnosis, offering promising prospects for clinical application. The heterogeneity of diagnostic yield may be driven by different diagnostic criteria. Moreover, the current studies of RAB in pulmonary nodule diagnosis are single-arm studies, and more large-scale randomized controlled trials are needed.

Keywords: diagnostic performance, pulmonary nodules, robotic-assisted bronchoscopy, safety

Introduction

With the widespread application of diagnostic computed tomography (CT) scans and lung cancer screening programs, the detection rate of pulmonary nodules increases yearly[1]. More than 4.8 million Americans have undergone chest CT scans, with about 1.6 million diagnosed with pulmonary nodules (over 60 000 diagnosed with lung cancer within 2 years)[2]. Pulmonary nodules are defined as focal, rounded opacities with a diameter of ≤3 cm observed on imaging tiny abnormal areas[3], which may be associated with the development of lung cancer[4]. According to global epidemiological data from 2022, lung cancer persists as the predominant contributor to worldwide cancer burden, with approximately 2.5 million new cases (12.4% of total cancer diagnoses), and over 1.8 million deaths (18.7% of all cancer-related fatalities)[5]. The 5-year survival rate for lung cancer patients is only 25%, mainly because most cases are diagnosed at an advanced stage[6,7]. Screening has been

HIGHLIGHTS

- This study explored the diagnostic yield under different criteria in the diagnosis of pulmonary nodules with RAB.
- The influencing factors of the diagnosis yield, the sensitivity for malignancy as well as complications of RAB for pulmonary nodule diagnosis were also summarized.
- Our results not only demonstrate the efficacy and safety of RAB in the diagnosis of pulmonary nodules but also emphasize the importance of different diagnostic criteria (especially strict criteria) for the assessment of RAB performance.

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found to effectively detect asymptomatic tumors in high-risk groups and reduce mortality[8,9].

Surgical resection, transthoracic needle biopsy (TTNB), and bronchoscopy are common biopsy techniques for lung lesions[10]. TTNB has a good diagnostic yield for pulmonary nodules ranging from 88% to 93%, with the occurrence of complications[11-13], while traditional bronchoscopy, primarily indicated for central lesions, has a lower success rate for peripheral nodules smaller than 2 cm (over 70% of pulmonary nodules are located in the peripheral lung)[14,15]. Bronchoscopy has made rapid progress in the diagnosis of pulmonary nodules in the past decade with new navigation techniques that utilize different techniques and tools[16]. A meta-analysis conducted on the guided-bronchoscope including electromagnetic navigation bronchoscopy (ENB), virtual bronchoscopy (VB), radial endobronchial ultrasound (r-EBUS), ultrathin bronchoscope, and guide sheath, reported a pooled diagnostic yield of 70%, with a pneumothorax rate of 1.5%[17]. Recently, the emergence of robot-assisted bronchoscopy (RAB)[18] has brought new possibilities for the safety and efficacy of interventional diagnosis and treatment of pulmonary nodules which provide a biopsy technique with superior maneuverability, stability, and further reach. Using a robotic arm to guide a catheter with a camera, light source, and biopsy tools, RAB expands access to pulmonary nodules through the patient's airway[19]. Low *et al*[20] reported a 77% diagnostic yield in patients who underwent biopsy for peripheral pulmonary lesions, significantly improving the diagnostic performance of conventional bronchopulmonary[14]. In another multicenter retrospective evaluation of consecutive patients with pulmonary nodules, RAB achieved an overall diagnostic yield of 87.6%, which was even comparable to that of TTNB[21].

The current published evidence on RAB in the diagnosis of pulmonary nodules indicates diagnostic yields varied from studies and ranged between 55.7% and 96.6%[22,23]. Different diagnostic yield criteria may have an impact on diagnostic yield. Saghaie *et al*[24] reported a diagnostic yield of 89.5% (strict criteria) to 94.7% (intermediate criteria) in patients with moderate-risk peripheral pulmonary nodules [nodule size of 1-3 cm (largest diameter in either axial, coronal or sagittal planes) and located in the outer third of the lung]. To date, only two meta-analysis articles have evaluated the efficacy of RAB in the diagnosis of peripheral pulmonary lesions[25,26]. A meta-analysis conducted by Zhang *et al*[26] reconstructed the diagnostic yield based on the intermediate criteria of definition. Another meta-analysis reported the pooled diagnostic yield and the complications for RAB[25]. However, these studies primarily focused on the diagnostic yield without considering differences in diagnostic criteria. Our research not only updates the latest findings but also distinguishes diagnostic yields under different definitions while accounting for prevalence rates for malignancy. This meta-analysis aims to comprehensively evaluate the diagnostic yield in different criteria, sensitivity for malignancy, and complications of RAB in pulmonary nodule diagnosis. Subgroups in pulmonary nodule patients with various features were further assessed, which may expand the applications of RAB.

Methods

Search strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[27], the Cochrane Handbook of Systematic Reviews[28] and the assessing the methodological quality of systematic reviews (AMSTAR)[29] guidelines, a comprehensive literature review was conducted. Up to 4 November 2024, PubMed, Embase, Cochrane Library, and Web of Science were extensively searched. The search formula of PubMed were (((Robotic-Assisted Bronchoscopy[Title/Abstract]) OR (robotic bronchoscopy[Title/Abstract])) OR (robotic bronchoscope[Title/Abstract])) AND ((pulmonary nodule[Title/Abstract]) OR (pulmonary nodules[Title/Abstract])). All records related to the diagnosis of pulmonary nodules using RAB were retrieved, and duplicate literature was removed. Subsequently, two independent authors excluded unrelated literature by title and abstract screening. Finally, the full text of the remaining articles was downloaded and further evaluated. Any discrepancies were addressed by discussion until a consensus was achieved. This meta-analysis registered at https://www.crd.york.ac.uk/prospero/.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) population: patients with pulmonary nodules that were deemed suspicious for cancer by a pulmonologist or surgeon; (2) intervention: RAB; (3) outcomes: diagnostic yield, sensitivity for malignancy, and complication rate (pneumothorax, pneumothorax that required intervention, and bleeding); (4) study design: cohort study.

The diagnostic yield proposed by Vachani *et al*[30] was defined as the proportion of accurate diagnoses produced, including true positive (TP) and true negative (TN) of malignant tumors. Negative cases of malignancy were defined as specific benign (SPB) diagnoses (infection, granuloma, etc.), nonspecific benign (NSB) findings (inflammation, etc.), or nondiagnostic (ND) findings (atypical cells, normal alveoli, etc.). The diagnostic yield calculations based on strict criteria were derived from contemporaneous data obtained during the bronchoscopy procedure; an approach that did not include longitudinal follow-up data. The diagnostic yields were calculated with the use of strict criteria: (TP + SPB)/total procedures. Under intermediate criteria, the diagnostic yield calculations were restricted the inclusion of follow-up data for cases with an NSB finding at bronchoscopy. Longitudinal assessment of NSB cases required subsequent histopathological confirmation through biopsy or radiographic evidence of nonmalignant etiology to qualify as true negative (NSBTN). Cases lacking definitive diagnostic confirmation due to lack of follow-up were systematically classified as ND. ND cases maintained their nondiagnostic status in final diagnostic yield calculations irrespective of subsequent investigative results, as these were excluded from TN classification. Cases with SPB diagnoses established at bronchoscopy were designated as TN. The diagnostic yield (intermediate criteria) was calculated as (TP + SPB + NSBTN)/total procedures. Sensitivity for malignancy was defined as the ratio of true malignancy diagnosed by RAB and the final malignant diagnosis by subsequent biopsy or imaging confirms[31]. Prevalence for malignancy was defined as the proportion of malignant diagnoses in the population sampled.

We excluded studies that were animal trials, studies that were conducted on cadaveric models, studies that were not published in English, studies that reported insufficient or unextractable data, or subjects not meeting the requirements. Case reports, conference abstracts, letters, reviews, or meta-analyses were also excluded.

Data extraction

The extracted information was as follows: first author, publication year, study design, study platform, number of lesions, procedure time, successful navigation rate, sensitivity for malignancy, prevalence for malignancy, diagnostic yield, complication rate, key elements of literature quality assessment, r-EBUS use (lesion localization: concentric, eccentric, and invisible), and cone beam computed tomography (CBCT) use. Two authors independently performed the process of literature screening and data extraction.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool[32] was used to evaluate the quality of the included studies. The quality of each literature was evaluated by the risk of bias and applicability. Applicability included patient selection, index test, and reference standard. Risk of bias included these factors as well as flow and timing. Each outcome was classified as high risk, low risk, or unclear risk.

Statistical analysis

All analyses were conducted using Stata 15.1 and R 4.1.3 software. Data transformation was performed using the Freeman-Tukey double arcsine transformation. The pooled diagnostic yield, sensitivity for malignancy, and complication rate were estimated with 95% confidence intervals (CIs). The random-effects model was used if the heterogeneity statistic I^2 ≥50%, otherwise the fixed-effects model was used. Subgroup analyses were conducted by included articles based on total number of biopsies (≤100 vs. >100), study design (prospective cohorts vs. retrospective cohorts), platform (Monarch vs. Ion vs. Galaxy), average lesion size (<20 mm vs. ≥20 mm), prevalence for malignancy (<60% vs. ≥60%), cone beam computed tomography (CBCT) use (yes vs. no), combinations of localization tool [r-EBUS or CBCT vs. r-EBUS + CBCT], year of publication (earlier than 2022 vs. 2022 vs. 2023 vs. 2024), r-EBUS view (concentric vs. eccentric vs. invisible) and bronchial signs (present vs. absent). The subgroup results from these individual studies were aggregated and compared. For studies with 10 or more included articles, the "Begg" test was used to assess publication bias. P <0.05 was considered statistically significant.

Results

Characteristics of the included studies

Figure 1 shows the flowchart of the article screening in this meta-analysis. A total of 328 records were obtained according to the search strategy. After excluding the articles which were not met the inclusion criteria, 27 articles were finally included. Table 1 summarizes the basic information of the included studies. There were 2,463 nodules involved, with a mean/median size range from 12.0 mm to 26.0 mm. The reported successful

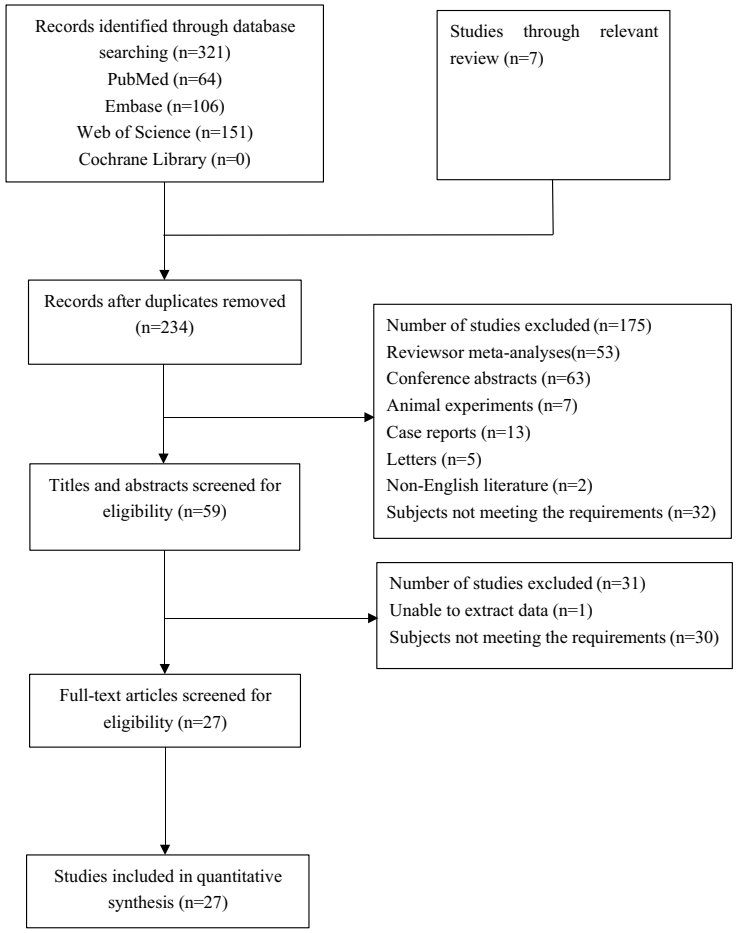


Figure 1. Flow chart of eligible studies.

Table 1

Characteristics of the included studies

Author	Year	Country	Study design	Platform	Patients (n)	Lesions (n)	Lesion size (mm)	Bronchus sign	Successful navigation	Procedure time (minutes)	Sensitivity for malignancy	Diagnostic yield	Complication rate	Prevalence for malignancy	r-EBUS	CBCT
Rojas-Solano	2018	Costa Rica	Prospective	Monarch	15	15	26.0 (10.0-63.0)	100.00%	93.30%	NR	77.80%	80.0% (strict)	0.0%	60.0%	No	No
Chaddha	2019	US	Retrospective	Monarch	165	167	25.0 ± 15.0	63.50%	88.60%	58.6 ± 31.4	NR	69.1% (strict), 77% (intermediate)	Overall: 6.0%, pneumothorax (3.6%), pneumothorax that required intervention (2.4%), bleeding (2.4%)	49.1%	Yes	No
Chen	2021	US	Prospective	Monarch	54	54	23.2 ± 10.8	59.30%	96.20%	51.0 (44.0, 64.0)	NR	66.7% (strict), 74.1% (intermediate)	Pneumothorax (3.7%), pneumothorax that required intervention (1.9%)	61.1%	Yes	No
Ekeke	2021	US	Retrospective	Monarch	25	25	8.0-69.0	84.00%	NR	NR	93.8% (15/16)	80% (strict), 96% (intermediate)	0.0%	64%	No	No
Cumbo-Nacheli	2022	US	Retrospective	Monarch	20	20	22.0 ± 7.0	50.00%	100%	36.4 (15.0-66.0)	86.7% (13/15)	65% (strict), 70% (intermediate)	NR	75%	Yes	Yes
Khan	2023	US	Retrospective	Monarch	264	264	19.3 (3.2-72.5)	30.10%	NR	62.3 ± 27.2	79.3% (115/145)	55.7% (strict), 85.6% (intermediate)	Overall: 7.6%, pneumothorax (5.7%), pneumothorax that required intervention (3.8%)	54.9%	Yes	Yes
Iwamoto	2023	US	Retrospective	Monarch	69	68	18.47 ± 15.01	NR	100%	NR	90.5% (38/42)	94.1% (strict)	Pneumothorax 1.4%	61.8%	No	No
Manley	2023	US	Prospective	Monarch	20	20	14.5 (8.0-28.0)	60.00%	95%	52.0	82.4% (14/17)	80% (strict)	NR	85%	Yes	No
Agrawal	2023	US	Retrospective	Monarch	124	124	20.5	75.00%	94.40%	NR	69.1% (65/94)	77% (strict)	Overall: 4.8%, pneumothorax (1.6%), bleeding (3.2%)	75.8%	Yes	No
Fielding	2019	Australia	Prospective	Ion	29	29	12.2 ± 4.2	58.60%	96.60%	63.9 ± 24.4	88.20%	79.30% (strict), 96.6% (intermediate)	0.0%	58.6%	Yes	No
Benn	2021	US	Prospective	Ion	52	59	21.9 ± 11.9	46%	100%	65.0 ± 25.0	84%	86% (intermediate)	Pneumothorax (3.8%)	62.7%	No	Yes
Simoff	2021	US	Prospective	Ion	60	67	20.0 (14.0, 27.0)	37.30%	97%	66.5 (50.0, 85.5)	NR	NR	Overall: 3.4%, arrhythmia (1.7%), pneumonia (1.7%)	NR	Yes	No
Kalcheim-Dekel	2022	US	Retrospective	Ion	130	159	18.0 (13.0, 27.0)	62.90%	98.70%	64.0 (40.0, 116.0)	NR	63.5% (strict), 81.7% (intermediate),	Overall: 3.0%, pneumothorax (1.5%)	NR	Yes	No
Yu Lee-Mateus	2023	US	Retrospective	Ion	113	113	Max:18.0 (13.0, 27.0); Min 14 (10, 20)	NR	100%	78.0 (62.5, 92.5)	82.10%	87.6% (intermediate)	Overall: 4.4%, pneumothorax (3.5%)	69%	Yes	No
Oberg	2022	US	Retrospective	Ion	112	120	22.0 (13.0, 34.3)	48%	100%	NR	NR	75.8% (strict), 90% (intermediate)	Overall: 8.0%, pneumothorax (5.4%), pneumothorax that required intervention (2.7%), bleeding (2.7%)	NR	Yes	No
Reisenauer	2022	US	Prospective	Ion	30	30	17.5 (10.0-30.0)	40%	100%	NR	91.70%	93.30% (strict)	Overall: 6.25% (arrhythmia, hypotension)	73.3%	Yes	Yes
Reisenauer	2022	US	Prospective	Ion	241	270	18.8 ± 6.5	NR	100%	63.1 ± 29.1	NR	NR	Overall: 4.5%, pneumothorax (3.3%), pneumothorax that required intervention (0.4%), bleeding (0.8%)	NR	Yes	No
Styrvoky	2022	US	Retrospective	Ion	198	209	19.0 (7.0-73.0)	60.30%	87.60%	NR	87.30%	91.40% (intermediate)	Pneumothorax (1.0%); pneumothorax that required intervention (0.5%)	64.10%	Yes	Yes
Hammad-Altaq	2023	US	Retrospective	Ion	42	42	12.0 (10.0, 18.0)	59.50%	100%	NR	97.00%	88.10% (strict)	0.0%	78.6%	Yes	No

(*Continues*)

Table 1
(Continued).

Author	Year	Country	Study design	Platform	Patients (n)	Lesions (n)	Lesion size (mm)	Bronchus sign	Successful navigation	Procedure time (minutes)	Sensitivity for malignancy	Diagnostic yield	Complication rate	Prevalence for malignancy	r-EBUS	CBCT
Low	2023	US	Retrospective	Ion	133	143	17.0 (12.0, 27.0)	40%	NR	NR	NR	77%(strict)	Pneumothorax (1.5%); pneumothorax that required intervention (1.5%)	NR	Yes	No
Xie	2024	China	Prospective	Ion	90	90	19.4 (19.3, 24.6)	75.6% (68/90)	90%	46.0 (34.0, 73.3)	87.70%	87.8% (intermediate)	Pneumothorax (1.1%)	90.0%	Yes	No
Abia-Trujı	2023	US	Retrospective	Ion	22	23	18	73.90%	NR	72 (57.5, 104)	88.90%	87.0% (intermediate)	0%	69.6%	Yes	No
Fernandez-Bussy	2024	US	Retrospective	Ion	22	46	14	82.60%	91.30%	93 (70-114)	100%	87.0% (intermediate)	Overall: 9%, pneumothorax (n = 1), pneumothorax that required intervention (n = 1); bleeding (n = 1)	54.3%	Yes	No
Fernandez-Bussy	2024	US	Retrospective	Ion	27	28	15	NR	NR	72 (57.0, 112.0)	86.40%	89.3% (intermediate)	Overall: 7.4%, pneumothorax that required intervention (n = 2)	67.9%	Yes	Yes
Abia-Trujillo	2024	US	Retrospective	Ion	173	192	12	50%	NR	69 (46, 100)	82.10%	85.4% (intermediate)	Pneumothorax (4%), pneumothorax that required intervention (n = 2)	60.9%	Yes	Yes
Bashour	2024	US	Prospective	Ion	67	67	17.0 (9.0-30.0)	37.30%	NR	51.0 (21.0-127.0)	88.10%	86.6% (strict)	0.0%	88.1%	No	Yes
Saghaie	2024	Australia	Prospective	Galaxy	18	19	20.0	37%	89.50%	NR	92.90%	89.50% (strict), 94.7% (intermediate)	Pneumothorax: 11%, pneumothorax that required intervention (5%), pneumonia (5%)	73.7%	Yes	No

Data were represented as mean ± standard deviation, median (P^{25}, P^{75}), mean (range), mean, or range. US, the United States of America; NR: not reported; r-EBUS, radial endobronchial ultrasound; CBCT, cone beam computed tomography; TP, true positive; SPB, specific benign; NSBTN, true negative nonspecific benign.

navigation rate ranged from 87.6% to 100.00%, and the mean/median procedure time ranged from 36.4 to 93.0 minutes.

Diagnostic yield for RAB in the diagnosis of pulmonary nodules

Using a strict definition of diagnostic yield, 17 studies were included in the random effects model (I^2 = 83.2%). The comparative diagnostic yields under strict [77.8% (95%CI: 71.8%–83.2%), Fig. 2A] and intermediate [86.6% (95%CI: 83.7%–89.2%), Fig. 2B] criteria were statistical differences (P = 0.004). Further exploration of factors that may affect the diagnostic yield is presented in Table 2. Based on the strict criteria, the pooled diagnostic yield of total number of biopsies ≤ 100 lesions group, and > 100 lesions group were 83.6% (95% CI: 77.1%–89.4%), and 69.6% (95%CI: 62.3%–776.3%), respectively (P = 0.006). Subgroups patients with a prevalence for malignancy (<60%, ≥ 60%), the pooled diagnostic yield (strict) was observed to be 66.6% (95%CI: 53.4%–78.5%), and 83.1% (95%CI: 76.6%–88.8%), respectively (P = 0.020). Additionally, subgroup patients as concentric (88.6%), eccentric (79.8%), and invisible (46.0%), a difference in diagnostic yield (intermediate) between groups can be found (P < 0.001).

Sensitivity for malignancy for RAB in the diagnosis of pulmonary nodules

Figure 2C exhibits the results of 20 studies that reported the sensitivity for malignancy. With an I^2 value of 48.4% from the heterogeneity test, a fixed-effects model was utilized. The pooled sensitivity for malignancy of RAB in the diagnosis of pulmonary nodules was 85.4% (95%CI: 83.0%–87.7%). Table 3 exhibits the further exploration of factors that may affect the sensitivity for malignancy. The polled sensitivity for malignancy of Monarch, Ion, and Galaxy were 80.3%, 87.6%, and 92.9%, respectively (P = 0.008). The average lesion size <20 mm group had a different pooled sensitivity for malignancy compared to the average lesion size ≥20 mm group (average lesion size <20 mm group vs. average lesion size ≥20 mm, 86.4% vs. 77.5%, P = 0.005).

Complications for RAB in the diagnosis of pulmonary nodules

The assessment of complication rates for RAB included 26 studies. The pooled overall complication rate was 3.0% (I^2=42.1%, 95%CI: 2.3%–3.9%) (Fig. 2D). Fig. 3A, 3B, and 3C shows the pooled incidence of pneumothorax, pneumothorax that required intervention, and bleeding were 2.0% (I^2 = 22.3%; 95%CI: 1.3%–2.7%), 0.5% (I^2 = 18.8%; 95%CI: 0.2%–1.0%), and 0.1% (I^2 = 1.1%; 95%CI: 0.0%–0.4%), respectively.

Publication bias

The funnel plots for diagnostic yield (intermediate criteria), sensitivity for malignancy, and complication rates were symmetric (Begg's test, P < 0.05), indicating the absence of publication bias (Table S1, available at: http://links.lww.com/JS9/E117). The diagnostic yield defined by strict criteria was adjusted to 69.6% (95%CI: 61.8%–76.8%) after addressing publication bias (P = 0.018).

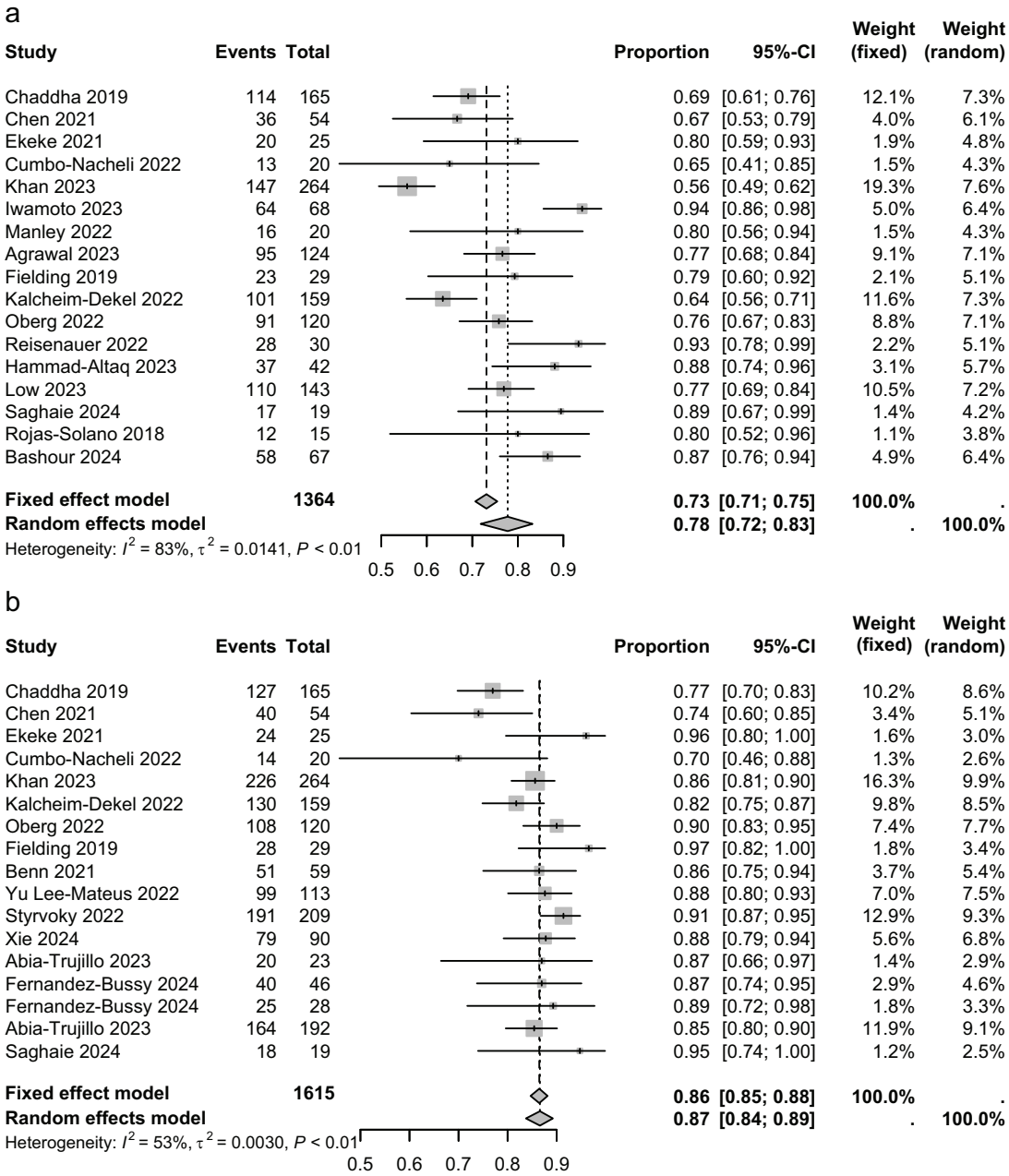
This study showed that RAB achieved a diagnostic yield of 69.6% under strict criteria and 88.6% under intermediate criteria. Furthermore, RAB demonstrated good sensitivity for

malignancy and significantly better safety compared to conventional methods.

Discussion

In this meta-analysis, the pooled diagnostic yield varied between groups, with strict criteria yielding 69.6% and intermediate criteria yielding 86.6%. Factors influencing diagnostic yield included total number of biopsies (≤100 vs. >100; 83.6% vs. 69.6%), the prevalence of malignancy (<60% vs. ≥60%; 66.6% vs. 83.1%), and r-EBUS view (concentric vs. eccentric vs. invisible; 88.6% vs. 84.5% vs. 46.0%). The pooled sensitivity for malignancy of RAB in pulmonary nodule diagnosis was 85.4%, which may be affected by the platform (Monarch vs. Ion vs. Galaxy; 80.3% vs. 87.6% vs. 92.9%) used and the average lesion size (<20 mm vs. ≥20 mm; 86.4% vs. 77.5%). Additionally, the overall complication rate was 3.0%, with the incidence of pneumothorax requiring intervention at 0.5%. Our findings suggest that the RAB is a novel navigational bronchoscope that combines diagnostic capability and safety for pulmonary nodules.

Apart from central pulmonary nodules, a considerable number of pulmonary nodules are located in the outer third of the lung, making them difficult to access with traditional navigation endoscopy[33]. The interventional diagnosis and treatment techniques for peripheral pulmonary nodules need to be balanced



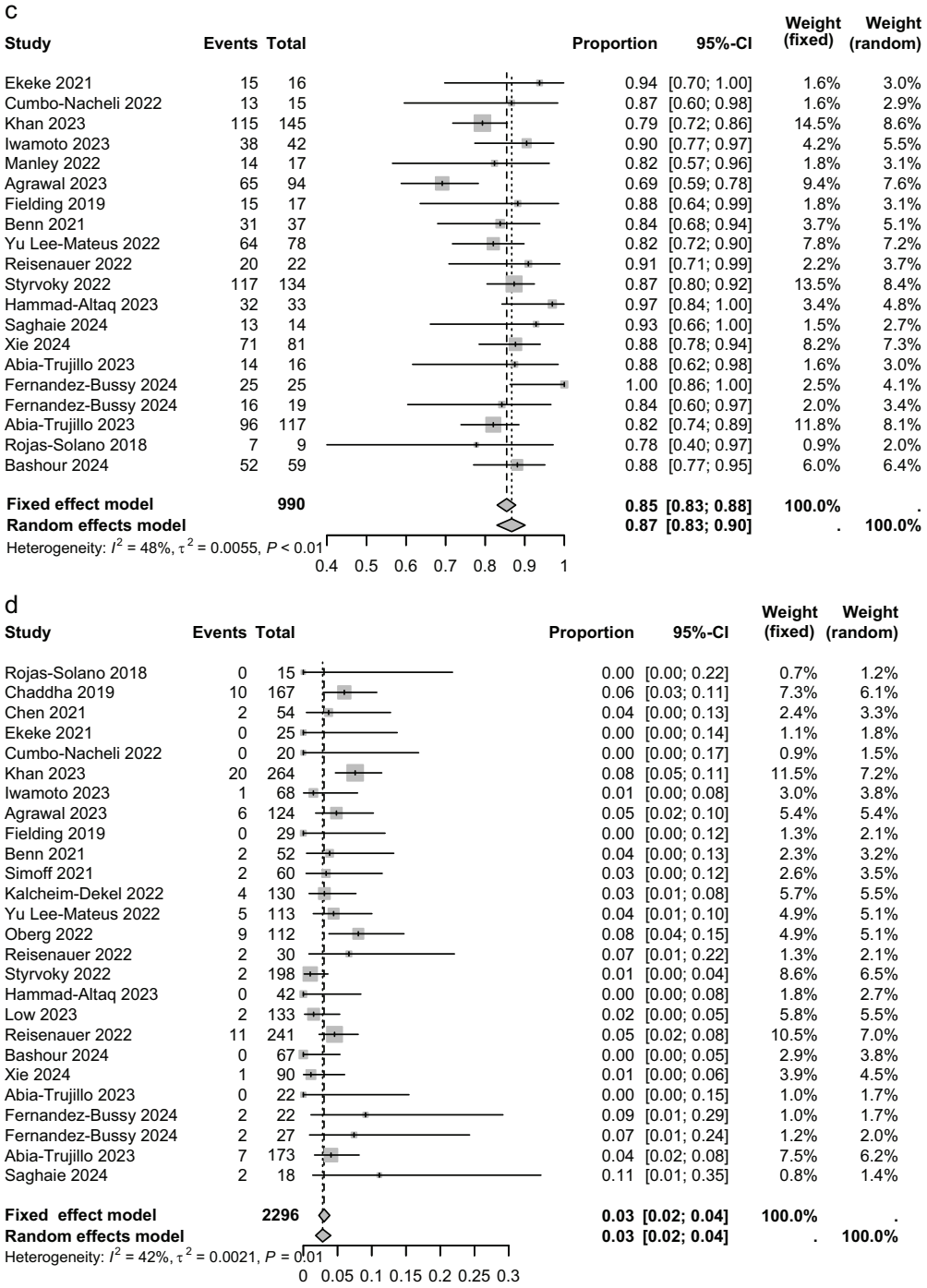


Figure 2. Forest plot of the diagnosis yield under strict criteria (A), diagnosis yield under intermediate criteria (B), sensitivity for malignancy (C), and overall complication rate (D). CI, confidence interval.

between efficacy and safety. To overcome the high complication risk of CT-guided percutaneous lung biopsy and the low diagnostic yield of traditional endoscopic technique, navigation bronchoscopy was proposed. Electromagnetic navigation (EMN) has increased the diagnostic yield of peripheral pulmonary nodules by bronchoscopy from 14%[14] to 68.8%, and new navigation bronchoscopy technologies such as RAB have increased this value to 77.5%[16]. RAB technology improves the precision and flexibility of bronchoscopy by providing a more accurate imaging system and a robotic arm operating system that can reach deep into the lung and branch complex airways[34]. The studies by Cho *et al*[35] and Talon *et al*[36] reported that RAB successfully addressed the diagnostic challenges in several previously undiagnosed cases. Kalchiem-Dekel *et al*[37] evaluated a shape-sensing RAB for pulmonary nodules and found diagnostic yield and sensitivity for malignancy were

Table 2

Diagnostic yield of RAB in pulmonary nodule diagnosis in different subgroups

Variables	No. of studies	Rate (95%CI)	I^2	*P*
Diagnostic yield (strict)				
Total number of biopsies				
≤ 100 lesions	11	0.836 (0.771-0.894)	59.2	0.006
lesions	6	0.696 (0.623-0.763)	88.4	
Study design				
Prospective cohorts	7	0.826 (0.745-0.894)	48.3	0.210
Retrospective cohorts	10	0.750 (0.670-0.824)	87.3	
RAB platform				
Monarch	9	0.744 (0.651-0.829)	86.0	0.299
Ion	7	0.801 (0.723-0.870)	77.4	
Galaxy	1	0.894 (0.658-0.967)	NA	
Average lesion size				
≤20 mm	8	0.778(0.680-0.864)	88.4	0.425
	7	0.738 (0.693-0.780)	17.9	
Prevalence for malignancy				
%	3	0.666 (0.534-0.785)	83.1	0.020
≥60%	11	0.831 (0.766-0.888)	63.2	
Prevalence for malignancy & total number of biopsies				
Prevalence for malignancy <60% & lesions ≤100	1	0.793 (0.600-0.910)	NA	<0.001
Prevalence for malignancy <60% & lesions >100	2	0.623 (0.489-0.749)	87.1	
Prevalence for malignancy ≥60% & lesions ≤100	10	0.840 (0.769-0.901)	62.4	
Prevalence for malignancy ≥60% & lesions >100	1	0.766 (0.687-0.860)	NA	
CBCT				
Yes	4	0.765 (0.564-0.920)	92.7	0.872
No	13	0.781(0.724-0.834)	71.3	
Combined use				
r-EBUS + CBCT	3	0.726 (0.458-0.930)	90.3	0.745
r-EBUS or CBCT	11	0.764 (0.713-0.813)	63.1	
Year of publication				
Earlier than 2022	5	0.716 (0.661-0.768)	0	0.017
2022	5	0.758 (0.639-0.862)	75.3	
2023	5	0.791 (0.649-0.904)	93.8	
2024	2	0.876 (0.794-0.940)	0.0	
Diagnostic yield (intermediate)				
Total number of biopsies				
≤100 lesions	10	0.874(0.824-0.917)	40.6	0.803
	7	0.858 (0.820-0.892)	68.4	
Study design				
Prospective cohorts	5	0.878(0.800-0.940)	57.6	0.766
Retrospective cohorts	12	0.863(0.831-0.893)	55.6	
RAB platform				
Monarch	5	0.816 (0.732-0.888)	69.7	0.162
Ion	11	0.881 (0.855-0.904)	11.7	
Galaxy	1	0.947(0.740-1.000)	NA	
Average lesion size				
≤20 mm	10	0.875(0.850-0.899)	83.0	0.331
	6	0.830 (0.754-0.894)	67.8	
Prevalence for malignancy				
%	4	0.858(0.780-0.922)	70.8	0.739
≥60%	11	0.874 (0.840-0.906)	41.9	
CBCT				
Yes	6	0.872(0.836-0.904)	44.0	0.778
No	11	0.866(0.824-0.904)	57.7	
Combined use				
r-EBUS + CBCT	5	0.872 (0.829-0.910)	54.9	0.619
r-EBUS or CBCT	11	0.858 (0.80-0.893)	52.3	
Year of publication				
Earlier than 2022	5	0.860(0.761-0.938)	73.5	0.866
2022	5	0.870(0.816-0.916)	67.2	
2023	3	0.860(0.826-0.891)	0	
2024	4	0.889(0.837-0.933)	0	
r-EBUS view				
Concentric	3	0.886 (0.798-0.955)	13.3	<0.001
Eccentric	3	0.845 (0.690-0.956)	68.2	
Invisible	3	0.460 (0.130-0.808)	74.2	
Bronchus sign				
Present	3	0.906 (0.761-0.993)	80.3	0.098
Absent	3	0.712 (0.494-0.891)	77.0	

(*Continues*)

Table 2

(Continued).

CI, confidence interval; RAB, robot-assisted bronchoscopy; CBCT, cone beam computed tomography; r-EBUS, radial endobronchial ultrasound.

81.7% and 79.8%. A prospective study using shape-sensing RAB on 90 patients at three centers yielded a diagnostic yield of 87.8% and a sensitivity for malignancy of 87.7%[38]. In another study that assessed the performance of RAB in lung lesion samples at four centers in the US, a diagnostic yield range of 69.1% to 77% was reported[39]. The diagnostic yield

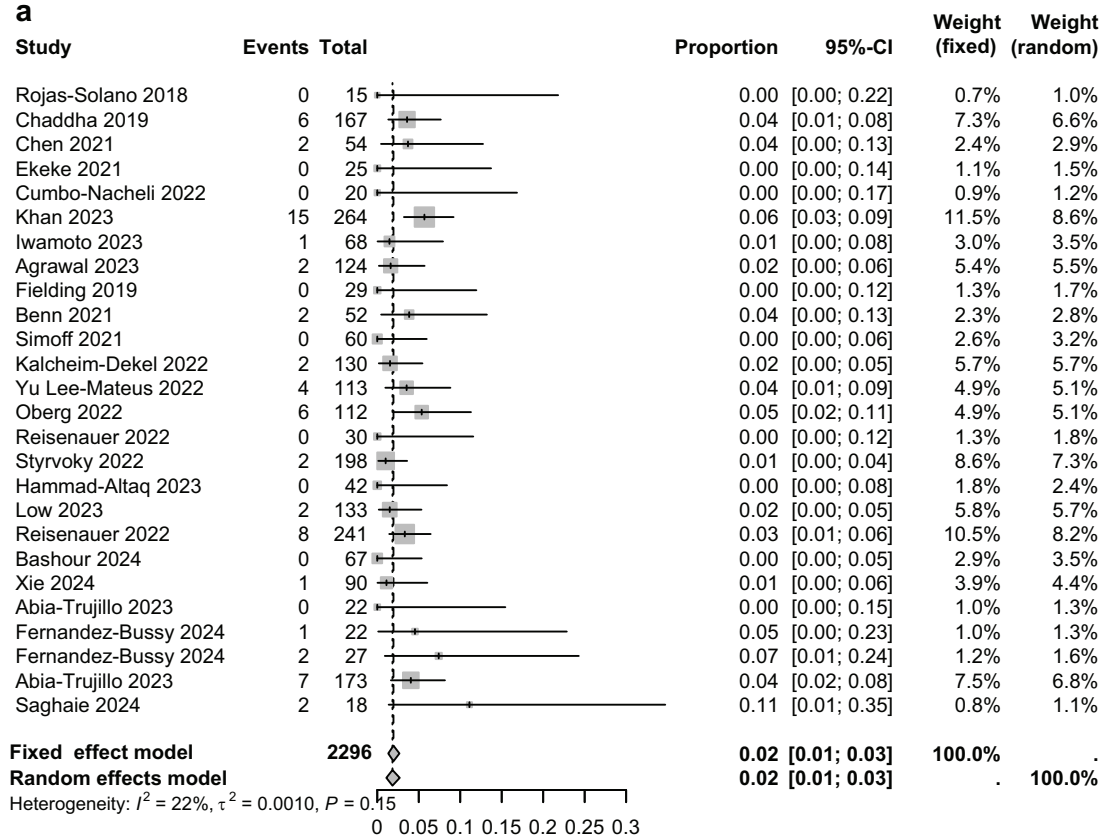
Table 3

Sensitivity for malignancy of RAB in pulmonary nodules biopsy diagnosis in different subgroups

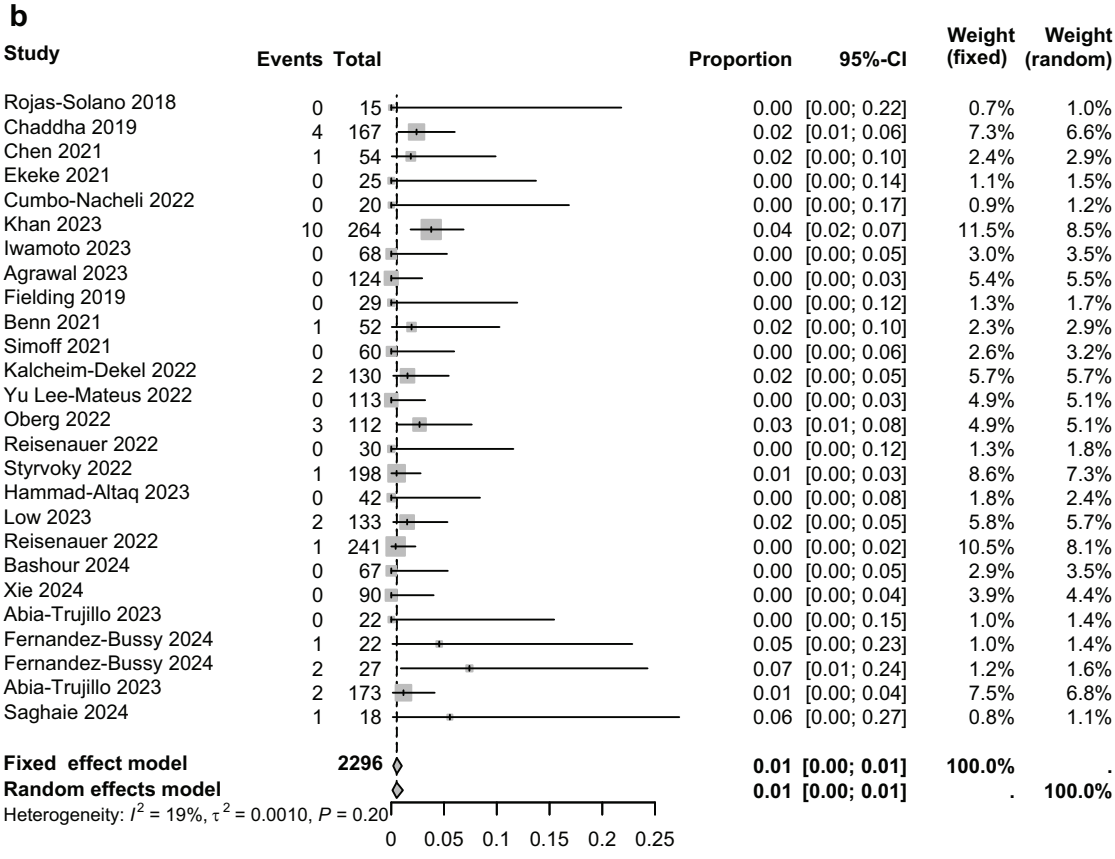
Variables	Number of studies	Rate (95%CI)	I^2	*P*
Total number of biopsies				
≤ 100 lesions	17	0.866 (0.834-0.894)	50.9	0.324
lesions	3	0.830 (0.791-0.866)	38.7	
Study design				
Prospective cohorts	9	0.879 (0.834-0.919)	0.0	0.272
Retrospective cohorts	11	0.8643(0.814-0.870)	70.2	
RAB platform				
Monarch	7	0.803(0.756-0.846)	46.4	0.008
Ion	12	0.876(0.848-0.902)	30.7	
Galaxy	1	0.929 (0.650-0.980)	NA	
Average lesion size				
≤20 mm	13	0.864 (0.837-0.889)	41.9	0.005
	5	0.775(0.705-0.839)	37.3	
Prevalence for malignancy				
%	3	0.849 (0.791-0.900)	83.8	0.867
≥60%	17	0.856 (0.829-0.881)	34.5	
r-EBUS				
Yes	15	0.848 (0.821-0.873)	58.3	0.271
No	5	0.886 (0.828-0.934)	0.0	
Combined use				
r-EBUS + CBCT	6	0.841(0.804-0.875)	0.0	0.581
r-EBUS or CBCT	11	0.857(0.822-0.889)	66.6	

CI, confidence interval; RAB, robot-assisted bronchoscopy; CBCT, cone beam computed tomography; r-EBUS, radial endobronchial ultrasound.

a


Study
Events Total
Proportion 95%-CI
Weight (fixed) Weight (random)
Rojas-Solano 2018 0 15 0.00 [0.00; 0.22] 0.7% 1.0%
Chaddha 2019 6 167 0.04 [0.01; 0.08] 7.3% 6.6%
Chen 2021 2 54 0.04 [0.00; 0.13] 2.4% 2.9%
Ekeke 2021 0 25 0.00 [0.00; 0.14] 1.1% 1.5%
Cumbo-Nacheli 2022 0 20 0.00 [0.00; 0.17] 0.9% 1.2%
Khan 2023 15 264 0.06 [0.03; 0.09] 11.5% 8.6%
Iwamoto 2023 1 68 0.01 [0.00; 0.08] 3.0% 3.5%
Agrawal 2023 2 124 0.02 [0.00; 0.06] 5.4% 5.5%
Fielding 2019 0 29 0.00 [0.00; 0.12] 1.3% 1.7%
Benn 2021 2 52 0.04 [0.00; 0.13] 2.3% 2.8%
Simoff 2021 0 60 0.00 [0.00; 0.06] 2.6% 3.2%
Kalcheim-Dekel 2022 2 130 0.02 [0.00; 0.05] 5.7% 5.7%
Yu Lee-Mateus 2022 4 113 0.04 [0.01; 0.09] 4.9% 5.1%
Oberg 2022 6 112 0.05 [0.02; 0.11] 4.9% 5.1%
Reisenauer 2022 0 30 0.00 [0.00; 0.12] 1.3% 1.8%
Styrvoky 2022 2 198 0.01 [0.00; 0.04] 8.6% 7.3%
Hammad-Altaq 2023 0 42 0.00 [0.00; 0.08] 1.8% 2.4%
Low 2023 2 133 0.02 [0.00; 0.05] 5.8% 5.7%
Reisenauer 2022 8 241 0.03 [0.01; 0.06] 10.5% 8.2%
Bashour 2024 0 67 0.00 [0.00; 0.05] 2.9% 3.5%
Xie 2024 1 90 0.01 [0.00; 0.06] 3.9% 4.4%
Abia-Trujillo 2023 0 22 0.00 [0.00; 0.15] 1.0% 1.3%
Fernandez-Bussy 2024 1 22 0.05 [0.00; 0.23] 1.0% 1.3%
Fernandez-Bussy 2024 2 27 0.07 [0.01; 0.24] 1.2% 1.6%
Abia-Trujillo 2023 7 173 0.04 [0.02; 0.08] 7.5% 6.8%
Saghaie 2024 2 18 0.11 [0.01; 0.35] 0.8% 1.1%
Fixed effect model 2296 0.02 [0.01; 0.03] 100.0% .
Random effects model 0.02 [0.01; 0.03] . 100.0%
Heterogeneity: I^2 = 22%, τ^2 = 0.0010, P = 0.15
0 0.05 0.1 0.15 0.2 0.25 0.3

b


Study
Events Total
Proportion 95%-CI
Weight (fixed) Weight (random)
Rojas-Solano 2018 0 15 0.00 [0.00; 0.22] 0.7% 1.0%
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Abia-Trujillo 2023 2 173 0.01 [0.00; 0.04] 7.5% 6.8%
Saghaie 2024 1 18 0.06 [0.00; 0.27] 0.8% 1.1%
Fixed effect model 2296 0.01 [0.00; 0.01] 100.0% .
Random effects model 0.01 [0.00; 0.01] . 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.0010, P = 0.20
0 0.05 0.1 0.15 0.2 0.25

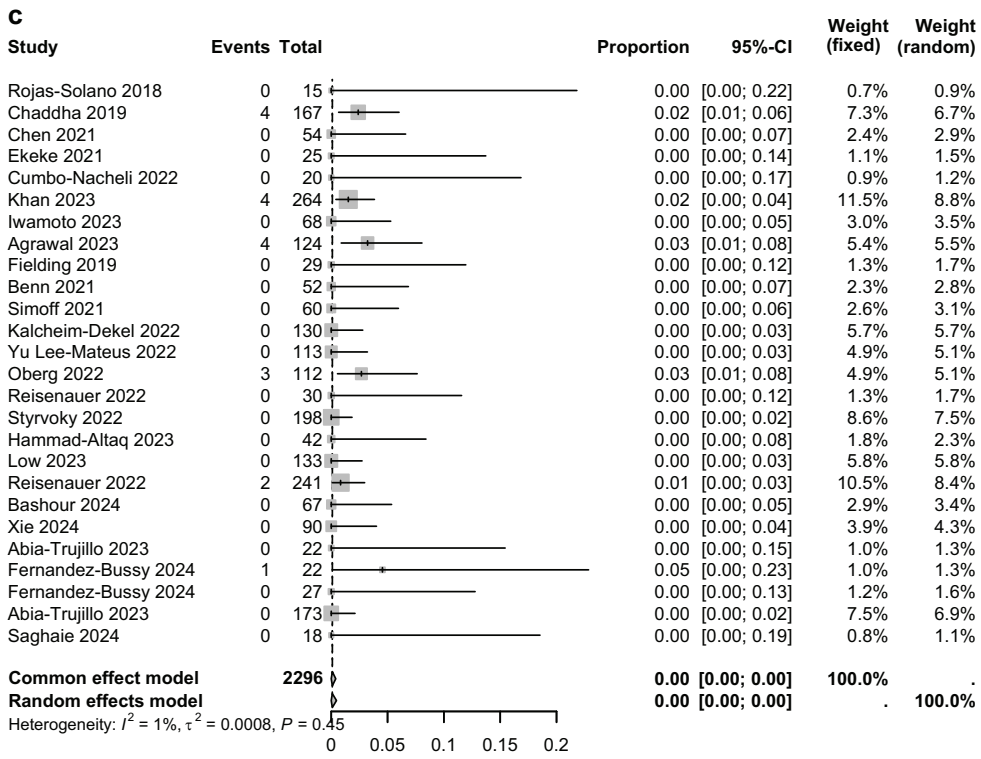

Figure 3. Forest plot of the incidence of pneumothorax (A), the incidence of pneumothorax that required intervention (B), and bleeding rate (C). CI, confidence interval.

of RAB for pulmonary nodule diagnosis exceeds that of EMN bronchoscopy[16] and is comparable to the results achieved with TTNB[21,40]. Vachani *et al*[30] recently demonstrated that the diagnostic yield in studies of bronchoscopy can vary more than 20%, depending on the different criteria employed. The study by Leonard *et al*[41] indicated that the strict diagnostic yield definition closely aligns with the diagnostic accuracy at the 2-year follow-up, with a difference of less than 1%, whereas the intermediate diagnostic yield exhibits greater variability. The pooled diagnostic yield and sensitivity for malignancy in our study are comparable with previous studies. It is noticed that the pooled diagnostic yield for strict and intermediate criteria was different (69.6% vs. 86.6%, P = 0.004). The observed differences in diagnostic yield may be attributed to the different definitions. Although the quality assessment of the included studies was generally low risk, the results showed a publish bias in the diagnostic yield defined by strict criteria. After adjusting the bias, the diagnostic yield (strict) was 69.6%, which the diagnostic criteria were determined with data available at the time of bronchoscopy procedure, and not considered the follow-up data. The bias may be associated with study design, patient characteristics, biopsy tools, number of procedures performed by the operator, and surgical experience, and our findings need to be interpreted with caution. Our results further indicated the importance of reporting diagnostic yield according to different criteria (particularly the strict criteria) in RAB research.

In this meta-analysis, a pooled complications rate was observed with a value of 3.0% (pneumothorax, 2.0%; pneumothorax that required intervention, 0.5%; bleeding rate, 0.1%) for pulmonary nodule diagnosis with RAB. The incidence of pneumothorax that required intervention was only 0.5%, indicating that most complications were mild and self-limited. A retrospective cohort analysis including 16 971 patients who underwent TTNB found that 25.8% of patients had complications within 3 days of surgery[42]. Pneumothorax is the major complication after lung biopsy[43]. Our result is similar to the studies by Pyarali *et al*[44] (incidence of pneumothorax, 2.2%; major bleeding rate, <0.01%) and Zhang *et al*[26] (complication rate, 3%; incidence of pneumothorax, 1.8%). A recent study reported no complications associated with RAB use in 30 patients who had a single targeted nodule[45]. Studies conducted by Oberg *et al*[46] and Monterroso[47] *et al* also found that patients undergoing RAB tolerated the procedure well without major adverse events. Our results further emphasize the safety of RAB in pulmonary nodule diagnosis.

We found a heterogeneity in diagnostic performance and further explored factors that may affect diagnostic performance. In the group with total number of biopsies (>100 lesions), lower malignancy prevalence (<60%), and invisible r-EBUS view, the diagnostic yield of RAB for pulmonary nodules was lower. In the population with a prevalence of malignancy <60%, the diagnostic yield for nodules was 79.3% for those with ≤100 nodules and 62.3% for those >100 nodules; the diagnostic yield for nodules was 84.0% for those ≤100 and 76.6% for those >100 in the population with a prevalence of malignancy ≥60%. This may be due to increased sample heterogeneity and low prevalence leading to increased false positive results[48], thus affecting the overall diagnostic yield. Our results also remind us that we should be cautious about seeing high diagnostic yields from small sample studies, as a small sample may overestimate the diagnostic power of RAB. The r-EBUS view is used to characterize the different lung lesions observed on ultrasound imaging to guide

physicians in accurately locating lung nodules. In our study, the diagnostic yield for the invisible group was only 46.0%, indicating that the lesions were not visible in EBUS imaging. This low diagnostic yield may be due to the lesions being located in the shadowing area of the ultrasound or being too small or poorly positioned for effective imaging[49]. Such situations can lead to missed diagnoses, particularly when assessing small nodules. High-resolution r-EBUS probes, artificial intelligence-driven navigation, alternative localization techniques, and virtual reality bronchoscopy simulators (Train operators to navigate complex airways to identify subtle r-EBUS signals) may be considered to improve the diagnostic yield in research and clinical practice. When utilizing the r-EBUS probe, it should be noted that the spatial orientation of pulmonary nodules displayed on the r-EBUS monitor does not correlate with their true anatomical position relative to the target airway. Consequently, when an eccentric r-EBUS image is observed, systematic evaluation of probe-to-airway wall interactions is required to localize the target lesion. This involves advancing the r-EBUS probe along multiple airway wall surfaces while analyzing dynamic changes in the ultrasound signal pattern. Procedural approaches differ between navigation platforms. With the Monarch Platform, real-time visualization enables direct manipulation of the r-EBUS probe across airway surfaces. In contrast, the Ion platform necessitates removal of the optical probe prior to r-EBUS insertion. Under these circumstances, fluoroscopically guided manipulation of the r-EBUS articulation guide permits systematic exploration of airway wall surfaces. Lesion confirmation is achieved through signal intensity maximization. Upon identification of the strongest r-EBUS signal, alignment of the bronchoscope working channel with the optimized trajectory is performed to facilitate subsequent tissue sampling. In addition to previously mentioned factors, the use of biopsy tools and learning curves also impacts diagnostic yield[36,50]. However, the lack of comparative studies on different diagnostic tools limits our understanding of their effects, highlighting the need for future research in this area. Notably, our study found no difference in diagnostic yields between groups based on tumor size (≤20 mm vs. >20 mm) and bronchus sign presence (present vs. absent). RAB may be an effective method[51] to improve these common influencing factors in the bronchoscopic diagnosis of pulmonary nodules[52]. As for sensitivity for malignancy, the platform used and average lesion size may be influencing factors. The difference in the RAB platform may probably be because it reduced CTBD effects[53] (a discrepancy between the location of a pulmonary nodule as determined by CT imaging before RAB examination and the actual anatomical location[54]), specific technical characteristics, operator experience, or patient selection factors. The Ion platform exhibited slightly higher sensitivity for malignancy compared to Monarch, which may be due to differences in tool stability and ability to maintain navigation during sampling[55]. Although the Galaxy system was reported in only one study, 92.9% of the diagnostic yield showed great potential for application, probably because of its reduction of CT-to-body dispersion (CTBD) effects[51]. During robotic bronchoscopy, discrepancies may arise between the location of pulmonary nodules determined by pre-biopsy CT imaging and their actual anatomical position, a phenomenon referred to as CTBD[56]. Saghaie *et al*[24] conducted an RAB system equipped with electromagnetic navigation and tilt-assisted lesion guidance (Galaxy) to reduce the effect of CTBD, with diagnostic yield even reaching 89.5% to 94.7%. While there is virtually no data directly comparing these RAB platforms, future prospective and comparative studies need to further assess the findings. The superior diagnostic performance of RAB in lesions <20 mm further emphasizes the great application prospect of RAB in small peripheral pulmonary nodules. Our results emphasized that RAB not only enhances the diagnostic yield but also expands the diagnostic depth and allows for more precise access to small lesions.

The high performance and safety of the RAB make it a promising tool for the diagnosis of pulmonary nodules, helping to improve the diagnostic performance of early diagnosis and thus the prognosis of lung cancer patients. For physicians, the RAB system's intuitive interface and automation features greatly reduce learning costs[50,56]. For patients, RAB diagnosis of pulmonary nodules offers a short operation time (36.4–93.0 minutes), less trauma, and rapid postoperative recovery, significantly reducing the pain of patients and the risk of complications. It is important to note that the diagnostic yields associated with RAB can vary based on differing diagnostic criteria, particularly when more stringent standards are employed, which underscores the necessity for careful interpretation of results in clinical settings. Additionally, several factors, including patient demographics, the total number of nodules included in studies, and the average lesion size, can impact the overall diagnostic performance of RAB. By considering these factors, clinicians can better understand the effectiveness of RAB in pulmonary nodule diagnosis, which may be conducive to the efficient diagnosis of disease and timely control of disease progression. Moreover, RAB can be combined with techniques such as cryotherapy or thermal ablation to assist physicians in accurately localizing pathological tissues for treatment, thereby minimizing damage to surrounding healthy tissues. By integrating RAB with these therapeutic approaches, clinicians can achieve more personalized and precise treatment plans, ultimately enhancing the overall therapeutic outcomes and quality of life for patients.

We must acknowledge that some limitations remain. (1) While RAB has shown high diagnostic performance, the variability in diagnostic yield highlights the need for standardized protocols, and more standardized prospective studies are needed to provide further evidence in the future. (2) The utilization of CBCT and r-EBUS in RAB remains limited, necessitating comparative studies to assess their incremental benefits regarding diagnostic yield and safety. (3) The literature on Galaxy is limited, and more studies need to be encouraged to provide evidence. (4) Although we have included what we could gather about potential influences, there is still information (e.g., biopsy tools, number of procedures performed by the operator, and learning curves, etc.) that we were not able to collect, which limits further analyses. (5) Most studies on RAB for pulmonary nodule diagnosis are single-arm studies. More high-quality, large-scale randomized controlled trials should be conducted to validate the performance and safety of RAB.

Conclusion

This study explored the diagnostic yield under different criteria in the diagnosis of pulmonary nodules with RAB. Moreover, the influencing factors of the diagnosis yield, the sensitivity for malignancy as well as complications of RAB for pulmonary nodule diagnosis were also summarized. Our results not only demonstrate the efficacy and safety of RAB in the diagnosis of pulmonary nodules but also emphasize the importance of

different diagnostic criteria (especially strict criteria) for the assessment of RAB performance. In future studies, more feasibility multicenter RAB studies based on real environments or in different clinical settings are expected.

Ethical approval

None.

Consent

None.

Sources of funding

None.

Author contributions

X.L. and Y.H. designed the study. X.L. wrote the manuscript. J. B., X.Z., T.W., and Y.Z. collected, analyzed, and interpreted the data. Y.H. critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

Conflicts of interest disclosure

None.

Guarantor

Yi Hu.

Research registration unique identifying number (UIN)

This meta-analysis registered at https://www.crd.york.ac.uk/prospero/ (study ID: CRD42024610508).

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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