Transbronchial Lung Cryobiopsy and Video-assisted Thoracoscopic Lung Biopsy in the Diagnosis of Diffuse Parenchymal Lung Disease

A Meta-analysis of Diagnostic Test Accuracy

Imran H. Iftikhar[1], Lana Alghothani[2], Alejandro Sardi[1], David Berkowitz[1], and Ali I. Musani[3]

[1]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Emory University School of Medicine, Atlanta, Georgia; [2]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University, Columbus, Ohio; and [3]Division of Pulmonary, Critical Care, and Sleep Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

Abstract

Rationale: Transbronchial lung cryobiopsy is increasingly being used for the assessment of diffuse parenchymal lung diseases. Several studies have shown larger biopsy samples and higher yields compared with conventional transbronchial biopsies. However, the higher risk of bleeding and other complications has raised concerns for widespread use of this modality.

Objectives: To study the diagnostic accuracy and safety profile of transbronchial lung cryobiopsy and compare with video-assisted thoracoscopic surgery (VATS) by reviewing available evidence from the literature.

Methods: Medline and PubMed were searched from inception until December 2016. Data on diagnostic performance were abstracted by constructing two-by-two contingency tables for each study. Data on *a priori* selected safety outcomes were collected. Risk of bias was assessed with the Quality Assessment of Diagnostic Accuracy Studies tool. Random effects meta-analyses were performed to obtain summary estimates of the diagnostic accuracy.

Results: The pooled diagnostic yield, pooled sensitivity, and pooled specificity of transbronchial lung cryobiopsy were 83.7% (76.9–88.8%), 87% (85–89%), and 57% (40–73%), respectively. The pooled diagnostic yield, pooled sensitivity, and pooled specificity of VATS were 92.7% (87.6–95.8%), 91.0% (89–92%), and 58% (31–81%), respectively. The incidence of grade 2 (moderate to severe) endobronchial bleeding after transbronchial lung cryobiopsy and of post-procedural pneumothorax was 4.9% (2.2–10.7%) and 9.5% (5.9–14.9%), respectively.

Conclusions: Although the diagnostic test accuracy measures of transbronchial lung cryobiopsy lag behind those of VATS, with an acceptable safety profile and potential cost savings, the former could be considered as an alternative in the evaluation of patients with diffuse parenchymal lung diseases.

Keywords: meta-analysis; diffuse parenchymal lung diseases; cryobiopsy; video-assisted thoracoscopy

(Received in original form January 29, 2017; accepted in final form April 11, 2017)

Author Contributions: I.H.I. conceptualized the study, extracted and analyzed data, and wrote the first draft. L.A. assisted in data extraction and provided critical review of the manuscript. A.S., D.B., and A.I.M. provided critical review of the manuscript.

Correspondence and requests for reprints should be addressed to Imran H. Iftikhar, M.D., 613 Michael Street, NE, Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Emory University School of Medicine, Atlanta, GA 30303-3073. E-mail: imran.hasan.iftikhar@emory.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Ann Am Thorac Soc Vol 14, No 7, pp 1197–1211, Jul 2017

DOI: 10.1513/AnnalsATS.201701-086SR
Internet address: www.atsjournals.org

Diffuse parenchymal lung diseases (DPLDs) are a heterogeneous group of more than 200 pulmonary conditions that manifest with diffuse and patchy involvement of lung parenchyma. DPLDs differ widely in their etiology, clinicopathologic features, therapeutic options, and prognosis (1). International consensus guidelines for the diagnosis and treatment of interstitial lung diseases (ILDs) (2, 3) indicate that in approximately 50% of cases, chest high-resolution computed tomography may not be sufficient to diagnose idiopathic pulmonary fibrosis (IPF), and surgical lung biopsy is recommended to distinguish usual interstitial pneumonia (UIP) from other ILDs (4). Although transbronchial lung forceps biopsy is not currently recommended to histologically confirm UIP, due to its low diagnostic yield (2, 5), surgical lung biopsy, whether video-assisted thoracoscopic surgery (VATS) or open-lung biopsy (OLB), is

burdened by its associated risks, postoperative complications, and prolonged hospitalization.

Transbronchial lung cryobiopsy is increasingly being used for the assessment of DPLDs. The major advantage of this procedure is that larger tissue samples with a higher percentage of alveolar tissue can be obtained with fewer crush artifacts and less atelectasis (6–8). The cryosurgical equipment operates by the Joule–Thompson effect (9), which dictates that a compressed gas released at high flow rapidly expands and creates a very low temperature. The cooling agent (carbon dioxide or nitrous oxide) is applied under high pressure through the central canal of the probe. The gas at the tip suddenly expands due to difference in pressure (relative to atmospheric pressure), causing a drop in temperature at the tip of the probe (in the tissue of approximately −50°C to −60°C). The probe is cooled for approximately 3 to 6 seconds (larger probe cooled for 7–8 s). The frozen tissue attached to the probe's tip is removed by pulling the cryoprobe together with the bronchoscope. The frozen specimen is then thawed in physiological saline and fixed in formalin.

Several meta-analyses (5, 10–12) have evaluated the diagnostic yield and safety of transbronchial lung cryobiopsy. The pooled diagnostic yield in the meta-analyses by Sharp and colleagues (5), Johannson and colleagues (11), and Ravaglia and colleagues (12) was reported to be 84% (75.9–91.4% on the basis of 11 studies and abstracts), 83% (73–94% on the basis of 11 studies), and 81% (75–87% on the basis of 12 studies and abstracts), respectively. The meta-analysis by Ganganah and colleagues (10) on the basis of two studies reported an 85% diagnostic yield. Although the pooled incidence of post-procedure pneumothorax reported in these meta-analyses (5, 10–12) was similar (6–12%), the incidence of moderate to severe bleeding differed widely (12–39%). In this "diagnostic test accuracy" meta-analysis, we sought to not only update the pooled diagnostic yield from all published studies in the literature but also report on other diagnostic test accuracy measures (pooled sensitivity, specificity, diagnostic odds ratio, and summary receiver operative curve [SROC]) as well as the safety profile of transbronchial lung cryobiopsy and compare these with studies on VATS.

Methods

Literature Search and Study Selection

A systematic search of the literature was performed in December 2016 to identify all studies that reported information on the diagnostic yield of transbronchial lung cryobiopsy and VATS in the diagnosis of diffuse parenchymal lung disease. We searched Medline and PubMed using the search strategy displayed in Figure 1. Full text articles of shortlisted abstracts were independently assessed by the two authors (I.H.I. and L.A) for inclusion in this meta-analysis. Disagreement on any study selection was resolved by independent review of a third author (A.M). Excluded from selection were review articles, non–peer-reviewed papers, and conference proceedings. Quality of included studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies tool, consisting of four key domains: patient selection, index test, reference standard, and the flow and timing (*see* data supplement).

Data Extraction

Extracted data included the following items: type of study, description of study population (age and sex distribution), site and number of biopsies, final histopathological diagnosis, and data on diagnostic performance. The latter were abstracted by constructing two-by-two contingency tables for each study, with patients categorized into one of four options: true positive (TP), false positive (FP), false negative (FN), and true negative (TN). The primary outcome was diagnostic yield. Success with transbronchial lung cryobiopsy or VATS (TP) was defined as a definitive diagnosis that was yielded by biopsy. When the benign diagnosis was initially yielded by biopsy from either procedure and confirmed by clinical and radiological consensus, it was also considered as a success (TN). Transbronchial lung cryobiopsy/VATS failure represented a biopsy that was either nondiagnostic or yielded a

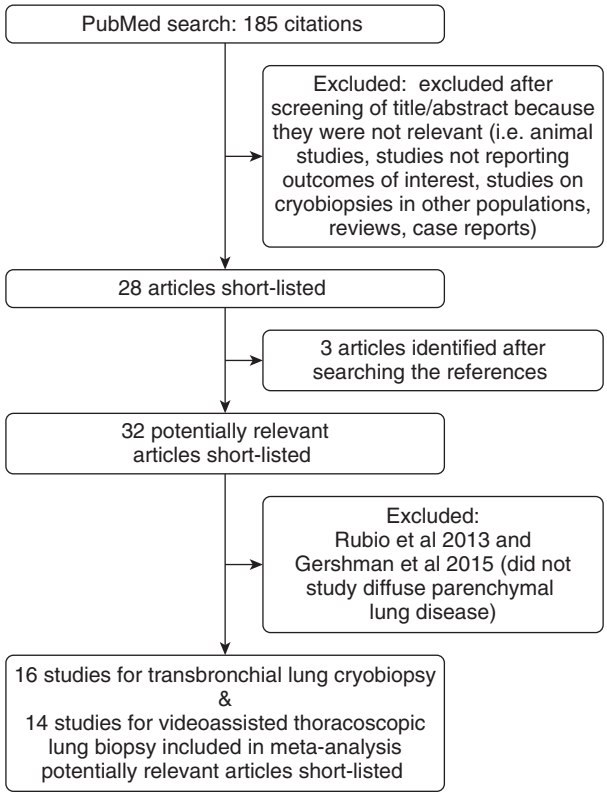

Figure 1. Flow chart for study search and selection process.

Table 1. Baseline characteristics of study population

Reference	Type of Study	N	Age (*yr*)*	Female Sex (%)	Pathology	Size of Biopsies
Transbronchial lung cryobiopsy						
Babiak and colleagues 2009 (14)	Retrospective	41	N/A	N/A	Primarily UIP, NSIP and sarcoidosis. Rest were either DIP, LAM, HP, pharmacologically induced pneumonitis	N/A
Griff and colleagues 2011 (7)	Prospective	N/A	N/A	N/A	N/A	17.1 ± 10.7 μm^2
Fruchter and colleagues 2013 (16)	Retrospective	14	54.3 (27–67)	14.28	Noncaseating granulomatous inflammation 13.3% Drug-induced AIP 33.3% DAD 20% NSIP 6.6% OP 20% Cryptococcal pneumonia 6.6%	9 (6–13) mm^2
Kropski and colleagues 2013 (20)	Retrospective	37	57.1 (27–75)	48	UIP 28% BOOP/COP 8% RBILD/DIP 8% HP 4% Malignancy 8% Drug-induced 8% CB 4% BO 4% Normal 4% Nondiagnostic 20%	N/A
Yarmus and colleagues 2013 (22)	Prospective	21	52 (13)	29	N/A	N/A
Casoni and colleagues 2014 (15)	Prospective	69	60 (29–77)	49	UIP 75% Rest was NSIP, DIP, RBILD, FB, OP, HP, DAD, eosinophilic pneumonia	43.11 mm^2
Pajares and colleagues 2014 (8)	Randomized controlled trial	39	60.3 (10.3)	48.7	NSIP 30.8% DAD 2.6% OP 7.7% Sarcoidosis 2.6% Bronchiolitis-associated ILD 5.1% HP 7.7% UIP 17.9%	N/A
Griff and colleagues 2014 (17)	Retrospective	52	63 (13)	31	COP 17% Rheumatoid ILD 3% Sarcoidosis 21% Alveolar microlithiasis 1.7% NSIP 1.7% Drug induced 3.5% HP 12.5% ILD from scleroderma 3.5% Histiocytosis 3.5% p-ANCA vasculitis 1.7% IPF 23%	6.9 ± 4.4 mm
Hernández-González and colleagues 2015 (19)	Retrospective	33	64 (30–79)	68	UIP	0.5 ± 0.19 cm
Pourabdollah and colleagues 2016 (21)	Prospective	41	N/A	N/A	Granuloma, carcinoma, Lymphangitic carcinomatosis, PCP, PAP, PLCH, Pulmonary hemorrhage syndrome, conditions associated with intravenous drug abuse, or findings suggestive of aspiration or HP	22 (19.1) mm^2

(Continued)

Table 1. (*Continued*)

Reference	Type of Study	N	Age (*yr*)*	Female Sex (%)	Pathology	Size of Biopsies
Fruchter and colleagues 2014 (6)	Retrospective	75	56.2	45.3	COP 14.6% NSIP 28% PLCH 4% LAM 1.3% UIP 7% Sarcoidosis 1.3% Lipoid pneumonia 1.3% Alveolar proteinosis 1.3% DIP 1.3% HP 1.3% Silicosis 1.3% Eosinophilic pneumonia 1.3% Lymphangitis carcinomatosis 1.3% Interstitial fibrosis 29.3% Normal lung tissue 2.6%	9 (6–18) mm^2
Hagmeyer and colleagues 2016 (18)	Retrospective	32	65.4 (45–83)	31	UIP (mostly)	N/A
Ussavarungsi and colleagues 2016 (24)	Retrospective	74	63 (13.8)	45	Nonnecrotizing granulomatous inflammation 31.5% OP 30% Respiratory bronchiolitis 8% Acute fibrinous and organizing pneumonia 5.2% DAD 2.6% DIP 2.6% Necrotizing granulomatous Inflammation 2.6% Eosinophilic pneumonia 2.6% Pulmonary alveolar proteinosis 2.6% Amyloidosis 2.6% Lymphoma 5.2% Invasive mucinous adenocarcinoma 2.6% Bronchiolitis with food particle 2.6%	9.2 (3.9) mm (diameter)
Tomassetti and colleagues 2016 (25)	Cross-sectional	58	59 (29–77)	53	IPF	N/A
Ravaglia and colleagues 2016 (12)	Prospective	297	60 (21–78)	42.1	DIP/RBILD 4.0% UIP 31.0% NSIP 8.4% DAD 1.3% OP 10.4% HP 8.1% SAR 7.4% Other	N/A
Ramaswamy and colleagues 2016 (23)	Retrospective	56	60 (12)	46	ILD 12.5% OP 12.5% HP 5.3% Sarcoid 3.5% Malignancy 9% Drug reaction 10.7% Other 12.5%	0.1–0.8 cm
Video-assisted thoracoscopic surgery						
Ayed and Raghunathan, 2000 (28)	Randomized controlled trial	32	N/A	N/A	N/A	N/A
Uramoto and colleagues, 2001 (37)	Retrospective	7	46.4 (4–61)	N/A	N/A	N/A
Ayed, 2003 (27)	Prospective	79	38.9 (15–75)	N/A	N/A	N/A
Qureshi and Soorae, 2003 (34)	Observational case series	100	N/A	N/A	N/A	15.6 cm^3
Zaraca and Ebner, 2006 (38)	Prospective	31	58.17 ± 11.84	48	N/A	N/A

(Continued)

Table 1. (*Continued*)

Reference	Type of Study	N	Age (*yr*)*	Female Sex (%)	Pathology	Size of Biopsies
Kreider and colleagues, 2007 (32)	Retrospective	68	58 (38–84)	56	UIP 34% Sarcoidosis 9% Honeycomb lung 9% Chronic hypersensitivity 7.5% NSIP 6% DIP 4.5% Normal lung 3% AIP 1.5% Bronchiolitis 1.5% Nonclassifiable 23.5%	N/A
Zhang and Liu, 2010 (39)	Retrospective	189	16–76	N/A	N/A	N/A
Fibla and colleagues, 2012 (29)	Prospective	224	57.1 (25–77)	52.6	IPF 26.1% NSIP 25.1% COP 11.8% Respiratory bronchiolitis 8.2% Sarcoidosis 7.2% AIP 4.6% Inhaled organic substances (pneumonitis due to hypersensitivity) 4.6% PLCH 3% Diffuse ILD associated with connective tissue disease 2.5% DIP 2% Inhaled inorganic substances (pneumoconiosis) 1.5% LIP 1% LAM 1% Pulmonary eosinophilia 1%	N/A
Kayatta and colleagues, 2013 (30)	Retrospective	194	58	48	IPF 42% NSIP 6.7% COP 10% AIP 3.6% RBILD 0.5% DIP 3.6% ILD, not specified 11.6% Granulomatous disease 5.2% HP 5.6% Other 10.8%	N/A
Ambrogi and Mineo, 2014 (26)	Prospective	40	61 (48–70)	N/A	IPF 62.5% NSIP 12.5% COP 10% AIP 5% RBILD 5% DIP 5% ILD, not specified 12.5% Granulomatous disease 5% HP 5% Other 10%	6.4 (5.3–6.9) cm^3
Morris and Zamvar, 2014 (33)	Retrospective	79	58.9	53	HP 31.8% UIP 28.8% CTD 13.6% NSIP 12.1% Sarcoidosis 10.6% Aspiration 4.6% PLCH 4.6% Infection 4.6% Stoneworkers pneumoconiosis 3.0% End-stage fibrosis 3.0% Other 31.8%	16.8 cm^2
Rotolo and colleagues, 2015 (35)	Retrospective	151	N/A	N/A	Sarcoidosis 29.8% UIP 24.2% COP 18.6% NSIP 8.1%	N/A

(Continued)

Table 1. (*Continued*)

Reference	Type of Study	N	Age (*yr*)*	Female Sex (%)	Pathology	Size of Biopsies
Samejima and colleagues, 2015 (36)	Retrospective	285	65 (18–85)	43	IPF 21% NSIP 21% Fibrotic NSIP 18% Cellular NSIP 2.45% COP 1.4% AIP 0.35% RBILD 0.35% Unclassified 15% Collagen vascular disease associated 16% Chronic HP 5% Lymphoproliferative disorders 4.9% Summer-type HP 1.4% Pneumoconiosis 1.4% Acute lung injury 1.05% Drug-induced pneumonia 0.7% Bronchitis 0.7% Eosinophilic pneumonia 0.35% Upper lobe IPF 0.35% PLCH 0.35% Pulmonary alveolar proteinosis 0.35% Alveolar hemorrhage 0.35% Pulmonary ossification 0.35% Sarcoidosis 0.35% Asbestosis 0.35% Other granulomatous disease 0.35% Others 0.7	N/A
Khalil and colleagues, 2016 (31)	Retrospective	115	N/A	N/A	BOOP 8.7% DIP 11.3% Extrinsic allergic alveolitis 10.4% IPF 3.5% UIP 27% NSIP 14% DAD 0.87% LH 1.7% Sarcoidosis 5.21% HP 3.5% Lymphomatoid granulomatosis 0.87% Follicular bronchiolitis 0.87% Mild nonspecific inflammation 6% Adenocarcinoma 0.87% Alveolar pneumonitis 0.87% Goodpasture's syndrome 0.87% Tuberculosis 1.7% Rheumatoid 0.87% Nonspecific fibrosis (emphysematous) 0.87%	$3 \times 3 \times 2$ cm

Definition of abbreviations: AIP = acute interstitial pneumonitis; BO = bronchiolitis obliterans; BOOP = bronchiolitis obliterans organizing pneumonia; CB = constrictive bronchiolitis; COP = cryptogenic organizing pneumonia; CTD = connective tissue disease related; DAD = diffuse alveolar damage; DIP = desquamative interstitial pneumonia; FB = follicular bronchiolitis; HP = hypersensitivity pneumonitis; ILD = lung disease; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; LH = Langerhan's histiocytosis; LIP = lymphocytic interstitial pneumonia; N/A = data not available; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; p-ANCA = perinuclear anti-neutrophil cytoplasmic antibodies; PAP = pulmonary alveolar proteinosis; PCP = *Pneumocystis* pneumonia; PLCH = pulmonary Langerhans cell histiocytosis; RBILD = respiratory bronchiolitis interstitial lung disease; SAR = sarcoidosis; UIP = usual interstitial pneumonia.
*Data presented as mean (SD or range).

benign diagnosis that was overturned when a follow-up diagnostic procedure (VATS or OLB after an initial lung cryobiopsy or OLB after an initial VATS) was performed (FN). We also included data on *a priori* selected safety outcomes, specifically, incidence of endobronchial bleeding, pneumothorax, and 30- to 60-day mortality post transbronchial lung cryobiopsy, and incidence of prolonged air leak (defined as air leak lasting for $\geq$4 d post VATS), as well as the 30- to 60-day mortality post VATS.

Statistical Analysis

Extracted data were pooled with weighted averages using a random effects model. The weight of each study was proportionate to its sample size. Comprehensive Meta-Analysis (CMA) version 2.2.064 software was used to compute the pooled diagnostic

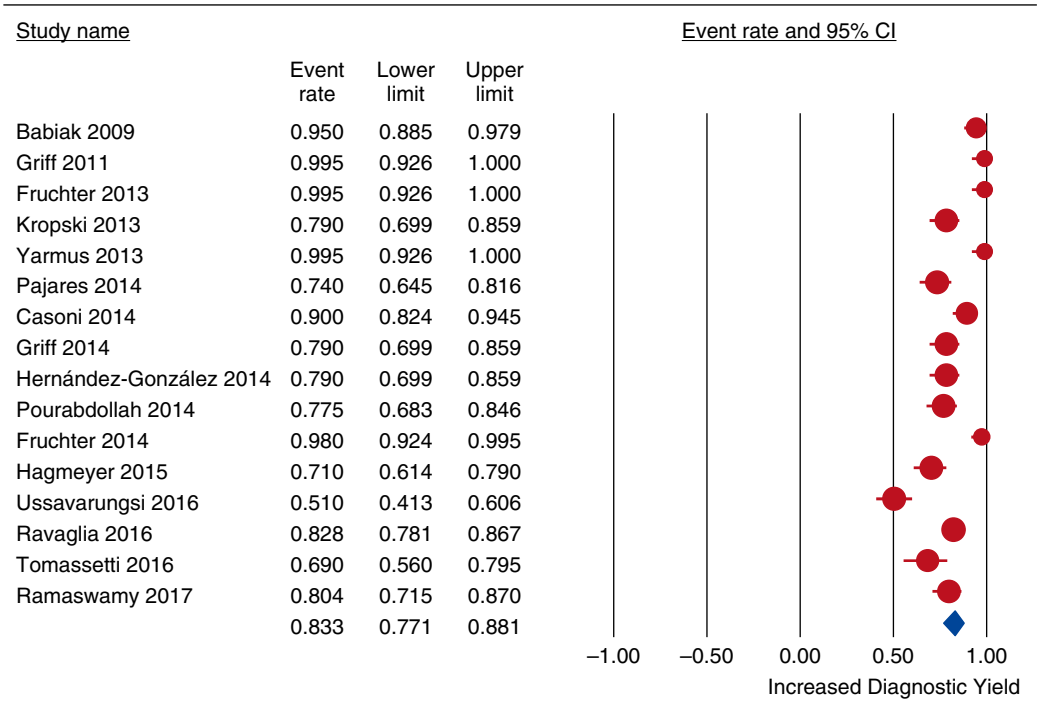

Figure 2. Meta-analysis of the diagnostic yield of transbronchial lung cryobiopsy. The size of the *circle* indicates the weight of the effect size as determined by the number of studies and participants. The *diamond* indicates the pooled effect. CI = confidence interval.

yield. Meta-DiSc version 1.4 was used to pool the data on sensitivity and specificity for each data set, and the results were presented by constructing forest plots. A *P* value less than 0.05 was considered statistically significant. Diagnostic odds ratios (DORs) were also computed, but, as no diagnostic threshold exists for histological diagnoses, regression of the log DOR on the measure of diagnostic threshold was not applicable to this meta-analysis.

Mathematically, the DOR was defined as:

$$DOR = [TP/FN]/[FP/TN].$$

Meta-DiSc was also used to construct SROCs, as described by Moses and colleagues (13). From the SROC, the area under the curve with SE was also calculated. Heterogeneity was assessed with I^2 index.

Data on safety profile were analyzed using Comprehensive Meta-Analysis version 2.2.064 software.

Results

The study selection process is shown in Figure 1. A total of 16 studies (6–8, 12, 14–25) for transbronchial lung cryobiopsy and 14 studies (26–39) for VATS were included in the meta-analyses of diagnostic test accuracy. This meta-analysis analyzed data from a total of 2,533 patients who underwent transbronchial lung cryobiopsy (N = 642) and VATS (N = 1,594). Table 1 lists the demographics of the study population and the final histopathologic diagnosis.

Test Performance

Data for analysis of pooled diagnostic yield were available for 16 of 16 of transbronchial lung cryobiopsy studies (6–8, 12, 14–25) and 14 of 14 VATS studies (26–39). The pooled diagnostic yields for transbronchial lung cryobiopsy and VATS were 83.7% (76.9–88.8%; I^2, 86%) and 92.7% (87.6–95.8%; I^2, 85%), respectively (Figures 2 and 3).

Sensitivity and Specificity

Only 14 (6–8, 14–24) out of the total 16 transbronchial lung cryobiopsy studies had data that allowed for computation of pooled sensitivity, specificity, DORs, and SROC. All of the included VATS studies were analyzed for pooled sensitivity, specificity, DORs, and SROC.

Pooled sensitivity and specificity of transbronchial lung cryobiopsy were 87% (85–89%; I^2, 94%) and 57% (40–73%; I^2, 0%), respectively. Pooled sensitivity and specificity of VATS were 91% (89–92%; I^2, 91%) and 58% (31–81%; I^2, 0%), respectively.

Diagnostic Odds Ratio

Diagnostic odds ratio for transbronchial lung cryobiopsy and VATS were 25.53 (8.92–73.04) and 21.06 (7.08–62.60), respectively (Figures 4 and 5).

SROC

SROC from the data on transbronchial lung cryobiopsy and VATS was calculated as 0.85 (SE = 0.07) and 0.74 (SE = 0.12), respectively (Figures 6 and 7).

Safety Outcomes

Safety outcomes are tabulated in Tables 2 and 3. The incidence of grade 2 (moderate to severe) endobronchial bleeding requiring bronchoscopic intervention reported in 16 studies (6–8, 14–25) (where these data were available) after transbronchial lung

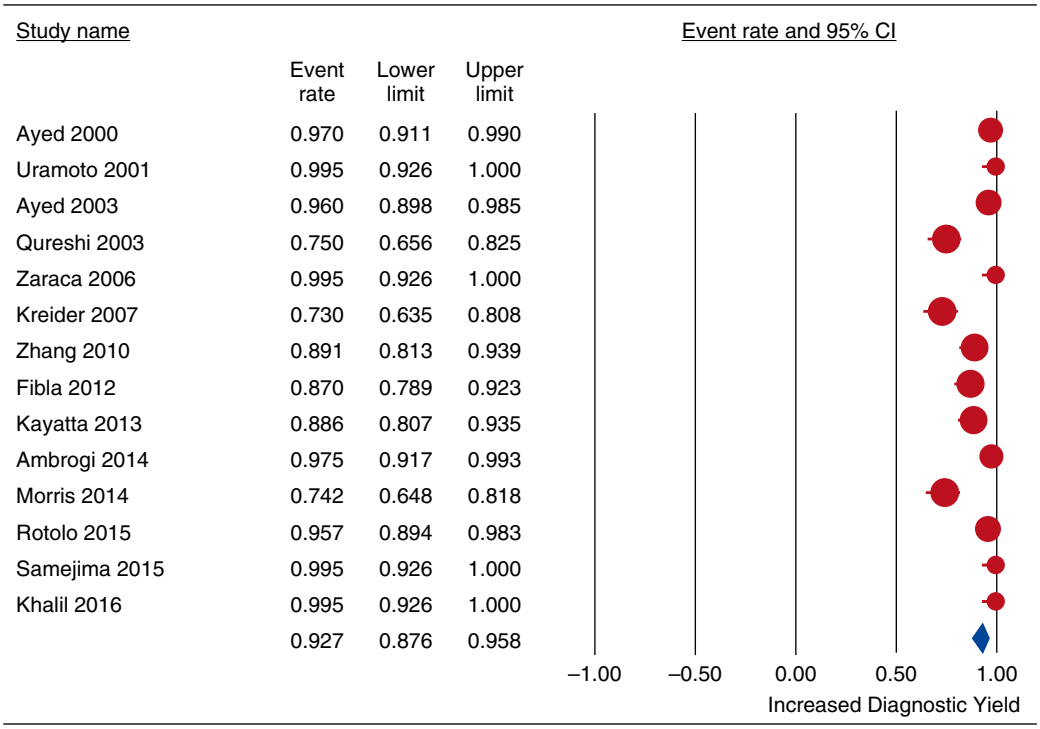

Figure 3. Meta-analysis of the diagnostic yield of video-assisted thoracoscopic lung biopsy. The size of the *circle* indicates the weight of the effect size as determined by the number of studies and participants. The *diamond* indicates the pooled effect. CI = confidence interval.

cryobiopsy was 4.9% (2.2–10.7%), as shown in Figure 8. Only four studies (8, 18, 19, 21) reported high incidence (Table 2). The incidence of pneumothorax reported in 13 studies (6–8, 12, 14–25) was 9.5% (5.9–14.9%), as shown in Figure 9. Only five studies (15, 18, 19, 23, 25) reported high incidence (Table 2). Most studies on VATS did not report data on the incidence of prolonged air leak (Table 3). In the five studies (29, 32, 33, 35, 36) that reported these data, the incidence was 2% (0.9–4%), as shown in Figure 10. Figure 11 compares the incidence of 30- to 60-day

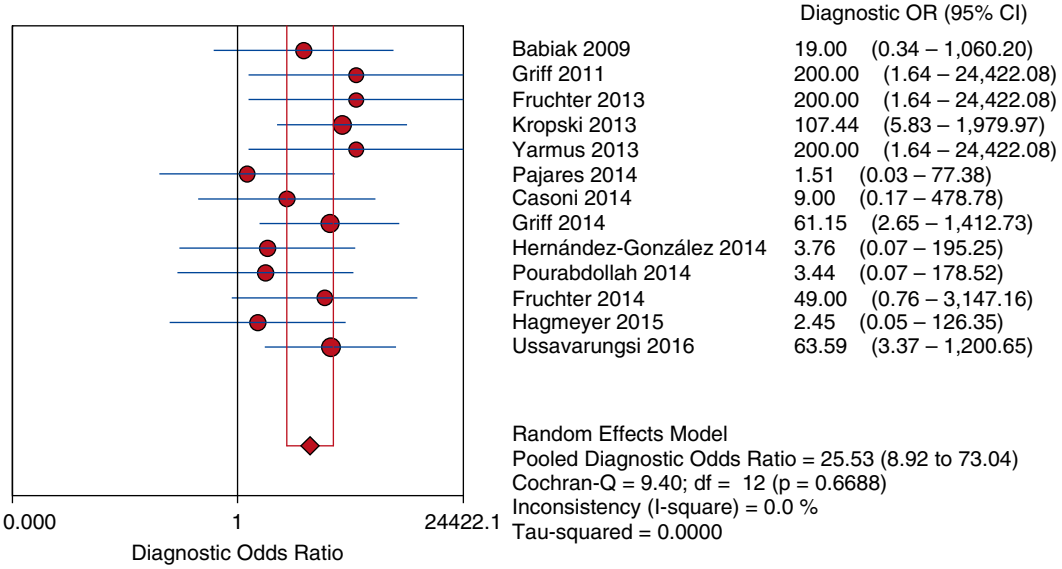

Figure 4. Pooled diagnostic odds ratio (OR) of transbronchial lung cryobiopsy. The size of the *circle* indicates the weight of the effect size as determined by the number of studies and participants. The *diamond* indicates the pooled effect. CI = confidence interval.

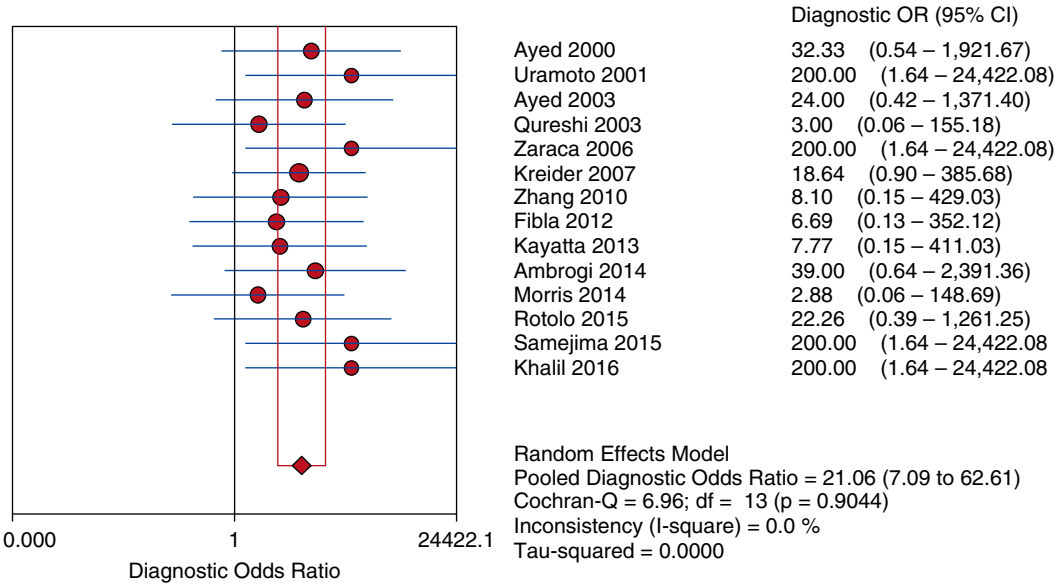

Figure 5. Pooled diagnostic odds ratio (OR) of video-assisted thoracoscopic lung biopsy. The size of the *circle* indicates the weight of the effect size as determined by the number of studies and participants. The *diamond* indicates the pooled effect. CI = confidence interval.

mortality after both procedures: 0.7% (0.4–1.2%) after transbronchial lung cryobiopsy and 1.8% (1.0–3%) after VATS. Only three studies (12, 15, 25) reported mortality after transbronchial lung cryobiopsy, which was believed to be secondary to acute exacerbation of IPF presumably resulting from procedural complications. The incidence of 30- to 60-day mortality after VATS was 1.8%. This was either due to acute respiratory failure (35, 39), pulmonary embolism (39), acute exacerbation of pulmonary fibrosis (32, 39), pulmonary infection (39), sepsis (33), or unknown (30).

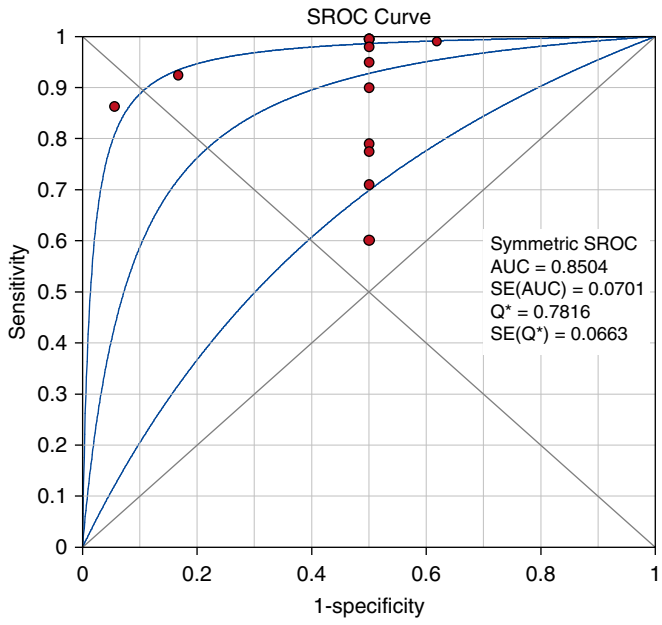

Figure 6. Summary receiver operating curve (SROC) for transbronchial lung cryobiopsy. AUC = area under the curve; Q = heterogeneity.

Discussion

With a 4.9% (2.2–10.7%) incidence of grade 2 endobronchial bleeding and 9.5% (5.9–14.9%) incidence of pneumothorax after transbronchial lung cryobiopsy (Figures 8 and 9), 0.7% 30- to 60-day mortality post lung cryobiopsy compared with 1.8% with VATS (Figure 11), reported median hospitalization time of 2.6 days compared with the 6.1 days with VATS ($P < 0.0001$), and diagnostic test accuracy approaching that of VATS, transbronchial lung cryobiopsy should be considered an alternative to surgical lung biopsy (OLB or VATS) or attempted first in patients with DPLDs, elderly patients, and those with significant comorbidities. The incidence of post-procedure pneumothorax in our meta-analysis is higher than that reported for the conventional transbronchial forceps biopsy (6% [3.2–9.6%]) (5).

However, the increased diagnostic yield (84% with transbronchial lung cryobiopsy vs. 64% with conventional forceps biopsy) and the increased sample size provided by transbronchial lung cryobiopsy need to be considered in clinical practice. The diagnostic yield of 84% with transbronchial lung cryobiopsy is comparatively less than the 92.7% diagnostic yield with VATS, as shown in our meta-analysis. With a sensitivity of 87% and specificity of 57%, transbronchial

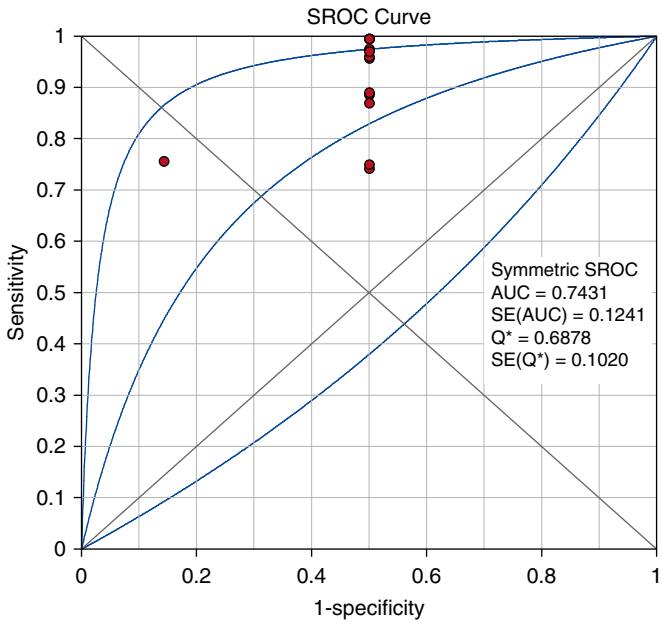

Figure 7. Summary receiver operating curve (SROC) for video-assisted thoracoscopic lung biopsy. AUC = area under the curve; Q = heterogeneity.

lung cryobiopsy lags somewhat behind VATS, which has a relatively higher sensitivity and specificity (91% and 58%, respectively). Variable diagnostic yield with transbronchial lung cryobiopsy in different studies could partially be explained by the size of the cryoprobes: 70 to 95% with a 2.4-mm probe (6, 8, 14, 15, 18, 21) and 79 to 80% with a 1.9-mm probe (17, 19, 20).

Furthermore, optimal tissue yield can also be affected by several factors: number of biopsies, short versus long freeze time, operating room versus bronchoscopy area, method of sedation (moderate sedation vs. a deeply sedated patient), method of bronchoscopy (flexible vs. rigid), and measures to treat complications such as hemoptysis (prophylactically using Fogarty balloon). The use of general anesthesia could theoretically reduce the risk of iatrogenic complications (less patient movement and coughing) and improve tissue yield. However, transbronchial lung cryobiopsy under moderate sedation (with preservation of spontaneous breathing) has been shown to perform just as well, with a lower risk of iatrogenic pneumothorax than transbronchial lung cryobiopsy under general anesthesia (18). Although an increased number of cryoprobe biopsies would theoretically improve the diagnostic yield, it could also lead to more bleeding and pneumothorax complications (18). Typically, two to four biopsies are considered sufficient for pathological examination. Our meta-analysis also shows a trend for 2.4-mm size cryoprobe to be associated with significant pneumothorax rate (12, 18, 23, 25). Although the use of flexible versus rigid bronchoscopy and choice of moderate versus deep sedation are dependent on the comfort level of the bronchoscopist, we recommend, at the very least, to have a bronchial blocker in place and the

Table 2. Safety outcomes for transbronchial lung cryobiopsy

Reference	Incidence of Endobronchial Bleeding ⩾Grade 2 (%)	Incidence of Pneumothorax (%)	Incidence of 30- to 60-Day Mortality (%)	Hospitalizations Days Post Procedure
Babiak and colleagues, 2009 (14)	0	4.8	0	N/A
Griff and colleagues, 2011 (7)	0	0	0	N/A
Fruchter and colleagues, 2013 (16)	6.6	0	0	N/A
Kropski and colleagues, 2013 (20)	0	0	0	1
Yarmus and colleagues, 2013 (22)	4.76	0	0	1
Casoni and colleagues, 2014 (15)	1.40	28	1.40	3 (0–9)
Pajares and colleagues, 2014 (8)	56	7.7	0	∼1
Griff and colleagues, 2014 (17)	0	0	0	N/A
Hernández-González and colleagues, 2015 (19)	21	12	0	N/A
Pourabdollah and colleagues, 2016 (21)	20	N/A	N/A	N/A
Fruchter and colleagues, 2014 (6)	4.0	26	0	1
Hagmeyer and colleagues, 2016 (18)	39	19	0	N/A
Ussavarungsi and colleagues, 2017 (24)	1.4	12	0	1–3
Tomassetti and colleagues, 2016 (25)	0	33	1.7	3 (0–9)
Ravaglia and colleagues, 2016 (12)	N/A	20	0.33	
Ramaswamy and colleagues, 2016 (23)	1.8	19.6	0	N/A

Definition of abbreviation: N/A = data not available.

Table 3. Safety outcomes for video-assisted thoracoscopic lung biopsy

Reference	Incidence of Prolonged Air Leak Lasting ⩾ 4 d	Incidence of 30- to 60-Day Mortality	Hospitalizations Days Post Procedure
Ayed and Raghunathan, 2000 (28)	N/A	0	3
Uramoto and colleagues, 2001 (37)	N/A	0	N/A
Ayed, 2003 (27)	N/A	1.2	N/A
Qureshi and Soorae, 2003 (34)	N/A	N/A	3
Zaraca and Ebner, 2006 (38)	N/A	0	N/A
Kreider and colleagues, 2007 (32)	4.4	4.4	Prolonged hospital stay (>5 d): in only 4.4% of patients
Zhang and Liu, 2010 (39)	N/A	1.4	N/A
Fibla and colleagues, 2012 (29)	0.9	0	89.7% discharged within 48 h
Kayatta and colleagues, 2013 (30)	N/A	6.7	N/A
Ambrogi and Mineo, 2014 (26)	N/A	0	3.7 (1–6)
Morris and Zamvar, 2014 (33)	1.5	1.5	3.5
Rotolo and colleagues, 2015 (35)	11.8	3.1	N/A
Samejima and colleagues, 2015 (36)	0.7	0	N/A
Khalil and colleagues, 2016 (31)	N/A	0	2–3

Definition of abbreviation: N/A = data not available.

bronchoscopy room equipped with ultrasound and emergency chest tube equipment, to be prepared for any potential immediate complications post procedure.

Although baseline FVC affects the suitability of the candidate for surgical lung biopsy and predicts the risk of adverse events postsurgery (40, 41), complications after transbronchial lung cryobiopsy seem to occur independent of lung function values (12). Median time of hospitalization after surgical lung biopsy for any cause is between 4 and 8 days, elderly patients being at higher risk for prolonged hospitalization (42, 43). Prolonged hospitalization along with operating room time, anesthesia time, and professional charges of different disciplinary teams increase the associated costs with VATS or any surgical lung biopsy. According to a recent cost-effective analysis conducted in Spain by Hernández-González and colleagues (19), cryobiopsies have the potential to save about €31,451.97 (€953.09/patient) for outpatient surgical lung biopsy

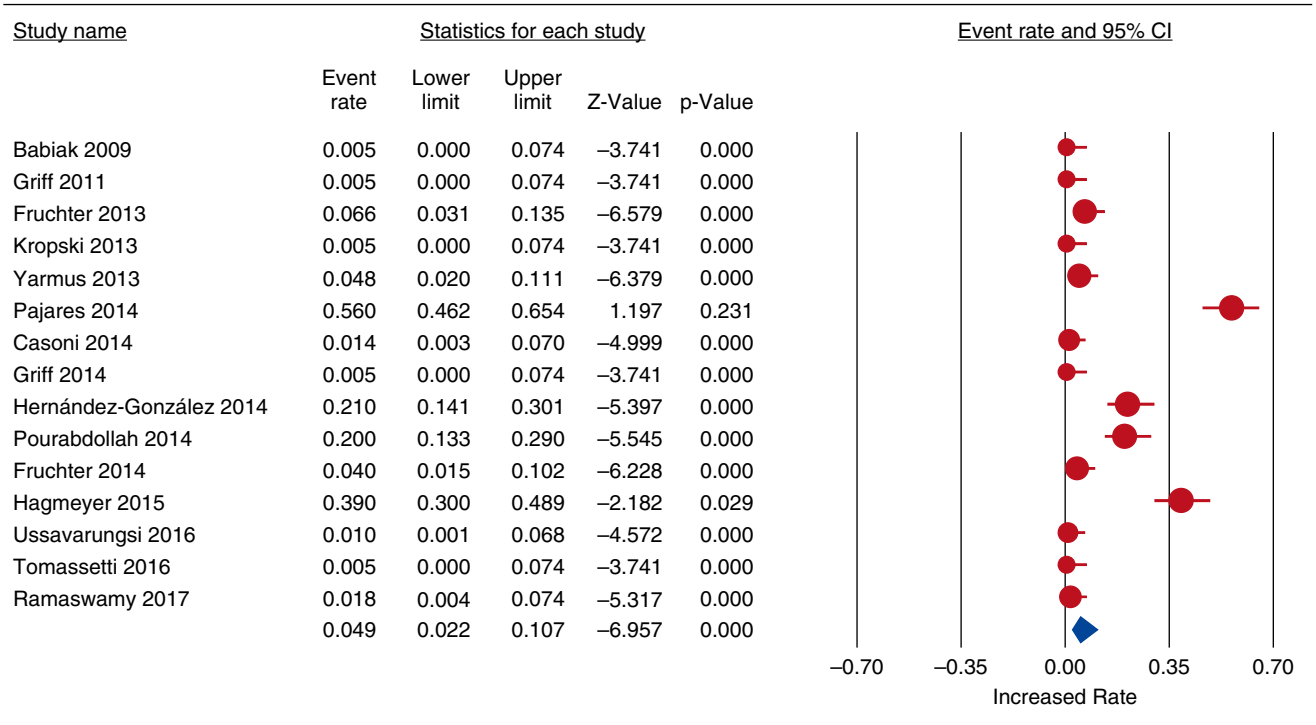

Figure 8. Endobronchial bleeding with transbronchial lung cryobiopsy. The size of the *circle* indicates the weight of the effect size as determined by the number of studies and participants. The *diamond* indicates the pooled effect. CI = confidence interval.

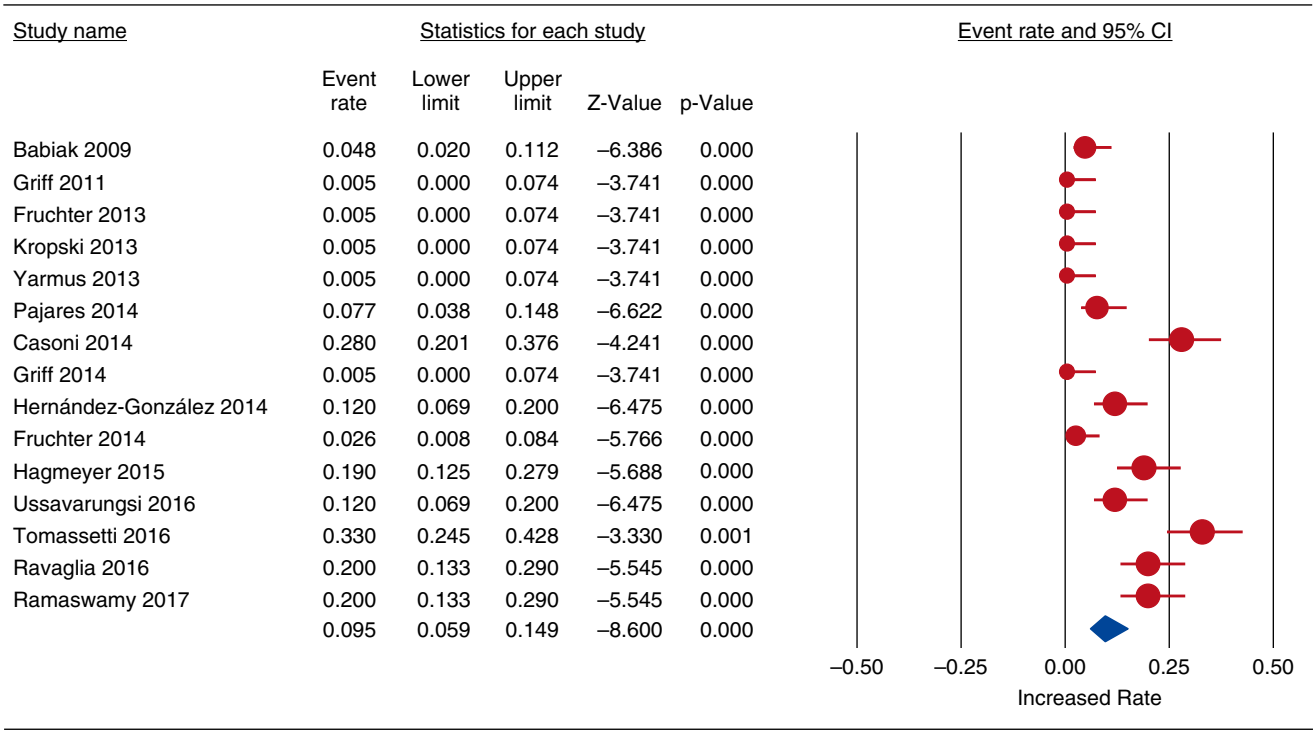

Figure 9. Pneumothorax after transbronchial lung cryobiopsy. The size of the *circle* indicates the weight of the effect size as determined by the number of studies and participants. The *diamond* indicates the pooled effect. CI = confidence interval.

procedures and €59,846.29 (€1925.29/patient) for surgical lung biopsies requiring hospitalization. Similarly, on the basis of a theoretical cost analysis, Sharp and colleagues (5) report that transbronchial lung cryobiopsy has the potential to save £210 per patient in the first year and £647 in subsequent years.

The yield of lung parenchyma resulting in clinically useful histopathological diagnoses from conventional transbronchial biopsy specimens is on the order of 38% (44), and the yield of nonspecific inflammation and fibrosis varies from 21 to 48% (45). Thus, conventional transbronchial biopsy does not compare well with transbronchial lung cryobiopsy, which has a specificity of 57% for DPLDs. In a cross-sectional study of 117 patients with UIP on high-resolution computed tomography, where half of the patients underwent either transbronchial lung cryobiopsy or surgical lung biopsy, Tomassetti and colleagues (25) observed that the proportion of IPF cases diagnosed with a high degree of confidence increased from 16 to 63% after adding cryobiopsy in the process. Pathologists experienced in cryobiopsy analysis had an agreement nearly equivalent to surgical lung biopsy (0.73 for cryobiopsy vs. 0.86 for surgical lung biopsy), and the diagnoses obtained by multidisciplinary team discussion were similarly distributed in the two groups (transbronchial lung cryobiopsy and surgical lung biopsy) (25). The current gold standard for the diagnosis of interstitial lung diseases, when surgical lung biopsy is incorporated into a multidisciplinary discussion, is limited by modest interobserver agreement by expert pathologists: "moderate to good" agreement for those interpreting ILD patterns, "good" agreement for IPF and connective tissue disease–related ILD, "moderate" agreement for nonspecific interstitial pneumonia, and "fair" agreement for hypersensitivity pneumonitis (46).

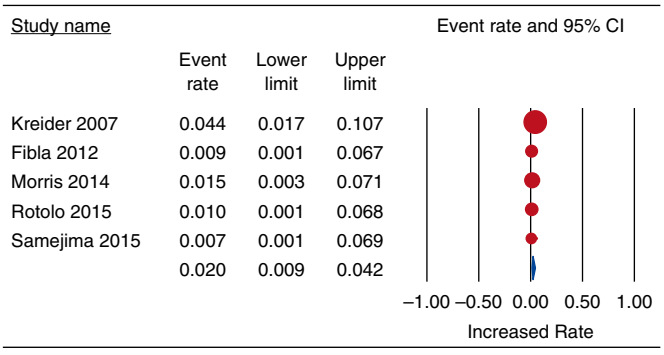

Figure 10. Prolonged air leak after video-assisted thoracoscopic lung biopsy. The size of the *circle* indicates the weight of the effect size as determined by the number of studies and participants. The *diamond* indicates the pooled effect. CI = confidence interval.

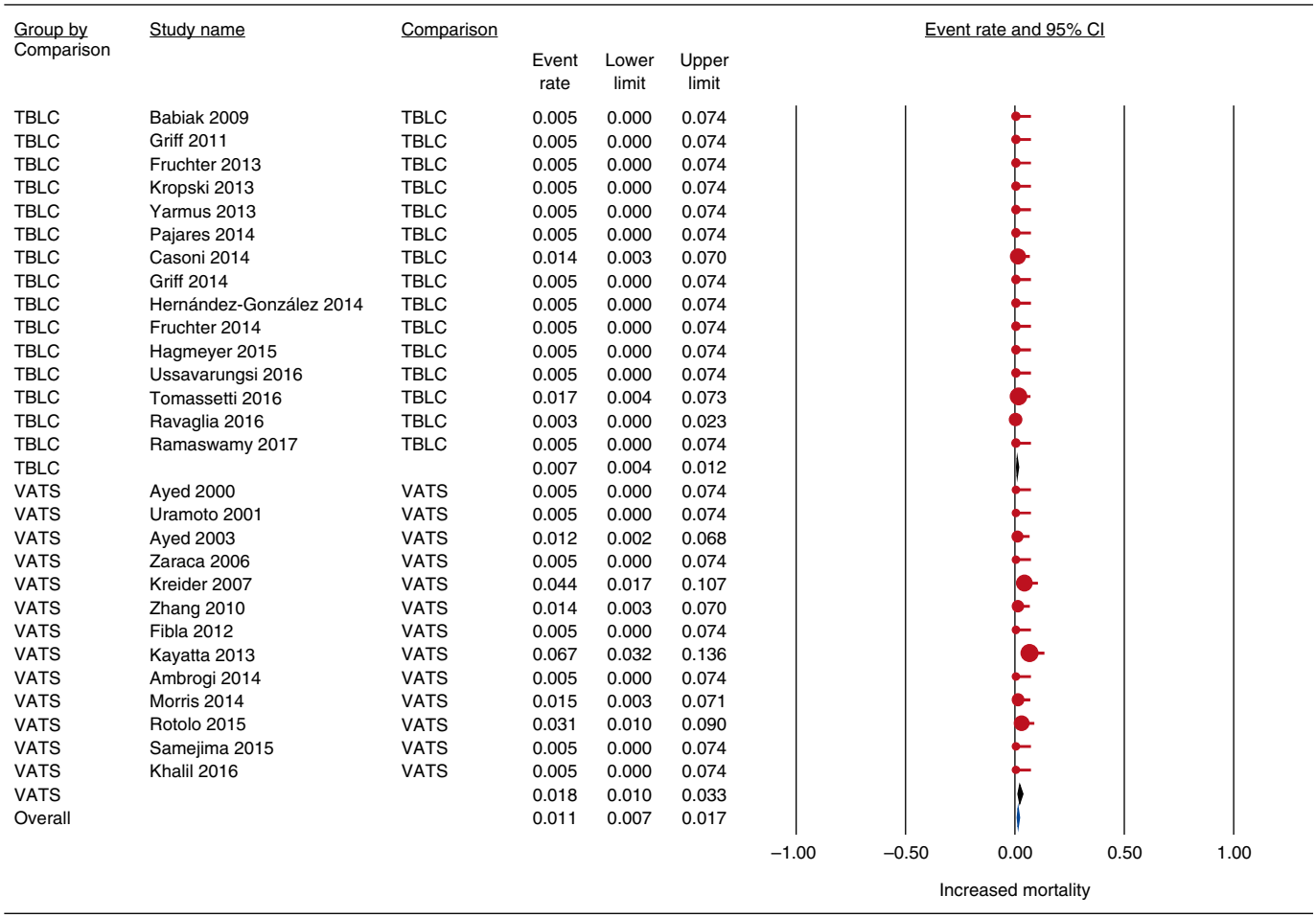

Figure 11. Comparison of 30- to 60-day mortality between transbronchial lung cryobiopsy and video-assisted thoracoscopic lung biopsy. The size of the *circle* indicates the weight of the effect size as determined by the number of studies and participants. The *diamond* indicates the pooled effect. CI = confidence interval; TBLC = transbronchial lung cryobiopsy; VATS = video-assisted thoracoscopic lung biopsy.

Our meta-analysis confirms the results of prior meta-analyses (5, 10–12) that reported a pooled diagnostic yield of 81 to 85% for transbronchial lung cryobiopsy and 91 to 98% for VATS. However, there are important differences between ours and prior meta-analyses (5, 10–12). Unlike our meta-analysis, none of the prior meta-analyses (5, 10–12) analyzed other measures of diagnostic test accuracy (pooled sensitivity, specificity, diagnostic odds ratio, and SROC). Our meta-analysis excluded data from abstracts and conference proceedings, which were included in the pooled analyses by others (5, 12). Although the pooled incidence of post-procedural pneumothorax in our study (9.5% [5.9–14.9%]) is similar to what has been previously reported, that of moderate to severe bleeding differs greatly from a few (5, 10, 11). On the latter, our results are in contrast, probably because ours is a pooled data set from 16 studies, whereas, for example, Johannson and colleagues' (11) is from 4 studies, Sharp and colleagues' (5) is from 11 studies (including an abstract), Ravaglia and colleagues' (12) is from 12 studies (including abstracts), and Ganganah and colleagues' (10) is only from 3 studies.

Limitations

Our meta-analysis has a few limitations. We did not construct funnel plots for assessing publication bias. This was decided *a priori* on the basis of the evidence that the unique features of a meta-analysis of diagnostic test accuracy do not allow for the application of Begg, Egger, and Macaskill tests of funnel plot asymmetry and can be potentially misleading (47, 48). Estimates of sensitivity and diagnostic yield showed high heterogeneity, and the design of this meta-analysis limited us in exploring potential sources of heterogeneity. Heterogeneity can be explained by technical/procedural differences between bronchoscopists and selection bias in studies. Moreover, the reported endobronchial bleeding could have been underreported in different studies.

Conclusions

In conclusion, our meta-analysis demonstrates that in the evaluation of DPLDs, the diagnostic performance of

transbronchial lung cryobiopsy is comparable to that of VATS. However, the risk of potential procedural complications, such as pneumothorax and moderate to severe bleeding, need to be weighed in when considering this procedure. Further research with head-to-head comparisons of transbronchial lung cryobiopsy and VATS or OLB, the current gold standard for surgically obtained lung tissue, is warranted to compare the diagnostic accuracy of both procedures in the evaluation of DPLD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Maher TM. A clinical approach to diffuse parenchymal lung disease. *Immunol Allergy Clin North Am* 2012;32:453–472.
2 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, *et al*.; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
3 Xaubet A, Ancochea J, Bollo E, Fernández-Fabrellas E, Franquet T, Molina-Molina M, Montero MA, Serrano-Mollar A; Sociedad Española de Neumología y Cirugía Torácica (SEPAR) Research Group on Diffuse Pulmonary Diseases. Guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis. *Arch Bronconeumol* 2013;49:343–353.
4 Hodnett PA, Naidich DP. Fibrosing interstitial lung disease: a practical high-resolution computed tomography-based approach to diagnosis and management and a review of the literature. *Am J Respir Crit Care Med* 2013;188:141–149.
5 Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease-a systematic review and cost analysis. *QJM* 2017;110:207–214.
6 Fruchter O, Fridel L, El Raouf BA, Abdel-Rahman N, Rosengarten D, Kramer MR. Histological diagnosis of interstitial lung diseases by cryo-transbronchial biopsy. *Respirology* 2014;19:683–688.
7 Griff S, Ammenwerth W, Schönfeld N, Bauer TT, Mairinger T, Blum TG, Kollmeier J, Grüning W. Morphometrical analysis of transbronchial cryobiopsies. *Diagn Pathol* 2011;6:53.
8 Pajares V, Puzo C, Castillo D, Lerma E, Montero MA, Ramos-Barbón D, Amor-Carro O, Gil de Bernabé A, Franquet T, Plaza V, *et al*. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology* 2014;19:900–906.
9 Reif F. Simple applications of macroscopic thermodynamics. In: Fundamentals of Statistical and Thermal Physics. New York, NY: McGraw-Hill; 1965.
10 Ganganah O, Guo SL, Chiniah M, Li YS. Efficacy and safety of cryobiopsy versus forceps biopsy for interstitial lung diseases and lung tumours: a systematic review and meta-analysis. *Respirology* 2016;21:834–841.
11 Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease: a systematic review and metaanalysis. *Ann Am Thorac Soc* 2016;13:1828–1838.
12 Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, Dubini A, Tantalocco P, Sanna S, Negri E, *et al*. Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. *Respiration* 2016;91:215–227.
13 Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med* 1993;12:1293–1316.
14 Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, Hetzel M. Transbronchial cryobiopsy: a new tool for lung biopsies. *Respiration* 2009;78:203–208.
15 Casoni GL, Tomassetti S, Cavazza A, Colby TV, Dubini A, Ryu JH, Carretta E, Tantalocco P, Piciucchi S, Ravaglia C, *et al*. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PLoS One* 2014;9:e86716.
16 Fruchter O, Fridel L, Rosengarten D, Rahman NA, Kramer MR. Transbronchial cryobiopsy in immunocompromised patients with pulmonary infiltrates: a pilot study. *Lung* 2013;191:619–624.
17 Griff S, Schönfeld N, Ammenwerth W, Blum TG, Grah C, Bauer TT, Grüning W, Mairinger T, Wurps H. Diagnostic yield of transbronchial cryobiopsy in non-neoplastic lung disease: a retrospective case series. *BMC Pulm Med* 2014;14:171.
18 Hagmeyer L, Theegarten D, Wohlschläger J, Treml M, Matthes S, Priegnitz C, Randerath WJ. The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnostic algorithm of interstitial lung disease. *Clin Respir J* 2016;10:589–595.
19 Hernández-González F, Lucena CM, Ramírez J, Sánchez M, Jimenez MJ, Xaubet A, Sellares J, Agustí C. Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost-effectiveness analysis. *Arch Bronconeumol* 2015;51:261–267.
20 Kropski JA, Pritchett JM, Mason WR, Sivarajan L, Gleaves LA, Johnson JE, Lancaster LH, Lawson WE, Blackwell TS, Steele MP, *et al*. Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. *PLoS One* 2013;8:e78674.
21 Pourabdollah M, Shamaei M, Karimi S, Karimi M, Kiani A, Jabbari HR. Transbronchial lung biopsy: the pathologist's point of view. *Clin Respir J* 2016;10:211–216.
22 Yarmus L, Akulian J, Gilbert C, Illei P, Shah P, Merlo C, Orens J, Feller-Kopman D. Cryoprobe transbronchial lung biopsy in patients after lung transplantation: a pilot safety study. *Chest* 2013;143:621–626.
23 Ramaswamy A, Homer R, Killam J, Pisani MA, Murphy TE, Araujo K, Puchalski J. Comparison of transbronchial and cryobiopsies in evaluation of diffuse parenchymal lung disease. *J Bronchology Interv Pulmonol* 2016;23:14–21.
24 Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial cryobiopsy in diffuse parenchymal lung disease: retrospective analysis of 74 cases. *Chest* 2017;151:400–408.
25 Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, Sverzellati N, Carloni A, Carretta E, Buccioli M, *et al*. Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;193:745–752.
26 Ambrogi V, Mineo TC. VATS biopsy for undetermined interstitial lung disease under non-general anesthesia: comparison between uniportal approach under intercostal block vs. three-ports in epidural anesthesia. *J Thorac Dis* 2014;6:888–895.
27 Ayed AK. Video-assisted thoracoscopic lung biopsy in the diagnosis of diffuse interstitial lung disease: a prospective study. *J Cardiovasc Surg (Torino)* 2003;44:115–118.
28 Ayed AK, Raghunathan R. Thoracoscopy versus open lung biopsy in the diagnosis of interstitial lung disease: a randomised controlled trial. *J R Coll Surg Edinb* 2000;45:159–163.
29 Fibla JJ, Molins L, Blanco A, Royo I, Martínez Vallina P, Martínez N, García Barajas S, Gomez A, Estors M, Moldes M, *et al*. Video-assisted thoracoscopic lung biopsy in the diagnosis of interstitial lung disease: a prospective, multi-center study in 224 patients. *Arch Bronconeumol* 2012;48:81–85.
30 Kayatta MO, Ahmed S, Hammel JA, Fernandez F, Pickens A, Miller D, Staton G Jr, Veerarghavan S, Force S. Surgical biopsy of suspected interstitial lung disease is superior to radiographic diagnosis. *Ann Thorac Surg* 2013;96:399–401.
31 Khalil M, Cowen M, Chaudhry M, Loubani M. Single versus multiple lung biopsies for suspected interstitial lung disease. *Asian Cardiovasc Thorac Ann* 2016;24:788–791.
32 Kreider ME, Hansen-Flaschen J, Ahmad NN, Rossman MD, Kaiser LR, Kucharczuk JC, Shrager JB. Complications of video-assisted thoracoscopic lung biopsy in patients with interstitial lung disease. *Ann Thorac Surg* 2007;83:1140–1144.

33 Morris D, Zamvar V. The efficacy of video-assisted thoracoscopic surgery lung biopsies in patients with interstitial lung disease: a retrospective study of 66 patients. *J Cardiothorac Surg* 2014;9:45.
34 Qureshi RA, Soorae AA. Efficacy of thoracoscopic lung biopsy in interstitial lung diseases: comparison with open lung biopsy. *J Coll Physicians Surg Pak* 2003;13:600–603.
35 Rotolo N, Imperatori A, Dominioni L, Facchini A, Conti V, Castiglioni M, Spanevello A. Efficacy and safety of surgical lung biopsy for interstitial disease: experience of 161 consecutive patients from a single institution in Italy. *Sarcoidosis Vasc Diffuse Lung Dis* 2015;32: 251–258.
36 Samejima J, Tajiri M, Ogura T, Baba T, Omori T, Tsuboi M, Masuda M. Thoracoscopic lung biopsy in 285 patients with diffuse pulmonary disease. *Asian Cardiovasc Thorac Ann* 2015;23:191–197.
37 Uramoto H, Osaki T, Nose N, Ichiki Y, Imoto H, Yoshimatsu T, Oyama T, Yasumoto K. Treatment and results of interstitial lung diseases in video assisted thoracoscopic lung biopsy [in Japanese]. *J UOEH* 2001;23: 45–50.
38 Zaraca F, Ebner H. Video-assisted thoracoscopic biopsy in the diagnosis of idiopathic interstitial lung disease [in Italian]. *Chir Ital* 2006;58:569–576.
39 Zhang D, Liu Y. Surgical lung biopsies in 418 patients with suspected interstitial lung disease in China. *Intern Med* 2010;49:1097–1102.
40 Nguyen W, Meyer KC. Surgical lung biopsy for the diagnosis of interstitial lung disease: a review of the literature and recommendations for optimizing safety and efficacy. *Sarcoidosis Vasc Diffuse Lung Dis* 2013;30:3–16.
41 Park JH, Kim DK, Kim DS, Koh Y, Lee SD, Kim WS, Kim WD, Park SI. Mortality and risk factors for surgical lung biopsy in patients with idiopathic interstitial pneumonia. *Eur J Cardiothorac Surg* 2007;31: 1115–1119.
42 Plönes T, Osei-Agyemang T, Elze M, Palade E, Wagnetz D, Loop T, Kayser G, Passlick B. Morbidity and mortality in patients with usual interstitial pneumonia (UIP) pattern undergoing surgery for lung biopsy. *Respir Med* 2013;107:629–632.
43 Rena O, Casadio C, Leo F, Giobbe R, Cianci R, Baldi S, Rapellino M, Maggi G. Videothoracoscopic lung biopsy in the diagnosis of interstitial lung disease. *Eur J Cardiothorac Surg* 1999;16:624–627.
44 Andersen HA. Transbronchoscopic lung biopsy for diffuse pulmonary diseases: results in 939 patients. *Chest* 1978;73:734–736.
45 Poe RH, Utell MJ, Israel RH, Hall WJ, Eshleman JD. Sensitivity and specificity of the nonspecific transbronchial lung biopsy. *Am Rev Respir Dis* 1979;119:25–31.
46 Walsh SL, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, Nunes H, Valeyre D, Brillet PY, Kambouchner M, *et al*. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. *Lancet Respir Med* 2016;4:557–565.
47 Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* 2005;58: 882–893.
48 Iftikhar IH, Musani AI. Narrow-band imaging bronchoscopy in the detection of premalignant airway lesions: a meta-analysis of diagnostic test accuracy. *Ther Adv Respir Dis* 2015;9:207–216.