SYSTEMATIC REVIEWS

Transbronchial Biopsy and Cryobiopsy in the Diagnosis of Hypersensitivity Pneumonitis among Patients with Interstitial Lung Disease

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Abstract

Rationale: Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) with a diagnosis based on clinical, radiological, and pathological findings. The evidence supporting transbronchial forceps lung biopsy (TBBx) and transbronchial lung cryobiopsy (TBLC) as sampling techniques to diagnose HP in patients with newly detected ILD has not been reviewed systematically.

Objectives: A systematic review was performed to assess the diagnostic yield and complication rates of TBBx or TBLC in patients with newly detected ILD whose differential diagnosis includes HP and to inform the development of the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana del Tórax clinical practice guidelines on the diagnosis of HP.

Methods: Medline, Excerpta Medica Database, and the Cochrane Library were searched through October 2019. Studies that enrolled patients with ILD and reported the diagnostic yield of TBBx or TBLC were selected for inclusion. Data related to diagnostic yield and safety outcomes were extracted and then pooled across studies via meta-analysis. The quality of the evidence was appraised using the grading of recommendations, assessment, development, and evaluation (GRADE) approach.

Results: The histopathologic diagnostic yields (number of procedures that yielded a histopathologic diagnosis divided by the total number of procedures performed) of TBBx and TBLC were 37% (95% confidence interval [CI], 32–42%) and 82% (95% CI, 78–86%), respectively, among patients with ILD. Among those diagnosed by TBBx, the proportion with HP could not be determined. However, among those diagnosed by TBLC, 13.4% had HP. TBBx was complicated by moderate to severe bleeding, severe bleeding, and pneumothorax in 4% (95% CI, 0–8%), 0% (95% CI, 0–1%), and 7% (95% CI, 2–13%) of patients, respectively. TBLC was complicated by any bleeding, severe bleeding, and pneumothorax in 11% (95% CI, 7–15%), 0% (95% CI, 0–1%), and 11% (95% CI, 9–14%) of patients, respectively. The quality of the evidence was very low because of the uncontrolled study designs, lack of consecutive enrollment, and inconsistent results.

Conclusions: Very low-quality evidence indicated that TBLC had a higher diagnostic yield than TBBx among patients with ILD, although complications were similar.

Keywords: transbronchial lung biopsy; cryobiopsy; diagnosis; hypersensitivity pneumonitis; interstitial lung disease

(Received in original form May 4, 2020; accepted in final form August 18, 2020)

*Co–first authors and contributed equally to this work.

A Systematic Review that Informed the American Thoracic Society/Japanese Respiratory Society/Asociación Latinoamericana del Tórax Guideline on the diagnosis of hypersensitivity pneumonitis.

Supported by the American Thoracic Society, Japanese Respiratory Society, and Asociacion Latinoamericana del Torax.

Author Contributions: H.A.C. and J.D.-M.: design of the project, preparing and validation of search strategy, title and abstract screening, full text screening, data extraction, data analysis, and drafting of the manuscript. A.C., A.D., A.R.J., S.P., and M.T.-K.: data analysis and drafting of manuscript. G.R.: conception and design of the project, verification and supervision over all parts of the project, and drafting of the manuscript. S.L.K.: preparation and validation of search strategy and searching bibliographic databases. K.C.W.: conception and design of the project, preparing and validation of search strategy, title and abstract screening, full text screening, data extraction, data analysis, drafting of the manuscript, and supervision over all parts of the project.

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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 18, No 1, pp 148–161, Jan 2021

DOI: 10.1513/AnnalsATS.202005-421OC
Internet address: www.atsjournals.org

Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) that manifests in susceptible individuals after an inciting exposure (1). Diagnosis of HP is challenging because the culprit exposure is often unrecognized, and the clinical and radiographic manifestations of HP vary (1–3). Fibrotic HP is particularly difficult to distinguish from other fibrotic ILDs and can be misdiagnosed as idiopathic pulmonary fibrosis (IPF) when a relevant exposure is not identified (4).

Histopathologic sampling of the lung may be helpful. A confident histopathologic diagnosis of HP requires a triad of interstitial pneumonia, chronic cellular bronchiolitis, and small and poorly formed nonnecrotizing granulomas or giant cells (3, 5–8). In fibrotic HP, these features are accompanied by fibrosis (9). The histopathologic criteria for HP apply to any type of specimen. Transbronchial forceps lung biopsy (TBBx) seems preferable to surgical lung biopsy because it is less invasive, but the size and quality of specimen might limit its value in establishing the diagnosis of HP (10, 11). Moreover, in patients with fibrotic HP, single-site biopsies may miss the cellular histopathologic features of HP, which are often subtle, patchy, and limited to less fibrotic lung tissue (12). Transbronchial lung cryobiopsy (TBLC) is an emerging sampling technique that provides larger histologic samples than TBBx and therefore, in theory, might improve the diagnostic yield of histopathologic diagnosis of HP (13–15).

This systematic review was performed to assess the diagnostic yield and complication rates of TBBx and TBLC in patients with ILD whose differential diagnosis includes HP. The findings of the systematic review informed a multidisciplinary panel of experts who developed American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana del Tórax clinical practice guidelines on the diagnosis of HP (16).

Methods

This review was conducted following the standards previously described in the Cochrane Handbook for Systematic Reviews of Interventions (17). This systematic review was performed as a component of guideline development before the requirement that such systematic review be registered; thus, it has not been registered.

Research Question

The following two questions were formulated using the population, intervention, comparator, outcome (PICO) format:

1. "Should patients with newly detected ILD in chest radiographs or a computed tomographic (CT) scan of the chest, with or without a history of exposure capable of causing HP, undergo TBBx to diagnose HP?"
2. "Should patients with newly detected ILD in chest radiographs or a CT scan of the chest, with or without a history of exposure capable of causing HP, undergo TBLC to diagnose HP?"

Literature Search

The guideline committee's medical librarian developed a sensitive search strategy and then searched Medline, the Excerpta Medica database, and the Cochrane database of systematic reviews in June 2019 (Table E1 in the online supplement). The search was updated by the lead methodologist in October 2019. Bibliographies of selected studies, systematic reviews, and review articles were also reviewed for relevant studies, as were articles suggested by committee members.

Study Selection

A priori study selection criteria included the following:

1. Enrolled patients with ILD, HP, or diffuse lung disease (DLD);
2. Evaluated TBBx or TBLC; and
3. Reported diagnostic test characteristics (i.e., yield, sensitivity, specificity, etc.) and/or complications of the sampling procedures.

The rationale for selecting studies that enrolled patients with ILD, HP, or DLD (as opposed to selecting only those that enrolled patients with ILD) was as follows: The evidence synthesis team knew in advance that the guideline committee planned to define two types of HP—nonfibrotic HP and fibrotic HP—and that different diagnostic recommendations might be appropriate for each type of HP. The team also suspected there would be no published studies that explicitly enrolled patients with nonfibrotic HP or fibrotic HP because the types were being newly defined. Thus, an *a priori* decision was made to cast a wide net and select studies that enrolled patients with known HP, ILD, or DLD. It was the team's expectation that the guideline committee would consider data from studies of patients with known HP as most applicable to the nonfibrotic type of HP, data from patients with ILD as most applicable to the fibrotic type of HP, and data from patients with DLD as potentially applicable to both.

Two methodologists (H.C. and J.D.M.) used a stepwise approach to screen the publications retrieved from the literature searches based on title and/or abstract initially and then on full text. Randomized trials that compared performing the diagnostic test of interest with not performing the test were sought first. If randomized trials were not identified, observational studies (i.e., prospective cohort, retrospective cohort, case-control, and before and after studies) that compared performing the diagnostic test with not performing the test were sought. If observational studies were not identified, case series that enrolled at least 20 patients with ILD, HP, or DLD who underwent TBBx or TBLC and reported diagnostic yields were sought. Case series with less than 20 patients, case reports, animal studies, and abstracts from 2016 or earlier were excluded. H.C. and J.D.M. reviewed and selected studies; K.C.W. subsequently reviewed the selected studies for compliance with the selection criteria. Disagreements were addressed through discussion and consensus.

Data Extraction

Data from the selected studies were extracted into an Excel spreadsheet developed specifically for this review. The extracted information included the study setting, design, and location; number of participants and their characteristics; definition and type of HP; intervention; outcomes; and risk of bias based on the grading of recommendations, assessment, development, and evaluation (GRADE) approach (18). H.C. and J.D.M. extracted data, which were subsequently reviewed by K.C.W.; disagreements were addressed through discussion and consensus.

Evidence Synthesis

Data amenable to weighted pooling (i.e., meta-analysis) were analyzed using a random effects model in the Cochrane Collaboration Review Manager (version 5.3) software. Relative risk (RR) was the summary estimate for dichotomous outcomes, and mean difference was the summary estimate for continuous outcomes. For uncontrolled studies, proportion was estimated using generic inverse variance. Individual values of 0 were replaced with 0.0001 and values of 1.0 were replaced with 0.9999. The 95% confidence interval (CI) was calculated for all summary estimates.

Statistical heterogeneity was measured using the I^2 statistic; I^2 values of 75% or more were considered severe, values of 50–75% were considered moderate, and values of 25–50% were considered mild. Sensitivity analyses were performed to evaluate heterogeneity. The sensitivity analyses consisted of removing studies whose results appeared to be similar from the meta-analysis and, if the I^2 statistic improved, reviewing the full text of the removed studies to determine whether those studies were similar to each other and different from the others in a way that might explain the different results. If no cause was found, outliers were eliminated. Estimates after the elimination of outliers are reported in the text and tables, whereas estimates before and after the elimination of outliers are shown in the figures and were presented to the guideline committee.

Quality of Evidence Appraisal and Profile

A baseline assumption about the quality of the evidence was based on study design in accordance with the GRADE approach, then downgraded if any of the following were present: risk of bias (internal validity), inconsistency (heterogeneity of estimates across studies), indirectness (external validity), imprecision of estimates (wide 95% CI), and likelihood of publication bias (19–24). An approach based upon the Newcastle-Ottawa and Quada-2 scales for observational studies was used to assess the risk of bias. Reasons to upgrade the quality of evidence were also sought, including a large magnitude of effect, dose-effect gradient, and potential confounders expected to have an effect opposite of the actual effect.

Results

A total of 3,160 articles were identified (2,465 for TBBx and 695 for TBLC). After screening the titles and abstracts, the full text of 59 articles was reviewed (25 for TBBx and 34 for TBLC) (Figure 1). Thirty-three studies were selected (10, 11, 25–55). None of the studies compared the sampling procedure with no sampling, and none of the studies reported diagnostic test characteristics. Rather, all studies reported various outcomes associated with sampling without including a control group (i.e., case series).

Thirteen studies evaluating TBBx were selected, ranging in size from 33 to 359 subjects (10, 11, 25–35). Four studies enrolled patients with known HP (10, 11, 25, 26), six enrolled patients with ILD (27–30, 33, 35), and three enrolled patients with DLD (31, 32, 34) (Table 1). The studies performed TBBx with (10, 31–33) or without fluoroscopy (11, 27). Most studies obtained 2–5 samples via flexible (27, 30–33) or rigid (34) bronchoscopy, although some did not describe the procedure in detail (25, 26, 28, 29).

Twenty-four studies addressed TBLC, ranging in size from 20 to 699 patients (27, 30, 32, 35–55) (Table 2). Nineteen studies enrolled patients with ILD (27, 30, 35–43, 45, 47, 49, 50, 52–55), four enrolled patients with DLD (32, 44, 46, 48), and one enrolled patients with known HP (51). Within the studies that enrolled patients with ILD or DLD, HP was occasionally identified.

Three studies compared TBBx with TBLC, ranging in size from 41 to 359 subjects (27, 30, 35). Other studies reported outcomes from the two procedures within the same population but did not directly compare TBBx with TBLC (32, 33).

Diagnostic Yield

Diagnostic yield was defined as the number of procedures that yielded a histopathologic diagnosis divided by the total number of procedures performed. It is

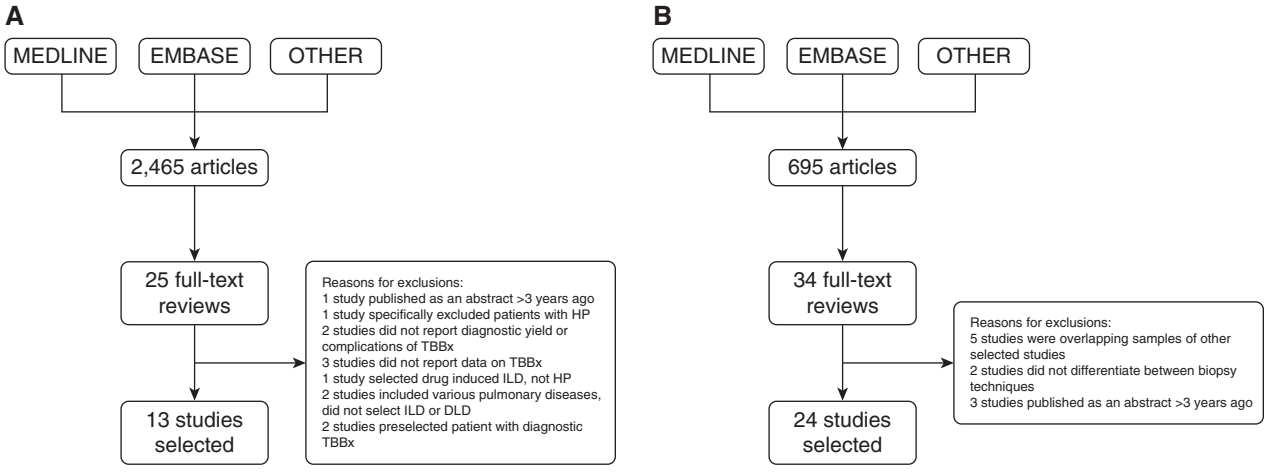

Figure 1. Flow of information diagram. (*A*) Transbronchial lung forceps biopsy. (*B*) Transbronchial lung cryobiopsy. DLD = diffuse lung disease; EMBASE = Excerpta Medica Database; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; TBBx = transbronchial lung forceps biopsy.

Table 1. Selected studies for the TBBx analysis

Study	Location	Population	Intervention	Outcomes	Risk of Bias
Patients with confirmed HP					
Adams 2018 (25)	United States Texas	72 patients with primarily fibrotic HP	TBBxs not described	Diagnostic yield and histopathological findings	Serious
Hanak 2007 (26)	United States Minnesota	47 patients with fibrotic and nonfibrotic HP (the proportion of each was not specified)	TBBxs not described	Diagnostic yield and histopathological findings	None
Lacasse 1997 (10)	Quebec Canada	55 patients with Farmer's lung plus 50 patients with non-HP ILD	4–8 TBBxs obtained from RLL under conscious sedation and fluoroscopy	Diagnostic yield and histopathological findings	None
Morell 2008 (11)	Spain Catalonia	33 patients with fibrotic and nonfibrotic Bird Fancier's Disease (the proportion of each was not specified)	TBBxs without fluroscopy	Diagnostic yield and histopathological findings	Serious
Patients with ILD					
Babiak 2009 (33)	Germany	41 patients with unspecified ILD	Under deep sedation with patient intubated, with fluoroscopy guidance to ensure forceps is 10 mm and perpendicular to chest wall; average of two specimens.	Diagnostic yield, histopathological findings, frequency of complications, and number of biopsies suitable for analysis	None
Hetzel 2019 (35)	Germany	359 patients with unspecified ILD	TBBxs performed with 1.8–2.6 mm forceps through rigid bronchoscope under GA or flexible with the patient intubated with deep sedation	Frequency of complications	Serious
Morell 2008 (28)	Spain	375 patients with unspecified ILD	4 TBBxs performed (procedure and forceps info not specified)	Diagnostic yield, histopathological findings, and number of biopsies suitable for analysis	None
Pajares 2014 (27)	Barcelona, Spain	38 patients with unspecified ILD	At least 3 TBBx (average, 3.5) under conscious sedation without fluoroscopy using Boston scientific model 1556 or Olympus FB-1556E biopsy forceps	Diagnostic yield, histopathological findings frequency of complications, and number of biopsies suitable for analysis	None
Pourabdollah 2016 (30)	Iran	41 patients with unspecified ILD	3–4 biopsies obtained by one bronchoscopist through video bronchoscope under deep sedation	Diagnostic yield, histopathological findings, and number of biopsies suitable for analysis.	Serious
Sheth 2017 (29)	United States Louisiana & Michigan	33 patients with unspecified ILD	Average of 2.8 TBBx (performed at two centers, procedure not further described, referred to as "standard TBBx" in the discussion, no forceps info)	Diagnostic yield, histopathological findings, number of biopsies suitable for analysis, and agreement with SLB findings	None
Patients with "diffuse lung disease"					
Casoni 2008 (34)	Italy	95 patients with unspecified DLD	5 biopsies obtained via rigid bronchoscope from lower lobes with normal forceps 1.4 mm (and 5 by 2.5 mm jumbo forceps in random order)	Diagnostic yield, histopathological findings, frequency of complications, and number of biopsies suitable for analysis	Serious
Ramaswamy 2016 (32)	United States Connecticut	56 patients with unspecified DLD	Up to 10 biopsies obtained through flexible bronchoscope (average, 4) using fluoroscopy under conscious sedation from various segments	Diagnostic yield, histopathological findings, frequency of complications, and number of biopsies "suitable" for analysis	Serious

(Continued)

Table 1. (*Continued*)

Study	Location	Population	Intervention	Outcomes	Risk of Bias
Sindhwani 2015 (31)	India	49 patients with unspecified DLD	6–8 biopsies obtained under fluoroscopy guidance from middle and lower lobes using Olympus FB-19C- forceps	Diagnostic yield, histopathological findings, frequency of complications, and number of biopsies suitable for analysis	None

Definition of abbreviations: DLD = diffuse lung disease; GA = general anesthesia; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; RLL = right lower lobe; TBBx = transbronchial biopsy; SLB = surgical lung biopsy.

worth emphasizing that it refers to any histopathologic diagnosis, HP or otherwise.

TBBx

Five studies reported specimen adequacy in patients with ILD who underwent TBBx (27, 29–31, 33). Among studies that had explicit adequacy criteria, adequate specimens were obtained in 74% (95% CI, 64–84%) of procedures (27, 29, 30). In contrast, among studies without explicit adequacy criteria, adequate specimens were obtained in 99% (95% CI, 97–100) of procedures (31, 33) (Figure E1). No study that enrolled patients with HP or DLD reported specimen adequacy.

Eleven of the TBBx studies reported diagnostic yield (10, 11, 25–32, 34). Four enrolled patients with HP (10, 11, 25, 26), four enrolled patients with ILD (27–30), and three enrolled patients with DLD (31, 32, 34). The diagnostic yield of TBBx alone in patients with ILD was 37% (95% CI, 32–42%) with no inconsistency across studies (I^2 statistic = 0%) (10, 11, 25–32, 34) (Figure 2 and Table 3). When TBBx was combined with clinical and radiographic findings, the diagnostic yield increased to 51% (95% CI, 38–64%), although there was variability depending on the process used to consider the clinical, radiographic, and histopathologic findings (27, 29, 30, 33) (Figure E2). A multimodality approach that included TBBx in addition to clinical history, chest CT imaging, and laboratory findings was more likely to yield a diagnosis than a multimodality approach that did not include TBBx in patients with ILD (RR, 1.67; 95% CI, 1.21–2.30) (28, 29, 33) (Figure E3).

The diagnostic yield of TBBx was higher among studies that enrolled patients with DLD. The diagnostic yield in patients with DLD was 68% (95% CI, 50–86%), although there was substantial variability across studies that may have been related to technique (I^2 statistic decreases from 89% to 53% when divided into subgroups based on technique) (31, 32, 34) (Figure 2). Specifically, diagnostic yield was higher in the study that obtained 6–8 biopsy samples (86%; 95% CI, 76–95%) (31) than in two studies that obtained fewer samples (60%; 95% CI, 48–71%) (32, 34) (Figure E4).

The diagnostic yield of TBBx in patients with known HP was similar to the diagnostic yield in patients with ILD (41%; 95% CI, 25–56%), although there was

Table 2. Selected studies for the TBLC analysis

Study	Location	Population	Intervention	Outcomes	Risk of Bias
Cascante 2016 (36)	Spain	55 patients with ILD	TBLC	Diagnosis yield, bleeding, and pneumothorax	Very serious
Fruchter 2014 (37)	Israel	75 patients with ILD	TBLC	Diagnosis yield, bleeding, and pneumothorax	None
Griff 2014 (38)	Germany	52 patients with ILD	TBLC	Diagnosis yield, characteristics of TBLC, and complications	Serious
Hernández-González 2015 (39)	Spain	33 patients with ILD	TBLC	Diagnosis yield, complications, and cost-effectiveness analysis	Serious
Kronborg-White 2017 (40)	Denmark	38 patients with ILD	TBLC	Diagnosis yield and complications	Serious
Kropski 2013 (41)	United States	25 patients with ILD	TBLC	Diagnosis yield and complications	Serious
Pajares 2014 (27)	Spain	39 patients with ILD	TBBx vs. TBLC (TBLC only analyzed)	Diagnosis yield, quality of biopsies, and complications	None
Pourabdollah 2016 (30)	Iran	41 patients with ILD	TBBx and TBLC (TBLC only analyzed)	Quality of biopsies, complications, and diagnostic yield	Very serious
Ramaswamy 2016 (32)	United States	56 patients with ILD	TBBx and TBLC (TBLC only analyzed)	Diagnostic yield and complications	Serious
Ussavarungsi 2017 (42)	United States	74 patients with ILD	TBLC	Diagnostic yield and complications	Serious
Gershman 2015 (43)	Israel	139 patients with ILD	TBLC	Complications per pathology group and technique of Bx	Serious
Ravaglia 2019 (44)	Italy	699 patients with DLD	TBLC	Diagnosis yield, complications, and mortality	Serious
Hetzel 2019 (35)	Germany	359 patients with ILD	TBBx and TBLC (TBLC only analyzed)	Bleeding complications only	Serious
Hagmeyer 2019 (45)	Germany	61 patients with ILD	TBLC (two different techniques)	Diagnostic yield and complications of two techniques	Very serious
Vlacic 2018 (abstract only) (46)	Slovenia	50 patients with DLD	TBBx and TBLC (TBLC only analyzed)	Diagnostic yield	Very serious
Gnass 2018 (47)	Poland	20 patients with ILD	TBLC with radial EBUS	Diagnostic yield and complications	Serious
Dhooria 2018 (48)	India	128 patients with DLD	TBLC	Diagnostic yield and complications	None
Morais 2017 (abstract only) (49)	Unknown	40 patients with ILD	TBLC	Diagnostic yield	Very serious
Li 2017 (abstract only) (50)	China	35 patients with ILD	TBLC	Diagnostic yield and complications	Very serious
De Sousa 2017 (abstract only) (51)	Unknown	45 patients with HP	TBLC	Diagnostic yield and complications	Very serious
Colella 2017 (abstract only) (52)	Italy	31 patients with ILD	TBLC	Diagnostic yield and complications	Very serious
Bondue 2017 (53)	Belgium	30 patients with ILD	TBLC	Diagnostic yield and complications	None
Wälscher 2019 (54)	Germany	109 patients with ILD	TBLC	Diagnostic yield and complications	None
Romagnoli 2019 (55)	Italy/France	21 patients with ILD	TBLC	Diagnostic yield	None

Definition of abbreviations: Bx = biopsy; DLD = diffuse lung disease; EBUS = endobronchial ultrasound; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; TBBX = transbronchial forceps lung biopsy; TBLC = transbronchial lung cryobiopsy.

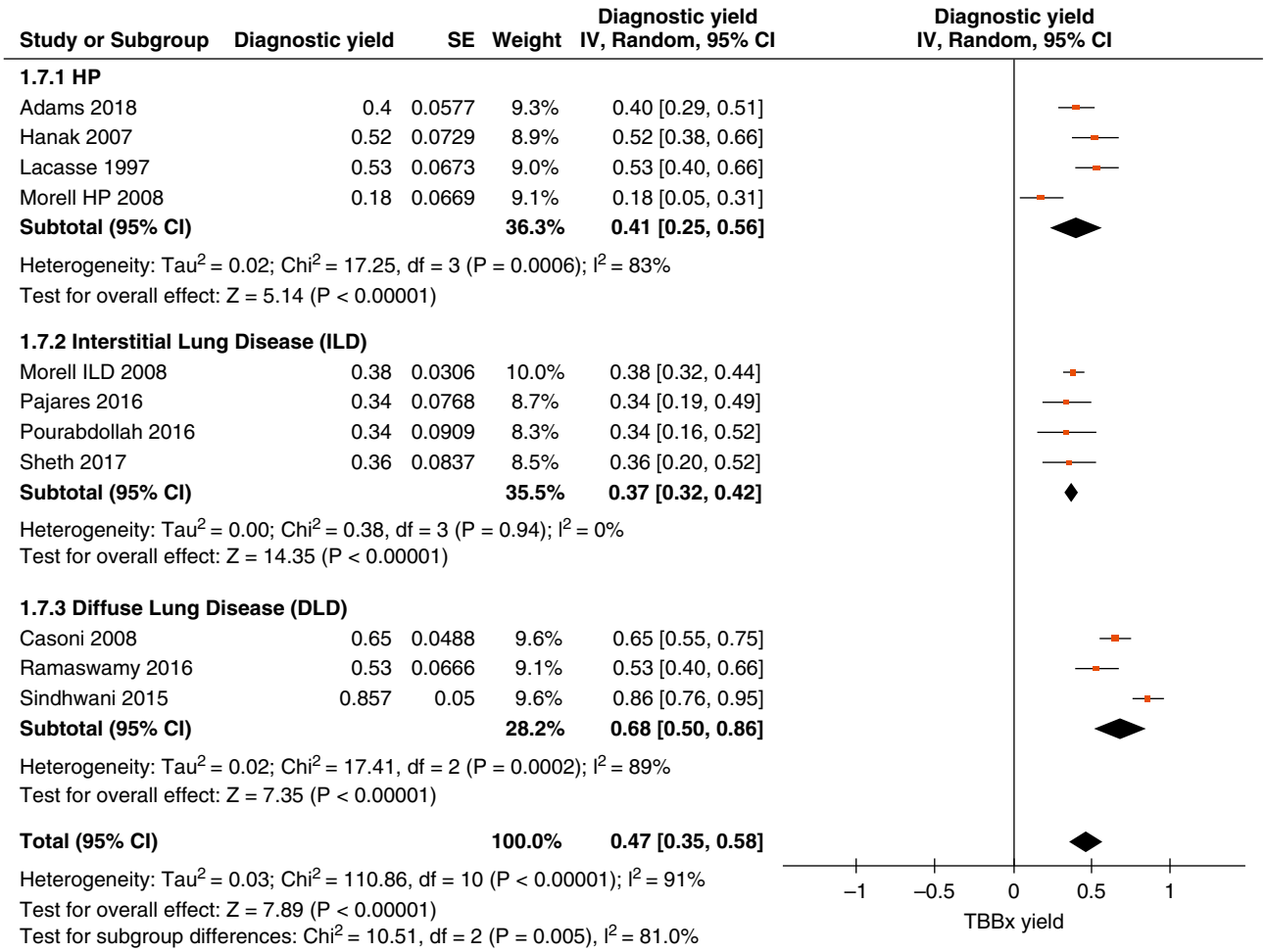

Figure 2. Diagnostic yield of transbronchial lung forceps biopsies. CI = confidence interval; df = degrees of freedom; DLD = diffuse lung disease; HP = hypersensitivity pneumonitis; I^2 = percentage of variation across studies due to heterogeneity; ILD = interstitial lung disease; IV = inverse variance; SE = standard error; TBBx = transbronchial lung forceps biopsy.

substantial variability across studies that may have been related to the rigor of the diagnostic criteria (I^2 statistic decreases from 83% to 27% when divided into subgroups based on the rigor of diagnostic criteria) (10, 11, 25, 26) (Figure 2). The diagnostic yield was only 18% (95% CI, 5–31%) in a study that used rigorous histopathologic diagnostic criteria (11), compared with 48% (95% CI, 39–56%) in studies that used less rigorous diagnostic criteria (10, 25, 26) (Figure E5).

Regarding the types of diagnoses, studies that enrolled patients with ILD reported that the final histopathologic diagnosis proved to be something other than ILD in 6.7% (95% CI, 3.6–12.2%) of patients. All other diagnoses were either HP or an alternative ILD, but the exact proportion of each could not be determined. Among patients with DLD, 2.9% (95% CI, 1.2–7.4%) had HP, 46.3% (95% CI, 38.1–54.7%) had another type of ILD, and 50.7% (95% CI, 42.4–59.1%) had something other than an ILD. Among patients with known HP, all patients were confirmed to have HP.

TBLC

Twenty-two of the TBLC studies reported diagnostic yield (27, 30, 32, 36–42, 44–55). The diagnosis was made by TBLC alone in 14 studies (30, 32, 37, 38, 41, 45–47, 49–54), whereas it was made after multidisciplinary discussion after TBLC in eight studies (27, 36, 39, 40, 42, 44, 48, 55). Four studies allowed a TBLC-based diagnosis to be changed by multidisciplinary discussion.

The diagnostic yield of TBLC in patients with ILD was 81% (95% CI, 75–88%), although there was serious inconsistency across studies (27, 30, 36–42, 45, 47, 49, 50, 52–55). The source of the inconsistency could not be identified, so outliers were removed (bringing the I^2 statistic from 85% to 40%), and the diagnostic yield was reassessed but remained nearly identical at 82% (95% CI, 78–86%) (Figure 3 and Table 4). The diagnostic yield was similar among studies that enrolled patients with DLD (82%; 95% CI, 73–90%) (32, 44, 46, 48) and known HP (91%; 95% CI, 83–99%) (51).

Regarding the types of diagnoses, studies that enrolled patients with ILD identified HP in 13.4% (95% CI, 10.9–16.2%) and diagnoses other than ILD (e.g., malignancy, infection, and others) in 15.1% (95% CI, 12.5–18.1%) of patients. All other diagnoses were types of ILD (e.g., IPF, sarcoidosis, nonspecific interstitial

Table 3. Evidence profile of diagnostic outcomes for TBBx in patients with ILD (does not include patients with known HP or DLD)

Quality Assessment							Patients (*n*)	Effect after Outliers Removed	Quality	Importance
Studies (*n*)	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other				
Specimen adequacy										
5*	NRS; noncomparative	Serious†	Serious‡	None	Serious§	None	202	87% (95% CI, 79–96%)	⊕○○○ Very low	Important
Diagnostic yield (histopathologic)										
4‖	NRS; noncomparative	Serious†	None	None	None	None	364	37% (95% CI, 32–42%)	⊕○○○ Very low	Critical
Diagnostic yield (multimodality with TBBx versus multimodality without TBBx)										
3¶	NRS; comparative	None	Serious‡	Serious**	None	None	574	RR = 1.67 (favoring with TBBx) (95% CI, 1.21–2.3)	⊕○○○ Very low	Important
Mortality										
2††	NRS; noncomparative	Serious†	None	None	Serious§	None	105	0%	⊕○○○ Very low	Important
Exacerbation/respiratory failure										
3‡‡	NRS; noncomparative	Serious†	None	None	Serious§	None	146	0%	⊕○○○ Very low	Important
Clinically important bleeding, moderate to severe§§										
4‖‖	NRS; noncomparative	Serious†	Serious‡	None	Serious§	None	533	4% (95% CI, 0–8%)	⊕○○○ Very low	Important
Severe bleeding										
6¶¶	NRS; noncomparative	Serious†	None	None	None	None	638	0%	⊕○○○ Very low	Important
Pneumothorax (all)										
2***	NRS; noncomparative	None	None	None	Serious§	None	87	7% (95% CI, 2–13%)	⊕○○○ Very low	Important
Pneumothorax (requiring chest tube)										
1†††	NRS; noncomparative	None	None	None	Serious§	None	49	6% (95% CI, 0–13%)	⊕○○○ Very low	Important
Pneumothorax (with prolonged air leak >72 h)										
2‡‡‡	NRS; noncomparative	None	None	None	Serious§	None	90	0%	⊕○○○ Very low	Important

Definition of abbreviations: CI = confidence interval; DLD = diffuse lung disease; ET = endotracheal tube; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; NRS = nonrandomized study; PICO = population, intervention, comparator, outcome; RR = risk ratio; TBBx = transbronchial lung forceps biopsy; TBLC = transbronchial lung cryobiopsy.

*Studies: Pajares, Sheth, Pouraboulah, Babiak, and Sindhwani (27, 29–31, 33).

†Some studies did not enroll consecutive patients.

‡Heterogeneity ($I^2 > 50\%$).

§Wide CIs (i.e., the ends of the 95% CI may lead to different clinical decisions) and/or $N < 200$.

‖Studies: Morell, Pajares, Pourabdollah, and Sheth (27, 29, 30).

¶Studies: Babiak, Sheth, and Morell (29, 33).

**PICO question is about TBBx specifically, but the studies used a multimodality intervention.

pneumonia, and other). Studies that enrolled patients with DLD identified HP in 7.2% (95% CI, 5.6–9.2%) and diagnoses other than ILD in 15.3% (95% CI, 13–18%) of patients. All other diagnoses were various types of ILD. Studies that enrolled patients with HP confirmed HP in all patients and did not identify any alternative diagnoses.

TBBx versus Cryobiopsy

Three studies assessed the diagnostic yield of TBBx and TBLC individually within the same population (27, 30, 32). Two studies enrolled patients with ILD (27, 30), and one enrolled patients with DLD (32). In patients with ILD, the diagnostic yield of TBBx and TBLC was 34% (95% CI, 19–49%) and 74% (95% CI, 60–88%), respectively, in one study (27) and 54% (95% CI, 35–71%) and 77% (95% CI, 63–88%), respectively, in the second study (30).

Pneumothorax

Only two TBBx studies measured pneumothorax rate as a complication; one study enrolled patients with ILD (27) and the other enrolled patients with DLD (31). Pneumothorax occurred in 7% (95% CI, 1–13%) of patients (Figure E6 and Table 3). Pneumothoraces that required a chest tube occurred after TBBx in 6% (95% CI, 0–13%) of patients in one study; none lasted longer than 72 hours (31). Another study that used regular and jumbo TBBx forceps sequentially in patients with DLD reported a pneumothorax rate of 4% (95% CI, 2–10%) and a chest tube rate of 1% (95% CI, 0–6%) (34).

Twenty-three TBLC studies measured pneumothorax rate as a complication (27, 32, 35–55). Most performed routine chest radiographs 1–4 hours after the procedure. Pneumothoraces complicated 9% (95% CI, 7–12%) of procedures, although this estimate was inconsistent across studies. The cause of variability could not be identified; therefore, outlying studies were eliminated, and the meta-analysis was repeated (bringing the I^2 statistic from 92% to 32%). The estimate remained similar, with pneumothoraces complicating 10% (95% CI, 8–13%) of procedures (Figure E7 and Table 4).

In the only study that randomized patients with ILD to TBBx or TBLC and measured pneumothorax rate, pneumothoraces occurred in 5% (95% CI, 2–12%) of patients undergoing TBBx and 8% (95% CI, 0–16%) of patients undergoing TBLC (27). Other studies that performed both TBBx and TBLC sequentially and measured pneumothorax rate could not attribute postprocedural pneumothorax to either procedure (32, 33, 35).

Bleeding

There was variation in the definition of bleeding across studies, but most used some type of qualitative scale. Six studies reported no cases of severe bleeding after TBBx (27, 31–35). Four of those studies reported moderate to severe bleeding complicating 4% (95% CI, 0–8%) of procedures, although there was serious inconsistency, with three studies reporting rates of 0– 4% (33–35) and one study reporting a rate of 34% (I^2 statistic = 92%) (27). The outlier study performed TBBx during flexible bronchoscopy under conscious sedation, whereas the others performed TBBx during rigid bronchoscopy or with the patient intubated (Figure E8 and Table 3).

Seventeen TBLC studies reported any bleeding (mild to severe) in 11% (95% CI, 7–15%) of patients, but the analysis was limited by inconsistent estimates across trials (27, 35–42, 44, 45, 48–51, 53, 54). The inconsistency could not be definitively explained but improved with the elimination of outlying studies (I^2 statistic decreased from 50% to 7%). Eighteen studies reported severe bleeding (27, 35–42, 44, 45, 48–54). They estimated that severe bleeding occurs in 1% (95% CI, 0–1%) of patients undergoing TBLC, which was similar at 0% (95% CI, 0–1%) after two outlying studies were removed (Figure E9 and Table 4).

In the only study that randomized patients with ILD to either TBBx or TBLC and compared postprocedural bleeding, there was no severe bleeding with either TBBx or TBLC; however, moderate bleeding was numerically higher during TBLC (56.4%) than TBBx (34.2%; $P = 0.07$) (27). A larger study that compared bleeding rates after both TBBx and TBLC were performed in random sequence in all participants reported higher bleeding rates of all severity during TBLC than TBBx (mild, 57% vs. 44%; moderate, 15% vs. 4%; severe, 1% vs. 0%; $P < 0.001$) (35).

Mortality

One study measured mortality as complication of TBBx at 24 hours, and another study measured mortality at 6 months after the procedure but did not report any deaths (31, 32) (Table 3). Sixteen studies reported mortality as a complication

†† Studies: Sindhwani and Ramaswamy (31, 32).
‡‡ Studies: Sindhwani, Ramaswamy, and Babiak (31–33).
§§ Variable definitions of bleeding among studies. We used the clinically significant bleed category moderate to severe excluding bleed managed by suction alone without the need for specific intervention. Grade 2 bleeding in Pajares was defined as bleeding requiring endoRx, cold saline, or bronchial occlusion; moderate bleeding in Hertzel was defined as bleeding requiring use of any additional intervention, such as instillation of ice-cold saline, vasoconstrictive drugs, or transient balloon tamponade, in order to prevent bleeding in the central airways; bleeding in Babiack was defined as bleeding requiring tamponade or other interventions (bleeding never necessitated any bronchoscopic interventions except for suction). Casoni defined bleeding as >200 ml or a Fogarty balloon placed on an aspirator in the lobar bronchus near the biopsied segment that was inflated in the case of bleeding (the number of instances the Fogarty balloon was used is not reported). Severe bleeding in Pajares was defined as bleeding requiring surgery; severe bleeding in Hertzel was defined as bleeding requiring additional prolonged monitoring or intensive care therapy after the procedure was necessary or if the bleeding was fatal; and severe bleeding in Babiak was defined as bleeding requiring intervention (tamponade, double lumen ET, or surgery).
|||| Studies: Babiak, Casoni, Hetzel, and Pajares (27, 33, 34, 35).
¶¶ Studies: Babiak, Casoni, Hetzel, Pajares, Sindhwani, and Ramaswamy (27, 31, 33, 34, 35).
*** Studies: Pajares and Sindhwani (27, 31); did not include Casoni (34), who reported 4% pneumothorax rate after TBBx because it used regular forceps followed by jumbo forceps. Other studies also reported the rate of pneumothoraces, but the patients had also undergone TBLC, therefore it was uncertain whether the pneumothorax was due to TBBx. Ramaswamy (32) reported 11 of 56 (19.6%) pneumothoraces after TBBx and TBLC and attributed them to TBLC. Hertzel reported 7.5% pneumothorax rate after TBBx and TBLC.
††† Study: Sindwhani. Casoni reported 1% pneumothorax requiring chest tube after TBBx; did not include Casoni because the study used regular forceps followed by jumbo forceps (34). Babiak reported 2 of 41 (4.8%) pneumothoraces requiring chest tube after TBBx and cryobiopsies; therefore, it was uncertain whether the pneumothorax was due to TBBx (33).
‡‡‡ Studies: Sindhwani and Babiak (31, 33).

A

Study or Subgroup	Diagnostic yield	SE	Weight	Diagnostic yield IV, Random, 95% CI
1.7.1 Known or presumed HP				
De Sousa 2017	0.91	0.04	5.2%	0.91 [0.83, 0.99]
Subtotal (95% CI)			**5.2%**	**0.91 [0.83, 0.99]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 22.75 (P < 0.00001)				
1.7.2 Diffuse Lung Disease (DLD)				
Dhooria 2018	0.78	0.0366	5.4%	0.78 [0.71, 0.85]
Ramaswamy 2016	0.66	0.063	4.2%	0.66 [0.54, 0.78]
Ravaglia 2019	0.88	0.0123	6.2%	0.88 [0.86, 0.90]
Vlacic 2018	0.9	0.0424	5.1%	0.90 [0.82, 0.98]
Subtotal (95% CI)			**20.9%**	**0.82 [0.73, 0.90]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 18.15$, df = 3 (P = 0.0004); $I^2 = 83\%$				
Test for overall effect: Z = 19.29 (P < 0.00001)				
1.7.3 Interstitial Lung Disease (ILD)				
Bondue 2017	0.9	0.054	4.6%	0.90 [0.79, 1.01]
Cascante 2016	0.87	0.045	5.0%	0.87 [0.78, 0.96]
Colella 2017	0.77	0.0756	3.6%	0.77 [0.62, 0.92]
Fruchter 2014	0.97	0.019	6.1%	0.97 [0.93, 1.01]
Gnass 2018	0.8	0.089	3.1%	0.80 [0.63, 0.97]
Griff 2014	0.79	0.056	4.5%	0.79 [0.68, 0.90]
Hagmeyer 2019	0.82	0.049	4.8%	0.82 [0.72, 0.92]
Hernández-González 2015	0.78	0.072	3.8%	0.78 [0.64, 0.92]
Kronberg-White 2017	0.84	0.059	4.4%	0.84 [0.72, 0.96]
Kropski 2013	0.72	0.0898	3.1%	0.72 [0.54, 0.90]
Li 2017	0.94	0.04	5.2%	0.94 [0.86, 1.02]
Morais 2017	0.99	0.049	4.8%	0.99 [0.89, 1.09]
Pajares 2014	0.74	0.07	3.9%	0.74 [0.60, 0.88]
Pourabdollah 2016	0.76	0.0667	4.0%	0.76 [0.63, 0.89]
Romagnoli 2019	0.81	0.085	3.3%	0.81 [0.64, 0.98]
Ussavarungsi 2017	0.51	0.058	4.4%	0.51 [0.40, 0.62]
Wälscher 2019	0.73	0.042	5.2%	0.73 [0.65, 0.81]
Subtotal (95% CI)			**73.8%**	**0.81 [0.75, 0.88]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 103.39$, df = 16 (P < 0.00001); $I^2 = 85\%$				
Test for overall effect: Z = 25.63 (P < 0.00001)				
Total (95 % CI)			**100.0%**	**0.82 [0.78, 0.87]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 122.75$, df = 21 (P < 0.00001); $I^2 = 83\%$				
Test for overall effect: Z = 37.19 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 3.99$, df = 2 (P = 0.14), $I^2 = 49.8\%$				

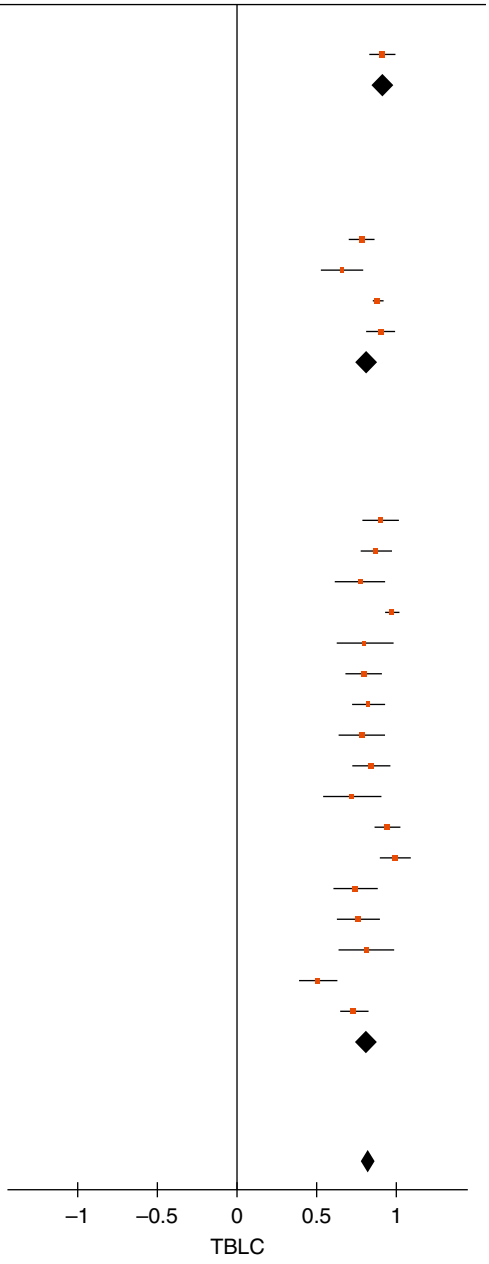

Figure 3. Diagnostic yield of transbronchial lung cryobiopsy (*A*) before outliers removed and (*B*) after outliers removed. CI = confidence interval; df = degrees of freedom; DLD = diffuse lung disease; HP = hypersensitivity pneumonitis; I^2 = percentage of variation across studies due to heterogeneity; ILD = interstitial lung disease; IV = inverse variance; SE = standard error; TBLC = transbronchial lung cryobiopsy.

of TBLC. Four studies reported 30-day mortality, one study reported 90-day mortality, and 11 studies did not specify a duration (27, 35–45, 48, 53–55). Only one death was reported, and the duration after the procedure was not reported (Table 4).

Exacerbation/Respiratory Failure

Three of the studies evaluating TBBx reported the frequency of periprocedural respiratory failure or exacerbation and reported no cases (31–33). Nine studies reported these outcomes after TBLC, which were rare, occurring in 0% (95% CI, 0–1%) of patients (35, 40–42, 44, 48, 52, 54, 55) (Table 4).

Quality of Evidence

The quality of evidence (i.e., confidence in the estimated effects) was very low for all outcomes. Nonrandomized studies

B

Study or Subgroup	Diagnostic yield	SE	Weight	Diagnostic yield IV, Random, 95% CI
1.7.1 Known or presumed HP				
De Sousa 2017	0.91	0.04	6.8%	0.91 [0.83, 0.99]
Subtotal (95% CI)			**6.8%**	**0.91 [0.83, 0.99]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 22.75 (P < 0.00001)				
1.7.2 Diffuse Lung Disease (DLD)				
Dhooria 2018	0.78	0.0366	7.2%	0.78 [0.71, 0.85]
Ramaswamy 2016	0.66	0.063	4.5%	0.66 [0.54, 0.78]
Ravaglia 2019	0.88	0.0123	9.9%	0.88 [0.86, 0.90]
Vlacic 2018	0.9	0.0424	6.5%	0.90 [0.82, 0.98]
Subtotal (95% CI)			**28.1%**	**0.82 [0.73, 0.90]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 18.15$, df = 3 (P = 0.0004); $I^2 = 83\%$				
Test for overall effect: Z = 19.29 (P < 0.00001)				
1.7.3 Interstitial Lung Disease (ILD)				
Bondue 2017	0.9	0.054	5.3%	0.90 [0.79, 1.01]
Cascante 2016	0.87	0.045	6.2%	0.87 [0.78, 0.96]
Colella 2017	0.77	0.0756	3.6%	0.77 [0.62, 0.92]
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Morais 2017	0.99	0.049	0.0%	0.99 [0.89, 1.09]
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Pourabdollah 2016	0.76	0.0667	4.2%	0.76 [0.63, 0.89]
Romagnoli 2019	0.81	0.085	3.1%	0.81 [0.64, 0.98]
Ussavarungsi 2017	0.51	0.058	0.0%	0.51 [0.40, 0.62]
Wälscher 2019	0.73	0.042	6.6%	0.73 [0.65, 0.81]
Subtotal (95 % CI)			**65.1%**	**0.82 [0.78, 0.86]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 21.57$, df = 13 (P = 0.06); $I^2 = 40\%$				
Test for overall effect: Z = 39.72 (P < 0.00001)				
Total (95 % CI)			**100.0%**	**0.82 [0.79, 0.86]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 47.00$, df = 18 (P = 0.0002); $I^2 = 62\%$				
Test for overall effect: Z = 46.22 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 4.56$, df = 2 (P = 0.10), $I^2 = 56.1\%$				

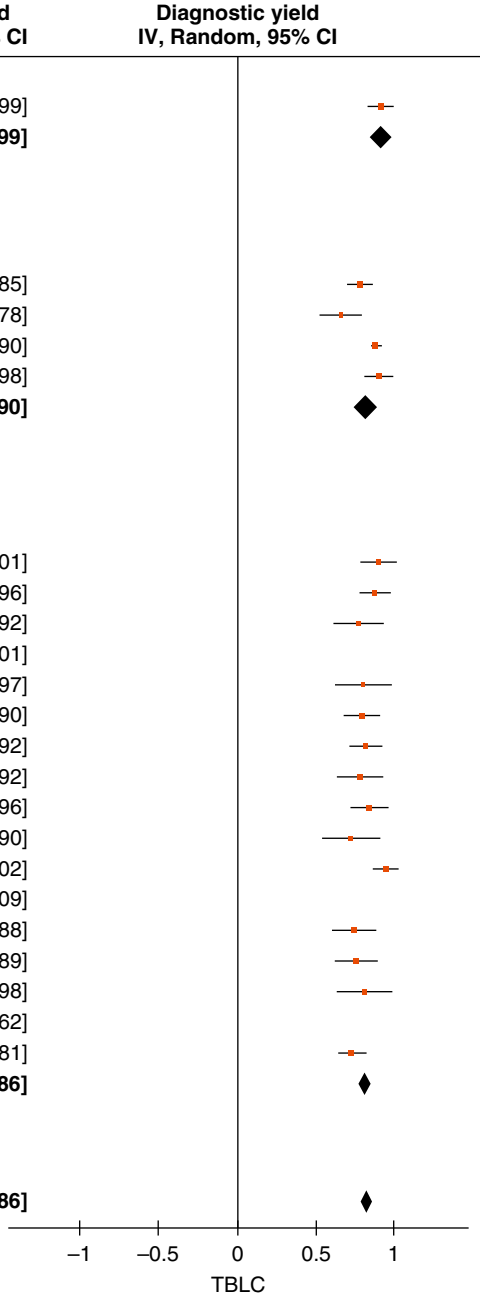

Figure 3. (*Continued*).

without a control group (i.e., case series) begin with an assumption of very low-quality evidence. Most individual studies had serious risk of bias because of a lack of consecutive enrollment, and many outcomes had inconsistency across studies; these limitations further emphasize the very low quality of the evidence.

Discussion

This is the only systematic review to date that evaluated the performance of TBBx and TBLC in patients with ILD and then used the findings to inform a multisociety clinical practice guideline. The systematic review indicates that TBBx and TBLC have diagnostic yields of 37% (95% CI, 32–42%) and 82% (95% CI, 78–86%), respectively, in patients with ILD. The diagnostic yield of TBBx improves to 51% (95% CI, 38–64%) with the incorporation of clinical and radiographic information. The reason for the difference in the diagnostic yields estimated from TBBx studies and TBLC studies is unknown. A possible explanation is that samples

Table 4. Evidence profile for TBLC in patients with ILD (does not include patients with known HP or DLD)

Quality Assessment							Patients (*n*)	Frequency [*(95% CI)*] after Outliers Removed	Quality	Importance
Studies (*n*)	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other				
Diagnostic yield										
17*	NRS	Serious†	None	None	None	None	466	0.82 (0.78–0.86)	⊕○○○ Very low	Critical
Mortality										
16‡	NRS	Serious†	None	None	None	None	1,323	0 (0.00–0.00)	⊕○○○ Very low	Important
Exacerbation/respiratory failure										
9§	NRS	Serious†	None	None	None	None	289	0 (0.00–0.00)	⊕○○○ Very low	Important
All bleeding										
17‖	NRS	Serious†	Serious¶	None	Serious**	None	1,991	0.11 (0.07–0.15)	⊕○○○ Very low	Important
Severe bleeding										
18††	NRS	Serious†	None	None	None	None	1,831	0.00 (0.00–0.01)	⊕○○○ Very low	Important
Pneumothorax										
23‡‡	NRS	Serious†	None	None	None	None	1,245	0.10 (0.08–0.13)	⊕○○○ Very low	Important

Definition of abbreviations: CI = confidence interval; DLD = diffuse lung disease; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; NRS = nonrandomized studies; TBLC = transbronchial lung cryobiopsy.
*Bondue, Cascante, Colella, Fruchter, Gnass, Griff, Hagmeyer, Hernandez-Gonzalez, Kronborg-White, Kropski, Li, Morais, Pajares, Pourabdollah, Romagnoli, Ussavarungsi, and Walscher (27, 36–42, 45, 47, 49, 50, 52, 53–55).
†Most studies had risk of bias because of not consecutively enrolling patients.
‡Bondue, Cascante, Dhooria, Fruchter, Gershman, Griff, Hagmeyer, Hernandez-Gonzalez, Hetzel, Kronborg-White, Kropski, Pajares, Ravaglia, Romagnoli, Ussavarungsi, and Walscher (27, 36–45, 48, 53–55).
§Colella, Dhooria, Hetzel, Kronborg-White, Kropski, Ravaglia, Romagnoli, Ussavarungsi, and Walscher. (40–42, 44, 48, 52, 54, 55)
‖Bondue, Cascante, Dhooria, Fruchter, Gershman, Griff, Hagmeyer, Hernandez-Gonzalez, Hetzel, Kronborg-White, Kropski, Li, Morais, Pajares, Ravaglia, Ussavarungsi, and Walscher (27, 36–45, 48–50, 53, 54).
¶Heterogeneity ($I^2 > 50\%$) even after removal of outliers.
**Imprecision (i.e., wide CIs) as indicated by the ends of the CI likely leading to different clinical decisions.
††Bondue, Cascante, Colella, Dhooria, Fruchter, Gnass, Griff, Hagmeyer, Hernandez-Gonzalez, Hetzel, Kronborg-White, Kropski, Li, Pajares, Ramaswamy, Ravaglia, Ussavarungsi, and Walscher (27, 32, 36–45, 48, 52–54).
‡‡Bondue, Cascante, Colella, Dhooria, Fruchter, Gershman, Gnass, Griff, Hagmeyer, Hernandez-Gonzalez, Hetzel, Kronberg-White, Kropski, Li, Morais, Pajares, Pourabdollah, Ramaswamy, Ravaglia, Romagnoli, Ussavarungsi, Vlacic, and Walscher (27, 32, 36–50, 52–55).

obtained by TBLC are larger and contain less "crushing" artifact than samples obtained by TBBx, which allows the pathologist to be more certain of the histopathologic diagnosis (30).

TBBx and TBLC have pneumothorax rates of 7% (95% CI, 2–13%) and 11% (95% CI, 9–14%), respectively. TBBx has a moderate to severe bleeding rate of 4% (95% CI, 0–8%), whereas TBLC has an overall bleeding rate of 11% (95% CI, 7–15%). Both TBBx and TBLC have severe bleeding rates of 0% (95% CI, 0–1%). Moderate bleeding was more common in TBLC than TBBx in studies that measured both; however, the differences were modest and it was not reported whether they were statistically significant. Taken together, the evidence suggests that TBLC has a higher diagnostic yield than TBBx in patients with ILD, with similar complication rates. The complication rate of TBLC is influenced by variations in technique, and therefore, protocols that standardize practice my improve safety by eliminating ineffective or dangerous outlying practices (56, 57).

The main strength of this systematic review is that it was done as a part of guideline development. Because there was a multidisciplinary international committee of experts and patients, the methodology team was able to ensure that the questions were clinically relevant to practicing clinicians who see such patients on a regular basis, that the outcomes were clinically important to patients, and, importantly, that studies were less likely to be missed. In addition, all estimated effects were reviewed and interpreted through lens of an expert in the field.

The primary limitation of the systematic review is the quality of the evidence. Confidence in the estimated effects is very low because of the uncontrolled study designs, risk of bias because of a lack of consecutive enrollment in many studies, and frequent inconsistent estimates across studies. Another important limitation is that only a few studies measured diagnostic yield (27, 30) and complications (27, 35) of TBBx and TBLC within the same population, thus providing limited supportive evidence to recommend either procedure. Finally, the studies did not compare the TBBx or TBLC specimens to surgical lung specimens; therefore, diagnostic accuracy (i.e., sensitivity, specificity, and accuracy) was not measured.

The limitations of the systematic review highlight the need for better evidence. Randomized trials or controlled observational studies are needed that directly compare TBBx with TBLC, TBBx with surgical lung biopsy, and TBLC with surgical biopsy in patients with ILD with possible nonfibrotic or fibrotic HP. ■

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

References

1 Lacasse Y, Selman M, Costabel U, Dalphin JC, Ando M, Morell F, *et al*.; HP Study Group. Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2003;168:952–958.
2 Elicker BM, Jones KD, Henry TS, Collard HR. Multidisciplinary approach to hypersensitivity pneumonitis. *J Thorac Imaging* 2016;31:92–103.
3 Myers JL. Hypersensitivity pneumonia: the role of lung biopsy in diagnosis and management. *Mod Pathol* 2012;25:S58–S67.
4 Morell F, Villar A, Montero MA, Muñoz X, Colby TV, Pipvath S, *et al*. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med* 2013;1:685–694.
5 Sahin H, Brown KK, Curran-Everett D, Hale V, Cool CD, Vourlekis JS, *et al*. Chronic hypersensitivity pneumonitis: CT features comparison with pathologic evidence of fibrosis and survival. *Radiology* 2007;244: 591–598.
6 Coleman A, Colby TV. Histologic diagnosis of extrinsic allergic alveolitis. *Am J Surg Pathol* 1988;12:514–518.
7 Reyes CN, Wenzel FJ, Lawton BR, Emanuel DA. The pulmonary pathology of farmer's lung disease. *Chest* 1982;81:142–146.
8 Takemura T, Akashi T, Ohtani Y, Inase N, Yoshizawa Y. Pathology of hypersensitivity pneumonitis. *Curr Opin Pulm Med* 2008;14:440–454.
9 Churg A, Muller NL, Flint J, Wright JL. Chronic hypersensitivity pneumonitis. *Am J Surg Pathol* 2006;30:201–208.
10 Lacasse Y, Fraser RS, Fournier M, Cormier Y. Diagnostic accuracy of transbronchial biopsy in acute farmer's lung disease. *Chest* 1997;112: 1459–1465.
11 Morell F, Roger A, Reyes L, Cruz MJ, Murio C, Muñoz X. Bird fancier's lung: a series of 86 patients. *Medicine (Baltimore)* 2008;87:110–130.
12 Herbst JB, Myers JL. Hypersensitivity pneumonia: role of surgical lung biopsy. *Arch Pathol Lab Med* 2012;136:889–895.
13 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.
14 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.
15 Iftikhar IH, Alghothani L, Sardi A, Berkowitz D, Musani AI. Transbronchial lung cryobiopsy and video-assisted thoracoscopic lung biopsy in the diagnosis of diffuse parenchymal lung disease: a meta-analysis of diagnostic test accuracy. *Ann Am Thorac Soc* 2017;14:1197–1211.
16 Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, *et al*. Diagnosis of hypersensitivity pneumonitis in adults: an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020;202:e36–e39.
17 Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London: The Cochrane Collaboration; 2011 [updated 2011 Mar; accessed 2020 Jul 30]. Available from https://training.cochrane.org/handbook/archive/v5.1/.
18 Schunemann H, Brozek J, Guyatt G, Oxman A, editors. GRADE handbook.] The GRADE Working Group; 2013 [updated 2013 Oct; accessed 2020 Jul 30]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html.
19 Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, *et al*. GRADE guidelines: 4. Rating the quality of evidence: study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407–415.
20 Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, *et al*. GRADE guidelines: 5. Rating the quality of evidence: publication bias. *J Clin Epidemiol* 2011;64:1277–1282.
21 Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, *et al*. GRADE guidelines 6. Rating the quality of evidence: imprecision. *J Clin Epidemiol* 2011;64:1283–1293.
22 Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, *et al*.; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence: inconsistency. *J Clin Epidemiol* 2011;64:1294–1302.
23 Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, *et al*.; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence: indirectness. *J Clin Epidemiol* 2011;64:1303–1310.
24 Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, *et al*.; GRADE Working Group. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol* 2011;64:1311–1316.
25 Adams TN, Newton CA, Batra K, Abu-Hijleh M, Barbera T, Torrealba J, *et al*. Utility of bronchoalveolar lavage and transbronchial biopsy in patients with hypersensitivity pneumonitis. *Lung* 2018;196:617–622.
26 Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin Proc* 2007;82:812–816.
27 Pajares V, Puzo C, Castillo D, Lerma E, Montero MA, Ramos-Barbón D, *et al*. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology* 2014;19:900–906.
28 Morell F, Reyes L, Doménech G, De Gracia J, Majó J, Ferrer J. [Diagnoses and diagnostic procedures in 500 consecutive patients with clinical suspicion of interstitial lung disease] [in Spanish]. *Arch Bronconeumol* 2008;44:185–191.
29 Sheth JS, Belperio JA, Fishbein MC, Kazerooni EA, Lagstein A, Murray S, *et al*. Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. *Chest* 2017; 151:389–399.
30 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.
31 Sindhwani G, Shirazi N, Sodhi R, Raghuvanshi S, Rawat J. Transbronchial lung biopsy in patients with diffuse parenchymal lung disease without 'idiopathic pulmonary fibrosis pattern' on HRCT scan: experience from a tertiary care center of North India. *Lung India* 2015; 32:453–456.
32 Ramaswamy A, Homer R, Killam J, Pisani MA, Murphy TE, Araujo K, *et al*. Comparison of transbronchial and cryobiopsies in evaluation of diffuse parenchymal lung disease. *J Bronchology Interv Pulmonol* 2016;23:14–21.
33 Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, *et al*. Transbronchial cryobiopsy: a new tool for lung biopsies. *Respiration* 2009;78:203–208.
34 Casoni GL, Gurioli C, Chhajed PN, Chilosi M, Zampatori M, Olivieri D, *et al*. The value of TBLB using jumbo forceps via rigis bronchoscope in DILD. *Monaldi Arch Chest Dis* 2008;69:59–64.
35 Hetzel J, Eberhardt R, Petermann C, Gesierich W, Darwiche K, Hagmeyer L, *et al*. Bleeding risk of transbronchial cryobiopsy compared to transbronchial forceps biopsy in interstitial lung disease

- a prospective, randomized, multicentre cross-over trial. *Respir Res* 2019;20:140.
36 Cascante JA, Cebollero P, Herrero S, Yagüe A, Echegoyen A, Elizalde J, *et al*. Transbronchial cryobiopsy in interstitial lung disease: are we on the right path? *J Bronchology Interv Pulmonol* 2016;23:204–209.
37 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.
38 Griff S, Schönfeld N, Ammenwerth W, Blum TG, Grah C, Bauer TT, *et al*. Diagnostic yield of transbronchial cryobiopsy in non-neoplastic lung disease: a retrospective case series. *BMC Pulm Med* 2014;14:171.
39 Hernández-González F, Lucena CM, Ramírez J, Sánchez M, Jimenez MJ, Xaubet A, *et al*. Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost-effectiveness analysis. *Arch Bronconeumol* 2015;51:261–267.
40 Kronborg-White S, Folkersen B, Rasmussen TR, Voldby N, Madsen LB, Rasmussen F, *et al*. Introduction of cryobiopsies in the diagnostics of interstitial lung diseases: experiences in a referral center. *Eur Clin Respir J* 2017;4:1274099.
41 Kropski JA, Pritchett JM, Mason WR, Sivarajan L, Gleaves LA, Johnson JE, *et al*. Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. *PLoS One* 2013;8:e78674.
42 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.
43 Gershman E, Fruchter O, Benjamin F, Nader AR, Rosengarten D, Rusanov V, *et al*. Safety of cryo-transbronchial biopsy in diffuse lung diseases: analysis of three hundred cases. *Respiration* 2015;90: 40–46.
44 Ravaglia C, Wells AU, Tomassetti S, Gurioli C, Gurioli C, Dubini A, *et al*. Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients. *BMC Pulm Med* 2019;19:16.
45 Hagmeyer L, Theegarten D, Wohlschläger J, Hager T, Treml M, Herkenrath SD, *et al*. Transbronchial cryobiopsy in fibrosing interstitial lung disease: modifications of the procedure lead to risk reduction. *Thorax* 2019;74:711–714.
46 Vlacic G, *et al*. Transbronchial cryobiopsy: a single-center experience. *Virchows Arch* 2018;473:s18.
47 Gnass M, Filarecka A, Pankowski J, Soja J, Bugalho A, Szlubowski A. Transbronchial lung cryobiopsy guided by endobronchial ultrasound radial miniprobe in interstitial lung diseases: preliminary results of a prospective study. *Pol Arch Intern Med* 2018;128:259–262.
48 Dhooria S, Mehta RM, Srinivasan A, Madan K, Sehgal IS, Pattabhiraman V, *et al*. The safety and efficacy of different methods for obtaining transbronchial lung cryobiopsy in diffuse lung diseases. *Clin Respir J* 2018;12:1711–1720.
49 Morais AM, Melo N, Mota P, Magalhães A, Guimarães S, Souto Moura C. Transbronchial criobiopsy (TCB) in two lung lobes-diagnostic accuracy. *Eur Respir J* 2017;50:PA860.
50 Li YS, Guo SL, Yi XH, Xiao ML, Jin XX, Xiao Y, *et al*. Efficacy and safety of transbronchial cryobiopsy in the etiologic diagnosis of diffuse lung disease [in Chinese]. *Zhonghua Yi Xue Za Zhi* 2017;97:3617–3623.
51 De Sousa Antunes Dias Padrao EF, Caetano Mota P, Melo N, Guimarães S, Souto Moura C, Magalhães A, *et al*. Transbronchial lung cryobiopsy in the diagnosis of hypersensitivity pneumonitis. *Eur Respir J* 2017;50: PA3018.
52 Colella S, Massaccesi C, Fioretti F, Panella G, Primomo GL, D'Emilio V, *et al*. Transbronchial Lung cryobiopsy in lung diseases: diagnostic yield and safety. *Eur Respir J* 2017;50:PA3025.
53 Bondue B, Pieters T, Alexander P, De Vuyst P, Ruiz Patino M, Hoton D, *et al*. Role of transbronchial lung cryobiopsies in diffuse parenchymal lung diseases: interest of a sequential approach. *Pulm Med* 2017; 2017:6794343.
54 Wälscher J, Groß B, Eberhardt R, Heussel CP, Eichinger M, Warth A, *et al*. Transbronchial cryobiopsies for diagnosing interstitial lung disease: real-life experience from a tertiary referral center for interstitial lung disease. *Respiration* 2019;97:348–354.
55 Romagnoli M, Colby TV, Berthet JP, Gamez AS, Mallet JP, Serre I, *et al*. Poor concordance between sequential transronchial lung cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung diseases. *Am J Respir Crit Care Med* 2019;199:1249–1256.
56 Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, *et al*. Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the cryobiopsy working group on safety and utility and a call for standardization of the procedure. *Respiration* 2018;95:188–200.
57 She S, Steinfort DP, Ing AJ, Williamson JP, Leong P, Irving LB, *et al*. Transbronchial cryobiopsy in interstitial lung disease: safety of a standardized procedure. *J Bronchology Interv Pulmonol* 2020;27: 36–41.