HHS Public Access

Author manuscript

Lung. Author manuscript; available in PMC 2021 February 22.

Published in final edited form as:

Lung. 2020 October ; 198(5): 803–810. doi:10.1007/s00408-020-00389-4.

Utility of Bronchoalveolar Lavage and Transbronchial Biopsy in Patients with Interstitial Lung Disease

Traci N. Adams[1], **Kiran Batra**[2], **Leann Silhan**[1], **Vikram Anand**[1], **Elena K. Joerns**[3], **Samantha Moore**[4], **Yasmeen M. Butt**[5], **Jose Torrealba**[4], **Chad A. Newton**[1], **Craig S. Glazer**[1]

[1]Division of Pulmonary and Critical Care Medicine, University of Texas Southwestern Medical Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75219, USA

[2]Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[3]Division of Rheumatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[4]Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[5]Department of Pathology, Mayo Clinic Scottsdale, Scottsdale, AZ, USA

Abstract

Purpose—Bronchoalveolar lavage and transbronchial biopsy can be a useful tool in the evaluation of interstitial lung disease (ILD), but patient selection for this procedure remains poorly defined. Determining clinical characteristics that help with patient selection for bronchoscopy may improve confidence of ILD classification while limiting potential adverse outcomes associated with surgical lung biopsy. The purpose of this study is to identify factors that were associated with change in multidisciplinary ILD diagnosis (MDD) before and after incorporation of BAL and TBBx data.

Methods—We conducted a retrospective cohort study of ILD patients at a single center who underwent bronchoscopy in the diagnostic workup of ILD. We performed sequential MDD both pre- and post-bronchoscopy to calculate the frequency of change in diagnosis after incorporating information from BAL and TBBx and identify features associated with change in diagnosis.

Results—245 patients were included in the study. Bronchoscopy led to a change in diagnosis in 58 patients (23.7%). The addition of TBBx to BAL increased diagnostic yield from 21.8 to 34.1% ($p = 0.027$). Identification of antigen, HRCT scan inconsistent with UIP, and absence of a pre-bronchoscopy diagnosis of CTD-ILD or IPAF were associated with a change in diagnosis after bronchoscopy.

Conclusion—Our study suggests clinical features that may assist with patient selection for bronchoscopy. We suggest bronchoscopy in patients with identified antigen or an HRCT that is

Traci N. Adams, traci.adams@utsouthwestern.edu.

Author Contributions TNA, KB, LS, VA, TB, YB, JT, JAN, and CSG contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Conflict of interest The authors TNA, KB, LS, VA, EJ, SM, YB, JT, JAN, and CSG have no conflicts of interest to report.

This abstract was presented at the Pulmonary Fibrosis Foundation Summit, November 7, 2019, San Antonio, TX.

consistent with a non-IPF diagnosis. Appropriate patient selection for bronchoscopy may improve ILD diagnostic confidence and avoid potential complications from more invasive and higher risk procedures.

Keywords

Bronchoscopy; Hypersensitivity pneumonitis; Interstitial lung disease

Introduction

The correct classification of interstitial lung disease (ILD) into specific subtypes requires assimilation of various clinical, radiographic, and sometimes pathologic information. Once these data are assembled, multidisciplinary discussion (MDD) involving pulmonologist, radiologist, and pathologist improves the consistency of ILD subclassification [1]. Bronchoscopy has been reported to add diagnostic information in up to 30% of patients with ILD, but it remains unclear which patients benefit from inclusion of information obtained by bronchoscopy in the diagnostic classification of ILD by MDD [2-8].

Recent guidelines on the diagnosis of IPF recommend bronchoscopy with BAL for ILD patients with a high-resolution computed tomography (HRCT) pattern that is probable usual interstitial pneumonia (UIP), indeterminate for UIP, or suggestive of an alternative diagnosis [2]. The IPF guidelines make no other recommendations for patient selection for bronchoscopy and do not make a recommendation for or against TBBx [2]. When a specific ILD diagnosis cannot be rendered confidently after incorporating other clinical and radiographic data, the guidelines recommend surgical lung biopsy (SLB), which has higher sensitivity but also much greater risk of morbidity and mortality than TBBx [2-8].

Determining clinical characteristics that help with patient selection for bronchoscopy may improve confidence of ILD classification while limiting potential adverse outcomes associated with SLB. Therefore, we sought to identify factors that were associated with change in multidisciplinary ILD diagnosis before and after incorporation of BAL and TBBx data. We hypothesized that the yield of bronchoscopy results would depend both on radiographic pattern and identification of an antigen.

Methods

We retrospectively identified ILD patients evaluated between 2011 and 2018 from the University of Texas Southwestern Medical Center (UTSW). Those who had a bronchoscopy for the diagnostic workup of their ILD were included in the study. Patients were excluded if the bronchoscopy was performed for a reason other than the diagnostic workup of their ILD such as evaluation for infection or malignancy. Patients with sarcoidosis were also excluded from this study.

Clinical data extracted from the medical record included age, gender, smoking history, potential fibrogenic antigen exposure, response to exposure removal, pulmonary function testing (PFTs), BAL cell count and differential, histopathologic interpretation of the transbronchial and Surgical Lung Biopsy (SLB), and connective tissue disease (CTD)

serologies. HRCTs were evaluated by a thoracic radiologist (KB) and reported as definite usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, or most consistent with a non-IPF diagnosis [9]. Findings from pathologic specimens were recorded by a thoracic pathologist (YB).

The sequential MDD format described here is adapted from prior studies [10, 11]. A retrospective chart review for each patient was conducted by pulmonologists with expertise in ILD (TNA, CAN). They presented cases in an MDD format to other expert pulmonologists (LS, VA, CG), radiologist (KB), and pathologists (YMB, HT) who were blinded to the aggregate clinical data. The pulmonologist who performed the chart review did not participate in the discussion or assist in providing a diagnosis.

Initially, each patient was assigned a “pre-bronchoscopy diagnosis” based on their clinical history, examination, serologic studies, and HRCT results without taking into account their BAL TBBx or SLB findings. A pre-bronchoscopy diagnosis of HP required an antigen exposure and a characteristic HRCT scan (defined as the presence of centrilobular nodules, mosaicism, and a mid or upper lung zone predominant interstitial disease [12]) or an exposure and a significant response to exposure removal (defined as a 10% improvement in forced vital capacity % predicted or radiographic improvement on follow-up CT within 3 months) [13, 14]. A pre-bronchoscopy diagnosis of IPF was made according to guidelines [2]. Patients meeting the American College of Rheumatology criteria for a defined connective tissue disease were assigned a pre-bronchoscopy diagnosis of connective tissue disease-related ILD (CTD-ILD). A diagnosis of interstitial pneumonia with autoimmune features (IPAF) was made according to a recently published research statement [15]. Those who did not meet criteria for IPF, HP, CTD-ILD, IPAF, or alternative cause of ILD were assigned a pre-bronchoscopy diagnosis of unclassifiable ILD.

Next, patients were assigned a “post-bronchoscopy diagnosis” after incorporating their bronchoscopy information in addition to the non-invasive testing. A diagnosis of IPF could be made on bronchoscopy only in the presence of patchy interstitial fibrosis and fibroblast foci or honeycomb change [16]. A BAL lymphocyte percentage of > 30% was used to support a diagnosis of HP [3, 17]. The TBBx result was considered characteristic of HP based on the presence of granulomas, particularly loose granulomas or giant cells, and at least one of the following: inflammatory bronchiolitis or a predominantly mononuclear cellular interstitial infiltrate [18-20].

Lastly, patients were assigned a “final diagnosis” taking into account all non-invasive testing, subsequent HRCT, bronchoscopy, SLB, and explant where available.

Statistical Analysis

Continuous variables were expressed as means and standard deviations; comparisons were made using Student’s t test or Wilcoxon signed rank sum test as appropriate. Categorical variables were expressed using counts and percentages; comparisons were made using Chi-squared test or Fisher’s exact test, where appropriate. Univariable logistic regression was performed to identify patient- and disease-specific factors that were associated with change in pre-bronchoscopy diagnosis after incorporating information obtained from the BAL

and/or TBBx. These variables were chosen based on clinical relevance and included demographic features, smoking status, presence of potential fibrogenic antigen, inconsistent with UIP pattern on HRCT, and pre-bronchoscopy diagnosis of CTD-ILD or IPAF. The variables that were significantly associated with change in diagnosis (p value < 0.1) were included in multivariable model to test independent associations. All p values less than 0.05 were considered significant. Statistical analyses were performed using R version 3.3.2 statistical analysis software (www.R-project.org).

Results

Patient Characteristics

In our retrospective cohort, 245 patients had a bronchoscopy performed for the purpose of ILD classification and were included in analysis. Mean age was 58.4 years at time of ILD diagnosis, 43% were male, and 71.4% were non-Hispanic white (Table 1). A potential fibrogenic antigen exposure was identified in 55.9% of the cohort.

At baseline, this cohort had mild impairment in lung function. The most common pre-bronchoscopy diagnoses in our cohort were unclassifiable (49.8%), CTD-ILD (18.4%), IPF (9%), IPAF (7.8%), and HP (7.3%) (Table 2). The majority of ILD patients that underwent bronchoscopy had a clinical suspicion of HP (75.9%) based on the presence of antigen, suggestive radiographic pattern, or absence of a clear alternative diagnosis.

Diagnostic Information Obtained from Bronchoscopy

BAL cell count was performed in 147 patients (60%), TBBx in 193 (78.8%), and both BAL and TBBx in 117 (47.8%). Seventy-three patients (49.7%) had a BAL lymphocyte percentage > 30%. The mean BAL lymphocyte percentage was 26.7% ± 21.9.

Data obtained from BAL or TBBx led to a change from pre-bronchoscopy diagnosis to post-bronchoscopy diagnosis in 58 (23.7%) of 245 patients (Table 2). Of those 58 patients, the pre-bronchoscopy diagnosis was unclassifiable in 54 patients (93.1%) and IPF in 4 patients (6.9%); post-bronchoscopy diagnosis included 51 cases (87.9%) of HP, 2 (3.4%) chronic eosinophilic pneumonia, 1 (1.7%) pulmonary alveolar proteinosis, 1 (1.7%) amyloid, 1 (1.7%) vasculitis, 1 (1.7%) primary biliary cirrhosis, and 1 (1.7%) IPF.

Incorporating BAL lymphocyte count > 30% alone led to a change in diagnosis for 32/147 patients (21.8%), while incorporating TBBx alone changed diagnosis in 50/195 (25.9%) (p = 0.44). Compared to BAL alone, the 117 patients who had both BAL and TBBx performed had a higher rate of change in diagnosis (21.8% vs 34.1%, respectively, p = 0.027).

Features Associated with Diagnosis Change

In the pre-specified univariable analysis, male gender (odds ratio 2.49; 95% CI 1.37–4.59), smoking status (odds ratio 2.01; 95% CI 1.11–3.67), presence of antigen (odds ratio 6.13; 95% CI 2.97–14.0), HRCT scan consistent with a non-IPF diagnosis (odds ratio 2.9; 95% CI 1.36–6.97) were positively associated with a change in diagnosis after bronchoscopy; a pre-bronchoscopy diagnosis of CTD-ILD or IPAF (odds ratio 0.03; 95% CI 0.002–0.15) was negatively associated with a change in diagnosis after bronchoscopy. In the multivariable

analysis, the presence of antigen (odds ratio, 4.48; 95% CI, 1.92–11.5) and HRCT scan consistent with a non-IPF diagnosis (odds ratio, 4.71; 95% CI, 1.94–13.0) were positively associated with a change in diagnosis after bronchoscopy. A pre-bronchoscopy diagnosis of CTD-ILD or IPAF was negatively associated with a change in diagnosis after bronchoscopy (odds ratio 0.05; 95% CI 0.003–0.26) (Table 3).

Results Based on Antigen Identification

Compared to patients without antigen identified, patients with an exposure to a potential fibrogenic antigen were more likely to have diagnosis after BAL alone (26.2% vs 12.5%, $p = 0.009$) and after both BAL and TBBx (42.1% vs 14.7%, $p = 0.005$) (Table 4). The addition of TBBx to BAL increased the yield in patients with antigen identified from 26.2 to 40.1% ($p = 0.028$), but there was no difference in diagnostic yield when TBBx was added to BAL for patients without antigen identified (12.5% vs 14.7%, $p = 1.0$).

Bronchoscopy Yield by Radiographic Pattern

HRCT was available for evaluation in 99.6% of patients. The HRCT pattern was definite UIP in 17 patients (7.0%), probable UIP in 12 (4.9%), indeterminate in 38 (15.6%), and inconsistent in 177 (72.5%) (Table 1).

Incorporating bronchoscopy data was associated with a change in diagnosis in 4 patients (13.8%) with a probable or definite UIP pattern, 4 (10.5%) with indeterminate for UIP pattern, and 50 (28.2%) with inconsistent with UIP pattern. Among the 7 patients whose diagnosis was changed after bronchoscopy to a diagnosis other than HP, 7 (100%) had an HRCT that was consistent with a non-IPF diagnosis. For those who underwent BAL alone, there was no difference in the frequency of diagnosis change after bronchoscopy between patients with an HRCT consistent with a non-IPF diagnosis and those with a definite, probable, or indeterminate for UIP HRCT pattern (25.5% vs 12.5%, $p = 0.12$) (Table 5). Incorporating both BAL and TBBx data was associated with a higher frequency of diagnosis change in patients with an inconsistent HRCT (40.0%) than in those with a definite, probable, or indeterminate HRCT (19.4%) ($p = 0.048$).

Discussion

In this study, we examined the sequential incorporation of information obtained from bronchoscopy (BAL and/or TBBx) to the MDD process to arrive at a confident diagnosis in a cohort of well-phenotyped ILD patients. Information obtained from BAL and TBBx led to a change in diagnosis of 23.7% of patients. Yield was higher when TBBx was added to BAL. Positive predictors of a change in diagnosis after bronchoscopy included identification of antigen and HRCT consistent with a non-IPF diagnosis. A pre-bronchoscopy diagnosis of IPAF or CTD-ILD was a negative predictor of a change in diagnosis after bronchoscopy. In patients with antigen identified, a confident diagnosis of HP could be made in 40% of patients by BAL and TBBx without the need for SLB.

The yield of TBBx in the workup of ILD aids in ILD classification of approximately 20–30% of patients [4], and the addition of BAL to TBBx likely further increases the yield. [21] These studies suggest that TBBx can be a useful tool in the workup of ILD; however, unlike

HRCT, the utility of bronchoscopy is not universal to all ILD patients. Reasons for the lack of uniformity are not only due to anatomic limitations and small pathologic samples from TBBx, but also stem from poor patient selection. Our study identified clinical factors that were associated with a change in multidisciplinary diagnosis after incorporation of bronchoscopy data, highlighting that the yield of minimally invasive tissue sampling is higher in enriched populations. Among the most predictive factors of a change in diagnosis after bronchoscopy in our cohort was identification of antigen, which supports the results from a prior study demonstrating that identification of antigen had the highest likelihood ratio of any factor in predicting a diagnosis of HP [22]. We also found that patients who had a radiographic pattern consistent with a non-IPF diagnosis had a stronger association with a useful bronchoscopy, which is not completely unexpected based on prior studies [2, 9, 12, 16]. However, we also found that 13% of patients with a definite or probable UIP radiographic pattern also had a change in diagnosis after incorporating information from bronchoscopy; each of these patients had an identified antigen and changed from a pre-bronchoscopy diagnosis of IPF to a post-bronchoscopy diagnosis of HP. We suggest that bronchoscopy can be useful in confirming a diagnosis of HP even for patients with a radiographic pattern that suggests IPF. Given that treatment with immunosuppression is associated with worse outcomes in IPF [23], but is the mainstay of treatment for progressive HP [24], confidently distinguishing these two disorders is of utmost importance.

It is particularly important to define the role of bronchoscopy in the workup of ILD because TBBx has a much lower complication rate than transbronchial lung cryobiopsy (TBLC) or SLB. Recent meta-analyses reported a 30- to 60-day mortality rate of 0.3–0.7% after TBLC and 1.8–2.7% after SLB; complication rates were 23.1% after TBLC [6, 25, 26]. TBBx, in contrast, has a complication rate ranging from 0.08 to 6.8% with a mortality rate ranging from 0 to 0.13% [5, 7, 25, 27]. Adding BAL to TBBx can help achieve a confident diagnosis in a sizable minority of patients (40%), thus avoiding the need for higher risk procedures such as TBLC or SLB.

Our study findings also support prior data regarding the role of lung biopsy in CTD-ILD patients. Lung biopsy, either surgical or transbronchial, is not routinely recommended in CTD-ILD patients because it is unclear whether biopsy is an independent predictor of prognosis in CTD-ILD when non-invasive data including HRCT and pulmonary function testing is available [28-33]. Further, a diagnosis of IPAF can be made without pathologic data, and many of the IPAF pathologic criteria cannot be met with confidence on a TBBx [15]. Our results suggest that bronchoscopy is unlikely to change the diagnosis in a patient with CTD-ILD or IPAF.

Strengths of our study include the serial incorporation of information obtained from bronchoscopy to the MDD process to arrive at a confident diagnosis in a cohort of well-phenotyped ILD patients across a range of diagnoses, thus limiting incorporation bias. While prior studies either focus on the yield of bronchoscopy for a particular diagnostic group or only included patients who underwent both bronchoscopy and SLB, our pragmatic cohort included patients with a variety of diagnoses, many of whom did not undergo SLB [4, 16]. As a result, we were able to diagnose conditions such as amyloid and pulmonary alveolar proteinosis that were not suspected before bronchoscopy. Although most patients in our

cohort had suspected HP, clinical suspicion for HP was not an inclusion criterion, which improves our generalizability. Further, our study evaluates the additive information of TBBx to BAL, which is important as current diagnostic guidelines do not make a recommendation for or against performing TBBx [9].

There are limitations to this study that should be acknowledged. Most patients (75.9%) in our cohort were suspected of having HP; however, we did not limit our cohort to those with a single diagnosis, and we included patients who had already had a bronchoscopy prior to being referred to our center, thus limiting potential selection bias. The diagnostic evaluation of ILD patients in this study was dictated by the treating physician; therefore, not all ILD patients at our center had BAL and/or TBBx performed. We maintained strict pre-specified pre- and post-bronchoscopy diagnostic criteria for each of the subtypes of ILD, thus potentially underestimating the clinical utility of bronchoscopy itself in achieving a high-confidence ILD diagnosis while reducing risk of bias in the interpretation of results. Further, we addressed potential investigator bias by having the diagnostic determination made by a team of experts that were blinded to all clinical information except for what was presented by the expert pulmonologist that performed the chart review. Lastly, given the retrospective nature of our study, we could not accurately assess the influence of treatment at the time of bronchoscopy on BAL lymphocyte count or TBBx characteristics.

In summary, accurate ILD diagnosis is absolutely essential since the diagnosis dictates treatment plans and provides prognostic information. The diagnostic evaluation should prioritize low-risk non-invasive or minimally invasive procedures when these approaches allow for confident diagnosis. Here, we identified specific clinical features that help with patient selection for bronchoscopy in the classification of ILD. We suggest that bronchoscopy with both BAL and TBBx be performed in patients with a sensitizing antigen identified even if imaging features suggest a diagnosis of IPF and in patients with an HRCT pattern that is consistent with a non-IPF diagnosis. We also suggest that bronchoscopy be avoided in patients with a diagnosis of CTD-ILD or IPAF. Appropriate patient selection for bronchoscopy may improve ILD diagnostic confidence and avoid potential complications from more invasive and higher risk procedures.

Acknowledgments

Funding Author CN has Grant funding from NHLBI (NHLBI K23HL148498).

Data Availability

De-identified data can be made available upon request.

References

1. Jo HE, Glaspole IN, Levin KC, McCormack SR, Mahar AM, Cooper WA, Cameron R, Ellis SJ, Cottee AM, Webster SE, Troy LK, Torzillo PJ, Corte P, Symons KM, Taylor N, Corte TJ (2016) Clinical impact of the interstitial lung disease multidisciplinary service. Respirology 21(8):1438–1444. 10.1111/resp.12850 [PubMed: 27427515]
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK,

Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendia-Roldan I, Selman M, Travis WD, Walsh S, Wilson KC, American Thoracic Society ERSJRS, Latin American Thoracic S (2018) Diagnosis of idiopathic pulmonary fibrosis, an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 198(5):e44–e68. 10.1164/rccm.201807-1255ST [PubMed: 30168753]

3. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, Drent M, Haslam PL, Kim DS, Nagai S, Rottoli P, Saltini C, Selman M, Strange C, Wood B, American Thoracic Society Committee on BALiILD (2012) An official American thoracic society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med 185(9):1004–1014. 10.1164/rccm.201202-0320ST [PubMed: 22550210]
4. Sheth JS, Belperio JA, Fishbein MC, Kazerooni EA, Lagstein A, Murray S, Myers JL, Simon RH, Sisson TH, Sundaram B, White ES, Xia M, Zisman D, Flaherty KR (2017) Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. Chest 151(2):389–399. 10.1016/j.chest.2016.09.028 [PubMed: 27729263]
5. Facciolongo N, Patelli M, Gasparini S, Lazzari Agli L, Salio M, Simonassi C, Del Prato B, Zanoni P (2009) Incidence of complications in bronchoscopy, Multicentre prospective study of 20,986 bronchoscopies. Monaldi Arch Chest Dis 71(1):8–14. 10.4081/monaldi.2009.370 [PubMed: 19522159]
6. Iftikhar IH, Alghothani L, Sardi A, Berkowitz D, Musani AI (2017) 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 14(7):1197–1211. 10.1513/AnnalsATS.201701-086SR [PubMed: 28399377]
7. Jin FG, Mu DG, Chu DL, Fu EQ, Xie YH, Liu TG (2008) Severe complications of bronchoscopy. Respiration 76(4):429–433. 10.1159/000151656 [PubMed: 18716395]
8. Ensminger SA, Prakash UB (2006) Is bronchoscopic lung biopsy helpful in the management of patients with diffuse lung disease? Eur Respir J 28(6):1081–1084. 10.1183/09031936.06.00013106 [PubMed: 16899488]
9. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, Goldin JG, Hansell DM, Inoue Y, Johkoh T, Nicholson AG, Knight SL, Raoof S, Richeldi L, Ryerson CJ, Ryu JH, Wells AU (2018) Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med 6(2):138–153. 10.1016/S2213-2600(17)30433-2 [PubMed: 29154106]
10. Tzilas V, Tzouvelekis A, Bouros E, Karampitsakos T, Ntasiou M, Katsaras M, Costabel U, Wells A, Bouros D (2019) Diagnostic value of BAL lymphocytosis in patients with indeterminate for UIP imaging pattern. Eur Respir J. 10.1183/13993003.01144-2019
11. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, Mahar A, Myers JL, Lai S, Mulyadi E, Torzillo PJ, Phillips MJ, Jo HE, Webster SE, Lin QT, Rhodes JE, Salamonsen M, Wrobel JP, Harris B, Don G, Wu PJC, Ng BJ, Oldmeadow C, Raghu G, Lau EMT, Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance I (2020) Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir Med 8(2):171–181. 10.1016/S2213-2600(19)30342-X [PubMed: 31578168]
12. Silva CI, Muller NL, Lynch DA, Curran-Everett D, Brown KK, Lee KS, Chung MP, Churg A (2008) Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 246(1):288–297. 10.1148/radiol.2453061881 [PubMed: 18096541]
13. Salisbury ML, Gu T, Murray S, Gross BH, Chughtai A, Sayyouh M, Kazerooni EA, Myers JL, Lagstein A, Konopka KE, Belloli EA, Sheth JS, White ES, Holtze C, Martinez FJ, Flaherty KR (2019) Hypersensitivity pneumonitis: radiologic phenotypes are associated with distinct survival time and pulmonary function trajectory. Chest 155(4):699–711. 10.1016/).chest.2018.08.1076 [PubMed: 30243979]
14. Morisset J, Johannson KA, Jones KD, Wolters PJ, Collard HR, Walsh SLF, Ley B, Collaborators HPD (2018) Identification of diagnostic criteria for chronic hypersensitivity pneumonitis: an international modified delphi survey. Am J Respir Crit Care Med 197(8):1036–1044. 10.1164/rccm.201710-1986OC [PubMed: 29172641]

15. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, Lee JS, Leslie KO, Lynch DA, Matteson EL, Mosca M, Noth I, Richeldi L, Strek ME, Swigris JJ, Wells AU, West SG, Collard HR, Cottin V, CTD-ILD EATFoUFo (2015) An official European respiratory society/American thoracic society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 46(4):976–987. 10.1183/13993003.00150-2015 [PubMed: 26160873]

16. Tomassetti S, Cavazza A, Colby TV, Ryu JH, Nanni O, Scarpi E, Tantalocco P, Buccioli M, Dubini A, Piciucchi S, Ravaglia C, Gurioli C, Casoni GL, Gurioli C, Romagnoli M, Poletti V (2012) Transbronchial biopsy is useful in predicting UIP pattern. Respir Res 13:96 10.1186/1465-9921-13-96 [PubMed: 23107232]

17. Ohshimo S, Bonella F, Cui A, Beume M, Kohno N, Guzman J, Costabel U (2009) Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 179(11):1043–1047. 10.1164/rccm.200808-1313OC [PubMed: 19246718]

18. Coleman A, Colby TV (1988) Histologic diagnosis of extrinsic allergic alveolitis. Am J Surg Pathol 12(7):514–518. 10.1097/00000478-198807000-00002 [PubMed: 3389449]

19. Sahin H, Brown KK, Curran-Everett D, Hale V, Cool CD, Vourlekis JS, Lynch DA (2007) Chronic hypersensitivity pneumonitis: CT features comparison with pathologic evidence of fibrosis and survival. Radiology 244(2):591–598. 10.1148/radiol.2442060640 [PubMed: 17641377]

20. Reyes CN, Wenzel FJ, Lawton BR, Emanuel DA (1982) The pulmonary pathology of farmer's lung disease. Chest 81(2):142–146. 10.1378/chest.81.2.142 [PubMed: 7035083]

21. Adams TN, Newton CA, Batra K, Abu-Hijleh M, Barbera T, Torrealba J, Glazer CS (2018) Utility of bronchoalveolar lavage and transbronchial biopsy in patients with hypersensitivity pneumonitis. Lung 196(5):617–622. 10.1007/s00408-018-0139-1 [PubMed: 29959521]

22. Lacasse Y, Selman M, Costabel U, Dalphin JC, Ando M, Morell F, Erkinjuntti-Pekkanen R, Muller N, Colby TV, Schuyler M, Cormier Y, Group HPS (2003) Clinical diagnosis of hypersensitivity pneumonitis. Am J Respir Crit Care Med 168(8):952–958. 10.1164/rccm.200301-137OC [PubMed: 12842854]

23. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE Jr., Lasky JA, Martinez FJ (2012) Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 366(21):1968–1977. 10.1056/NEJMoa1113354 [PubMed: 22607134]

24. Morisset J, Johannson KA, Vittinghoff E, Aravena C, Elicker BM, Jones KD, Fell CD, Manganas H, Dube BP, Wolters PJ, Collard HR, Ryerson CJ, Ley B (2017) Use of mycophenolate mofetil or azathioprine for the management of chronic hypersensitivity pneumonitis. Chest 151(3):619–625. 10.1016/j.chest.2016.10.029 [PubMed: 27816444]

25. Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, Dubini A, Tantalocco P, Sanna S, Negri E, Tramacere I, Ventura VA, Cavazza A, Rossi A, Chilosi M, La Vecchia C, Gasparini S, Poletti V (2016) 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 91(3):215–227. 10.1159/000444089 [PubMed: 26926876]

26. Sethi J, Ali MS, Mohananey D, Nanchal R, Maldonado F, Musani A (2019) Are transbronchial cryobiopsies ready for prime time?: A systematic review and meta-analysis. J Bronchol Interv Pulmonol 26(1):22–32. 10.1097/LBR.0000000000000519

27. Tukey MH, Wiener RS (2012) Population-based estimates of transbronchial lung biopsy utilization and complications. Respir Med 106(11): 1559–1565. 10.1016/j.rmed.2012.08.008 [PubMed: 22938740]

28. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, Haslam PL, Vassilakis DA, Black CM, du Bois RM (2002) Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 165(12):1581–1586. 10.1164/rccm.2106012 [PubMed: 12070056]

29. Park JH, Kim DS, Park IN, Jang SJ, Kitaichi M, Nicholson AG, Colby TV (2007) Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. Am J Respir Crit Care Med 175(7):705–711. 10.1164/rccm.200607-912OC [PubMed: 17218621]

30. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj A, Bozovic G, Denton CP, Black CM, du Bois RM, Wells AU (2008) Interstitial

lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 177(11):1248–1254. 10.1164/rccm.200706-877OC [PubMed: 18369202]

31. Assayag D, Elicker BM, Urbania TH, Colby TV, Kang BH, Ryu JH, King TE, Collard HR, Kim DS, Lee JS (2014) Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. Radiology 270(2):583–588. 10.1148/radiol.13130187 [PubMed: 24126367]
32. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, Frankel SK, Hobbs SB, Huie TJ, Ketzer J, Mannina A, Olson AL, Russell G, Tsuchiya Y, Yunt ZX, Zelarney PT, Brown KK, Swigris JJ (2016) Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 47(2):588–596. 10.1183/13993003.00357-2015 [PubMed: 26585429]
33. Volkmann ER, Tashkin DP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L, Pinckney A, Furst DE, Clements PJ, Khanna D, Steen V, Schraufnagel DE, Arami S, Hsu V, Roth MD, Elashoff RM, Sullivan KM, Sls I, groups SIs, (2019) Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. Ann Rheum Dis 78(1):122–130. 10.1136/annrheumdis-2018-213708 [PubMed: 30409830]

Table 1

Characteristics of patients with ILD who underwent bronchoscopy based on post-bronchoscopy MDD data (*N* = 245)

	ILD (*N* = 245)
Mean age (SD)	58.4 (12.3)
Male, No. (%)	106 (43.2)
Ethnicity, No. (%)	
Non-Hispanic white	175 (71.4)
Black	25 (10.2)
Hispanic or Latino	27 (11.0)
Asian	7 (2.9)
Other	3 (1.2)
Unknown	8 (3.3)
Ever smoker, *N* (%)	103 (42.0)
Antigen identified, No. (%)	137 (55.9)
Any Avian	95 (38.8)
Mold	76 (31.0)
Other	13 (5.3)
Baseline lung function, mean (SD), *N*	
FVC % predicted	71.6 (33.6), 240
DLCO % predicted	52.2 (16.9), 218
HRCT available for scoring	244 (99.6)
Consistent with a non-IPF diagnosis	177 (72.5)
Indeterminate UIP	38 (15.6)
Probable UIP	12 (4.9)
Definite UIP	17 (7.0)
Invasive procedure performed[a]	
Surgical biopsy	86 (35.1)
TBBx	193 (78.8)
BAL	147 (60.0)
BAL and TBBx	117 (47.8)

FVC forced vital capacity, *DLCO* diffusing capacity for carbon monoxide, *HRCT* high-resolution computed tomography, *UIP* usual interstitial pneumonia, *BAL* bronchoalveolar lavage, *TBBx* transbronchial biopsy

[a]27 patients had both transbronchial and surgical lung biopsy

Lung. Author manuscript; available in PMC 2021 February 22.

Table 2

Pre-bronchoscopy, post-bronchoscopy, and final diagnosis ($N = 245$)

	Pre-bronchoscopy diagnosis *N* (%)[a]	**Post-bronchoscopy diagnosis *N* (%)[b]**	**Final diagnosis *N* (%)[c]**
IPF	22 (9.0)	19 (7.8)[d]	20 (8.2)
HP	18 (7.3)	69 (28.2)	97 (39.6)
CTD-ILD	45 (18.4)	45 (18.4)	45 (18.4)
IPAF	19 (7.8)	19 (7.8)	21 (8.6)
Unclassifiable	122 (49.8)	68 (27.8)	27 (11.0)
Drug-induced	6 (2.4)	6 (2.4)	6 (2.4)
IPPFE	0 (0)	0 (0)	1 (0.4)
RB-ILD or DIP	1 (0.4)	1 (0.4)	2 (0.8)
Idiopathic NSIP	3 (1.2)	3 (1.2)	4 (1.6)
COP	6 (2.4)	6 (2.4)	6 (2.4)
Idiopathic bronchiolitis	0 (0)	0 (0)	2 (0.8)
Chronic eosinophilic pneumonia	0 (0)	2 (0.8)	2 (0.8)
Pulmonary alveolar proteinosis	0 (0)	1 (0.4)	1 (0.4)
Amyloid	0 (0)	1 (0.4)	1 (0.4)
Primary biliary cirrhosis	0 (0)	1 (0.4)	1 (0.4)
ANCA vasculitis	0 (0)	1 (0.4)	3 (1.2)
Pulmonary alveolar microlithiasis	1 (0.4)	1 (0.4)	1 (0.4)
Surfactant protein C deficiency	0 (0)	0 (0)	1 (0.4)
Langerhans cell histiocytosis	0 (0)	0 (0)	1 (0.4)
Inflammatory bowel disease	1 (0.4)	1 (0.4)	1 (0.4)
Post-ARDS fibrosis	0 (0)	0 (0)	1 (0.4)
Hypereosinophilic syndrome	1 (0.4)	1 (0.4)	1 (0.4)

IPF idiopathic pulmonary fibrosis, *HP* hypersensitivity pneumonitis, *CTD-ILD* connective tissue disease-related interstitial lung disease, *IPAF* interstitial pneumonia with autoimmune features, *IPPFE* idiopathic pleuroparenchymal fibroelastosis, *RB-ILD* respiratory bronchiolitis interstitial lung disease, *DIP* desquamative interstitial pneumonia, *NSIP* non-specific interstitial pneumonia, *COP* cryptogenic organizing pneumonia, *ANCA* antineutrophil cytoplasmic antibody, *ARDS* adult respiratory distress syndrome

[a] Pre-bronchoscopy diagnosis takes into account the history, examination, serologic studies, and initial HRCT results

[b] Post-bronchoscopy diagnosis takes into account the history, examination, serologic studies, initial HRCT, and bronchoscopy results

[c] Final diagnosis takes into account the history, examination, serologic studies, initial and subsequent HRCT, bronchoscopy, SLB, and explant results

[d] 4 patients with a pre-bronchoscopy diagnosis of IPF received a post-bronchoscopy diagnosis of HP, and 1 patient with a pre-bronchoscopy diagnosis of unclassifiable ILD received a post-bronchoscopy diagnosis of IPF based on the presence of fibroblastic foci on transbronchial biopsy. Therefore, there were 3 net fewer IPF diagnosis post-bronchoscopy compared to pre-bronchoscopy

Table 3

Clinical features associated with change in ILD diagnosis after incorporating bronchoalveolar lavage and/or transbronchial biopsy data

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
Age	1.01 (0.99–1.04)	0.25		
Male	2.49 (1.37–4.59)	0.0031	2.01 (0.96–4.30)	0.067
Non-Hispanic white	1.72 (0.87–3.62)	0.13		
Smoking status	2.01 (1.11–3.67)	0.022	1.69 (0.81–3.61)	0.17
Antigen identified	6.13 (2.97–14.0)	< 0.0001	4.48 (1.92–11.5)	0.0008
HRCT pattern consistent with a non-IPF diagnosis	2.90 (1.36–6.97)	0.0097	4.71 (1.94–13.0)	0.0012
Pre-bronchoscopy CTD or IPAF diagnosis	0.03 (0.002–0.15)	0.0006	0.05 (0.003–0.26)	0.0046

Table 4

Change in diagnosis after bronchoscopy based on the presence of antigen

	Change in diagnosis with BAL only (*N* = 147)	**Change in diagnosis with BAL + TBBx (*N* = 117)**	***P* value**
Antigen	26 (26.2)	35 (42.1)	0.028
No antigen	6 (12.5)	5 (14.7)	1.0
Overall	32 (21.8)	40 (34.1)	0.027

Table 5

Yield of bronchoscopy by HRCT pattern ($N = 244$)

	Inconsistent with UIP *N* (%)	**Definite, probable, or indeterminate UIP N (%)**	***p* value**
Change in diagnosis with BAL	27 (25.5%)	5 (12.5%)	0.12
Change in diagnosis with BAL + TBBx	34 (40.0)	6 (19.4)	0.048