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Bronchoscopic Cryobiopsy and Forceps Biopsy for the Diagnostic Evaluation of Diffuse Parenchymal Lung Disease in Clinical Practice

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Abstract

Objective: To assess the contribution and safety of bronchoscopic cryobiopsy vs traditional forceps biopsy used in clinical practice for diagnosing diffuse parenchymal lung disease (DPLD).

Patients and Methods: We identified 271 patients who underwent bronchoscopic biopsy for DPLD at Mayo Clinic, MN (June 1, 2013, through September 30, 2017). Medical records were reviewed including prebiopsy clinical and radiographic impressions. *Diagnostic yield* was assessed in terms of a specific histologic pattern resulting in a diagnosis when combined with the clinical-radiologic context. *Clinical utility* was defined as a biopsy result deemed useful in patient management.

Results: The cohort included 120 cryobiopsy and 151 forceps biopsy cases with mean age 61±14 years and 143 (53%) men. Diagnostic yield (55% vs 41%; odds ratio [OR], 1.73; 95% CI, 1.07 to 2.83; P=.026) and clinical utility (60% vs 40%; OR, 2.21; 95% CI, 1.36 to 3.63; P=.001) were higher for the cryobiopsy group, and the association remained after control for prebiopsy clinical impressions (OR, 2.21; 95% CI, 1.22 to 4.08; P=.010 and OR, 3.23; 95% CI, 1.76 to 6.10; P<.001, respectively). However, pneumothorax (5.4% vs 0.7%; P=.022) and serious bleeding (7.1% vs 0%; P=.001) rates were higher for the cryobiopsy group. Thirty-day mortality was 1.6% in the cryobiopsy group vs 0% for the forceps biopsy group (P=.20).

Conclusion: Bronchoscopic cryobiopsy revealed higher diagnostic yield and clinical utility than did forceps biopsy. However, procedure-related complications were higher in the cryobiopsy group. The choice of bronchoscopic biopsy procedure for patients with DPLD depends on the clinicalradiologic context.

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Histologic features provided by lung biopsy may be needed in the multidisciplinary diagnosis of diffuse parenchymal lung disease (DPLD), particularly when findings on chest computed tomography (CT) are nonspecific.[1-6] However, the optimal means for obtaining histology remains unclear. Surgical lung biopsy (SLB) has the highest diagnostic yield but is associated with significant morbidity and mortality.[7] Transbronchial forceps biopsy (TBFB) is safe and remains a common bronchoscopic modality[8] to obtain tissue in DPLD but with limited diagnostic yield, particularly for usual interstitial pneumonia (UIP).[9,10]

Transbronchial lung cryobiopsy (TBCB) is potentially safer than SLB yet more effective than TBFB because of larger biopsy samples with less crush artifact.[11,12] Furthermore, TBCB may provide sufficiently high agreement with SLB for histopathologic patterns to offer a safe yet reliable alternative.[13,14] Despite multiple studies,[11,15] however, the role of TBCB in the diagnostic algorithm for DPLD remains

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uncertain.[2,4,16-19] In addition, the clinical utility of bronchoscopic lung biopsy has not been studied with assessment of patient-related outcomes.

The Expert Statement from the Cryobiopsy Working Group[20] calls for further studies to clarify patient selection criteria, define clinically important end points, and compare TBCB to "standard of care," which remains to be defined. The objective of this study was to compare the diagnostic yield and safety of TBCB and TBFB used in the diagnostic evaluation of patients with DLPD in clinical practice.

PATIENTS AND METHODS

Patient Selection

The study was approved by the Mayo Clinic Institutional Review Board (IRB 15-008652). Using a computer-assisted search, we identified 826 patients who underwent bronchoscopic lung biopsy for the evaluation of DPLD at Mayo Clinic, Rochester, Minnesota, from June 1, 2013, through September 30, 2017. Patients were excluded if the procedure was performed for an indication other than DPLD (154 mass lesions and 129 cavitary lesions/infections). We also excluded lung transplant recipients (49 TBFB) and procedures for debulking of airway lesions (215 TBCB). Eight patients did not provide Minnesota research authorization and were excluded. The remaining 271 patients comprised the study cohort.

Data Collection

Medical records were reviewed for patient's demographic characteristics, body mass index (calculated as the weight in kilograms divided by the height in meters squared), smoking history, clinical presentation, comorbidities, resting oxygen saturation, pulmonary function test, echocardiography, prebiopsy clinical and radiologic impressions, treatment, subsequent procedures, and clinical outcome. *Prebiopsy clinical impressions* were organized by suspected clinical diagnoses for DPLD, and *radiologic impression* was categorized according to the revised international consensus criteria for idiopathic pulmonary fibrosis (IPF)[1,6]: UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and alternative diagnosis. Each biopsy procedure report was individually reviewed. Bronchoalveolar lavage (BAL) results were recorded when performed. Specific histologic patterns were categorized as "diagnostic" or "nondiagnostic."

Procedure

Patients were fiberoptically intubated with an 8.0-mm cuffed endotracheal tube using moderate to deep sedation in the bronchoscopy suite. The Mayo Clinic bronchoscopy protocol has been previously described.[12,14,17,19] For TBCB, we routinely placed a deflated 7F or 9F Arndt bronchial blocker (Cook Medical) external to the tube in the mainstem bronchus on the side chosen for biopsy to occlude the airway in case of bleeding.[21] In patients with advanced pulmonary disease, we blocked the entire lung before biopsy for approximately 1 minute to ensure the patient could tolerate single lung ventilation in the event of a severe bleeding episode or pneumothorax. All anticoagulants were discontinued before the procedure per guidelines.[22] The bronchoscope (Olympus XT180) was advanced to the segment chosen for biopsy. The 1.9-mm cryoprobe (Erbe Elektromedizin GmBH) was introduced through the working channel of a flexible bronchoscope and passed into the distal airways until meeting resistance, and then withdrawn typically 1 cm from the pleura, under fluoroscopic guidance. The cryoprobe was cooled for 3 to 7 seconds at the desired location and firmly pulled back, separating the frozen biopsy sample from the lung. The bronchial blocker balloon was inflated as the bronchoscope and cryoprobe were removed as a single unit. The tip of the cryoprobe was submerged in saline at room temperature to thaw the specimen, which was transferred to formalin. We inflated the balloon prophylactically to prevent any potential blood from spilling into the airway while the specimen thawed from the tip of the probe. A biopsy was performed on only 1 lung per patient, and 3 cryobiopsy samples were generally obtained from 1 to 2 lobes. The balloon was deflated once the bronchoscope was back in the airway, and bleeding was assessed. All procedures were performed or directly supervised by one of the coauthors (E.S.E., D.E.M., J.J.M., R.M.K., D.R.N.), who were experienced in advanced interventional procedures including TBCB.

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Procedural Complications

Complications were assessed according to similar studies and guidelines.[2,15,23] *Pneumothorax* was documented per procedural report, radiologic confirmation, and need for chest tube insertion. *Significant bleeding* was defined by prolonged or repeated balloon occlusion (per procedural note), use of adjunct measures (eg, cold saline), or blood product transfusion.[23] *Escalation of care* was defined by a change in the level of clinical care (eg, hospital/intensive care unit admission or increased oxygen/ventilator support).

Clinical Outcomes

The study had co-primary outcomes: diagnostic yield and clinical utility. Diagnostic yield was assessed in terms of a specific histologic pattern identified and resulting in a diagnosis when combined with the clinicalradiologic context. *Clinical utility* was defined as a biopsy result assessed to be useful in the treatment or management of the patient per the final diagnosis (eg, obviate the need for SLB or allow the initiation of therapy such as immunomodulators).[19,24] *Final diagnosis* was determined independently by 2 investigators (M.K. and J.H.R.) on review of all available data including length of follow-up. Discrepancies were reviewed to provide a composite final diagnosis.

Statistical Analyses

Data were analyzed with R software version 3.4.2 (R Core Team). Continuous variables were expressed as mean ± SD and median (interquartile range) and categorical variables as frequency and percentage. Kruskal-Wallis and chi-square tests were performed to compare the 2 groups (TBFB and TBCB) for continuous and categorical variables. The association of biopsy (TBFB vs TBCB) with diagnostic yield and clinical utility was assessed using logistic regression adjusted for prebiopsy clinical impressions that differed between groups. Length of follow-up was calculated as the time from the procedure date to the most recent clinical encounter and/or time of death. In all cases, *P* values less than .05 were considered statistically significant.

RESULTS

The baseline characteristics of the 271 patients were as follows: 53% men, mean age 61±14 years, and 34% with smoking history (Table 1). Comorbidities and lung functions did not differ between groups. The mean resting oxygen saturation was 93±11, and 5% of patients were receiving chronic supplemental oxygen. Most (92%) were outpatient procedures.

Prebiopsy clinical diagnoses (Table 2) were similar between groups, except fibrotic interstitial lung disease (ILD), including UIP and non-UIP fibrotic ILD, and aspiration were more frequently sampled with TBCB whereas eosinophilic pneumonia, organizing pneumonia, and infection were more frequently sampled with TBFB. The radiologic diagnosis (Table 3) of "alternative diagnosis" was more frequently associated with TBFB, while "indeterminate UIP" was more frequently associated with TBCB. Only 4 cases radiologically categorized as "probable UIP" and none categorized as "UIP pattern" were referred for bronchoscopic lung biopsy.

Table 4 lists procedural outcomes and complications. Diagnostic yield (55% vs 41%; OR, 1.73; 95% CI, 1.07 to 2.83; *P*=.026) and clinical utility (60% vs 40%; OR, 2.21; 95% CI, 1.36 to 3.63; *P*=.001) were higher for the TBCB group than for the TBFB group. The association of higher diagnostic yield and clinical utility with TBCB remained after control for prebiopsy clinical impressions associated with each procedure (OR, 2.21; 95% CI, 1.22 to 4.08; *P*=.010 and OR, 3.23; 95% CI, 1.76 to 6.10; *P*<.001, respectively) (Table 5).

Pneumothorax was more common in the TBCB group (5% vs 0.7%; *P*=.022) but few required chest tube insertion, with no significant difference observed between TBCB and TBFB groups (0.9% vs 0.7%; *P*=.59). Significant bleeding was more frequent in the TBCB group (7% vs 0%; *P*=.001), with no difference for procedure-related escalation of care (6% vs 2%; *P*=.09). Two deaths in the TBCB group occurred during the 30-day postprocedural period. The first death occurred in a 45-year-old woman with acute exacerbation of ILD. She received increasing oxygen supplementation postprocedure, requiring mechanical ventilator support and died on day 18; she was diagnosed with dermatomyositis-associated ILD. The second death occurred in a 56-year-old man with acute lung injury (acute fibrinous and organizing pneumonia

TABLE 1. Baseline Demographic and Clinical Features of Study Patients[a,b]

Parameter	Total (N=271)	TBFB (n=151)	TBCB (n=120)	*P* value[c]
Age (y)	61±14	59±14	62±14	.091
Male sex	143 (53)	76 (50)	67 (56)	.37
Smoking history	91 (34)	48 (32)	43 (36)	.51
COPD	16 (6)	11 (7)	5 (4)	.27
Pulmonary hypertension[d]	21 (8)	17 (12)	4 (3)	.011
Obstructive sleep apnea	37 (14)	24 (16)	13 (11)	.20
CTD	46 (17)	25 (17)	21 (18)	.90
Renal insufficiency	5 (2)	4 (3)	1 (1)	.26
Body mass index (kg/m^2)	30±7	30±8	30±6	.99
Resting Spo_2%	92.5±11	94±4	91±15	.22
Supplemental oxygen	13 (5)	7 (6)	6 (5)	.93
FEV_1% predicted	74±20	74±20	73±21	.84
FEV_1/FVC	77±12	77±11	76±12	.81
FVC% predicted	77±18	78±19	75±18	.27
TLC% predicted	82±17	84±17	79±17	.065
DLCO% predicted (corrected for Hgb)	64±19	65±19	51±27	.20

[a]COPD = chronic obstructive pulmonary disease; CTD = connective tissue disease; DLCO = single-breath diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; Hgb = hemoglobin (g/dL); Spo_2 = peripheral capillary oxygen saturation; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; TLC = total lung capacity.
[b]Data are presented as mean ± SD for continuous variables or as No. (percentage) for categorical variables.
[c]Kruskal-Wallis for continuous variables and χ^2 test for categorical variables.
[d]Echocardiographic results not available for 62 patients who underwent TBFB (44.9%) and 55 patients who underwent TBCB (47.4%).

pattern) in the setting of sepsis. He was readmitted for refractory status epilepticus of unknown etiology on postprocedure day 29 and died on day 30. Neither patient underwent autopsy.

The histologic diagnosis and corresponding clinical diagnosis per procedure are described in Supplemental Table (available online at http://www.mcpiqojournal.org). The median length of follow-up for TBFB and TBCB groups was 413.5 days (interquartile range, 65-915 days) and 248 days (interquartile range, 37-590 days), respectively.

Discordant Diagnostic Yield and Clinical Utility

Four biopsies (2 TBFB and 2 TBCB) were *diagnostic but deemed not clinically useful*. In 3 cases, the histologic pattern organizing pneumonia (1 TBFB and 2 TBCB) was associated with a final diagnosis of indeterminate fibrotic ILD (1 case), granulomatous polyangiitis (1 case), and IPF (1 case). The remaining TBFB case was respiratory bronchiolitis in a nonsmoker with a final diagnosis of UIP (per SLB).

Ten biopsies (1 TBFB and 9 TBCB) were considered *clinically useful despite nondiagnostic histology*. All histologic samples contained adequate lung tissue but nondiagnostic histologic patterns. In 7 cases, immunosuppressive therapy was initiated on the basis of the exclusion of infection and an alternative diagnosis. These cases included 4 hypersensitivity pneumonitis (HP) and 3 connective tissue disease (CTD)—associated nonspecific interstitial pneumonia (rheumatoid arthritis, undifferentiated CTD, and polymyositis). The remaining 3 cases included chronic HP, aspiration pneumonitis, and resolving *Pneumocystis jirovecii* pneumonia supported by clinicoradiologic correlation. Assessment of the subsequent clinical course in these patients did not suggest an alternative diagnosis.

Subsequent SLB and Other Procedures

Among 86 nondiagnostic TBFB cases, 14 (16%) underwent subsequent procedures (12 SLB, 1 CT-guided lung biopsy, and 1 rib biopsy [pulmonary Langerhans cell histiocytosis]) and a definitive diagnosis was revealed in

TABLE 2. Favored Prebiopsy Clinical Diagnosis[a,b]

Diagnosis	Total (N=271)	TBFB (n=151)	TBCB (n=120)	*P* value[c]
Granulomatous, noninfectious[d]	133 (49)	76 (50)	57 (48)	.64
Non-IPF fibrotic ILD[e]	66 (24)	28 (19)	38 (32)	.012
Infection[f]	60 (22)	46 (31)	14 (12)	<.001
Organizing pneumonia[g]	53 (20)	36 (24)	17 (14)	.046
Indeterminate ILD[h]	52 (19)	31 (21)	21 (18)	.53
IPF/UIP[i]	33 (12)	10 (7)	23 (19)	.002
Eosinophilic pneumonia	29 (11)	23 (15)	6 (5)	.007
Neoplasm[j]	27 (10)	14 (9)	13 (11)	.67
Vasculitis	21 (8)	13 (9)	8 (7)	.55
RB-ILD/DIP	19 (7)	10 (7)	9 (8)	.78
Aspiration[k]	17 (6)	5 (3)	12 (11)	.024
pLCH	4 (2)	3 (2)	1 (0.8)	.43
DAH	6 (2)	4 (3)	2 (2)	.59
Amyloid	3 (1)	1 (0.7)	2 (2)	.43
CHF[l]	3 (1)	2 (1)	1 (0.8)	.70
Bronchiolitis	3 (1)	2 (1)	1 (0.8)	.70
PAP	3 (1)	2 (1)	1 (0.8)	.70
LAM	1 (0.4)	1 (0.7)	0	.37
Pneumoconiosis	1 (0.4)	1 (0.7)	0	.37

[a]CHF = congestive heart failure; DAH = diffuse alveolar hemorrhage; DIP = desquamative interstitial pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; NSIP = nonspecific interstitial pneumonia; PAP = pulmonary alveolar proteinosis; pLCH = pulmonary Langerhans cell histiocytosis; RB-ILD = respiratory bronchiolitis-interstitial lung disease; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; UIP = usual interstitial pneumonia.

[b]Data are presented as No. (percentage).

[c]Chi-square test.

[d]Noninfectious granulomatous process, eg, sarcoidosis (well-formed noncaseating granulomas), hypersensitivity pneumonitis (poorly formed granulomas, lymphocytic interstitial infiltrates, and cellular bronchiolitis).

[e]Non-IPF fibrotic ILD such as NSIP.

[f]Infections presenting as ILD (eg, Cytomegalovirus pneumonia).

[g]Organizing pneumonia, eg, cryptogenic organizing pneumonia, connective tissue disease–associated ILD, and drug-induced lung disease.

[h]Indeterminate clinicoradiographic pattern.

[i]Cases in which a radiographic pattern consistent with UIP and clinical diagnosis with IPF.

[j]Neoplastic diseases presenting as ILD (eg, lymphangitis carcinomatosis and lymphoproliferative diseases).

[k]Aspiration (eg, food or vegetable matter with pneumonia).

[l]Congestive heart failure presenting as ILD.

93%. Among 45 nondiagnostic TBCB cases, 10 (22.2%) underwent subsequent SLB (2 UIP [IPF], 3 chronic HP, 1 cryptogenic constrictive bronchiolitis, 1 desquamative interstitial pneumonia, and 1 pulmonary veno-occlusive disease) and a definitive diagnosis was revealed in 80%.

DISCUSSION

We studied the diagnostic yield, clinical utility, and complications associated with the use of TBCB and TBFB in the diagnostic evaluation of DPLD in a tertiary care center experienced in both procedures. Transbronchial cryobiopsy revealed increased diagnostic yield and clinical utility, and the association remained after adjustment for prebiopsy clinical and radiologic impressions associated with each procedure. Procedure-related complications were uncommon in both groups; however, 2 deaths occurred in the TBCB group at postprocedure day 18 and day 30.

Diagnostic Yield and Clinical Utility

The diagnostic yield of TBCB was higher than that of TBFB in our cohort but lower compared to previous TBCB studies.[10,15] Possible explanations include technique and

TABLE 3. Prebiopsy Radiologic Diagnosis[a,b]

Diagnosis	Total (N=271)	TBFB (n=151)	TBCB (n=120)	*P* value[c]
UIP	0			.002
Probable UIP	4 (1.7)	2 (2)	2 (2)	
Indeterminate UIP	60 (25)	20 (16)	40 (36)	
Alternative diagnosis	174 (73)	104 (83)	70 (63)	

[a]TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; UIP = usual interstitial pneumonia.
[b]Data are presented as No. (percentage).
[c]Chi-square test.

patient selection. For example, a more peripheral placement of the cryoprobe might increase the diagnostic yield, particularly for predominantly subpleural disease process such as UIP, but is associated with an increased risk of pneumothorax.[4] Our group has not intentionally tried to include pleura in the biopsy. Diagnostic yield may be affected by patient selection. This was assessed in our study by prebiopsy clinical and radiographic impressions. Of 271 patients in our cohort, only 1.7% of patients with a "probable UIP pattern" and none with a "UIP pattern" imaging pattern were referred for bronchoscopic biopsy, which may reflect a preference in our practice to avoid biopsy in such patients. This may also explain the observation that UIP (3.3% TBFB and 7.5% TBCB) was far less common in our study compared with other TBCB studies.[15]

"Diagnostic" histopathologic patterns attained by bronchoscopic biopsies, in the absence of clinicalradiologic correlation, may be misleading as suggested by the recent study by Romagnoli et al[25] comparing TBCB and SLB. In contrast, Troy and coworkers[13,14] reported a good concordance between TBCB and SLB for both histopathologic pattern and consensus diagnosis in the context of multidisciplinary discussion, particularly for high-confidence patterns. Some cases without high-confidence diagnoses deserve a "provisional diagnosis" to emphasize the need to reassess over time.[26]

Clinical utility, in our study, was defined as a biopsy result useful in the treatment or management of the patient and consistent with the final diagnosis. In addition to subsequent SLB results (when available), the final diagnosis was supported by the clinicoradiologic course

TABLE 4. Procedural Outcomes and Complications per Bronchoscopic Procedure[a,b]

Parameter	Total (N=271)	TBFB (n=151)	TBCB (n=120)	*P* value[c]
BAL performed	223 (89)	137 (95)	86 (81)	<.001
Diagnostic yield	128 (47)	62 (41)	66 (55)	.025
Clinical utility	133 (49)	61 (40)	72 (60)	.001
Pneumothorax	7 (3)	1 (0.7)	6 (5)	.022
Chest tube insertion	2 (1)	1 (0.7)	1 (0.9)	.59
Significant bleeding[d]	8 (3.1)	0	8 (7)	.001
Escalation of care[e]	10 (4)	3 (2)	7 (6)	.09
30-d mortality	2 (0.7)	0	2 (1.6)	.20

[a]BAL = bronchoalveolar lavage; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy.
[b]Data are presented as No. (percentage).
[c]Chi-square test.
[d]*Significant bleeding* was defined as the need for blood products (n=0) or change in procedure protocol to control excessive bleeding (eg, prolonged tamponade).
[e]*Escalation of care* was defined as the change in disposition (hospitalization/intensive care unit admission) or increase in ventilator/oxygen requirements upon discharge from the postprocedural recovery unit.

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and strengthened the diagnostic reliability in certain cases. Ten cases (9 TBCB and 1 TBFB) were clinically useful despite nondiagnostic biopsies. In all cases, adequate lung tissue was obtained and deemed sufficient to exclude infection/alternative diagnoses and enable immunomodulatory therapy in 7 cases and confirm clinical suspicion in 3 cases.

Surgical Lung Biopsy for Nondiagnostic Bronchoscopy

Diagnostic bronchoscopy may prevent the need for SLB according to clinical pathways proposed in recent guidelines.[1,6,27] In our study, only 22.2% and 16.2% of nondiagnostic TBCB and TBFB cases, respectively, underwent SLB (or other procedures) for a definitive diagnosis. Of 14 TBFB and 10 TBCB nondiagnostic cases that underwent additional procedures (22 SLB, 1 CT-guided lung, and 1 CT-guided rib biopsy), 91.6% had a definitive diagnosis.

Mortality

The Expert Statement from the Cryobiopsy Working Group[20] recommends TBCB as a safer alternative to SLB. However, reports of life-threatening complications[28,29] and mortality,[2,3,16,30-32] including the 2 cases described in our study, raise some concern over the safety profile and patient selection criteria. If TBCB is to offer a safer alternative to SLB, then observations from the SLB literature may have relevance. For example, preoperative risk factors for mortality in patients undergoing SLB have included supplemental oxygen, ventilator dependence, increased age, and pulmonary hypertension[7,33-35] as well as specific underlying diagnoses, particularly IPF. In the study by Kreider et al,[34] the 3 patients who died shortly after SLB exhibited new infiltrates on chest CT unexplained by infection, congestive heart failure, or pulmonary embolism; postmortem examination revealed diffuse alveolar damage superimposed on UIP, suggesting acute exacerbation of IPF. In a similar report, Parambil et al[36] observed high mortality (86%) in patients after SLB in whom histopathology revealed diffuse alveolar damage superimposed on UIP; all patients presented with bilateral infiltrates, BAL neutrophilia without infection, and normal echocardiography at the time of presentation.

TABLE 5. Comparative Outcomes Adjusted by Prebiopsy Clinical and Radiographic Impressions[a,b,c]

	Odds ratio	95% CI	*P* value
Association with diagnostic yield			
TBCB	1.73	1.07-2.83	.026
TBCB adjusted for clinical impression	2.21	1.22-4.08	.010
Association with clinical utility			
TBCB	2.21	1.36-3.63	.001
TBCB adjusted for clinical impression	3.23	1.76-6.10	<.001

[a]ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; TBCB = transbronchial cryobiopsy; TBFB = transbronchial forceps biopsy; UIP = usual interstitial pneumonia.
[b]Prebiopsy clinical impressions UIP/IPF, non-IPF fibrotic ILD, and aspiration pneumonitis were associated with TBCB (*P*=.002, *P*=.012, and *P*=.024, respectively). Eosinophilic pneumonia, organizing pneumonia, and infection were associated with TBFB (*P*=.007, *P*=.046, and *P*=.001, respectively).
[c]Radiographic impression "indeterminate UIP" was associated with TBCB, whereas "alternative diagnosis" was associated with TBFB (*P*=.002).

Utz et al[37] observed increased mortality (16% vs 0%) in patients with idiopathic UIP (IPF) compared to CTD-associated UIP. Finally, Hutchinson et al[38] studied 32,022 cases of SLB for the diagnosis of ILD in which inpatient mortality ranged from 1.7% to 16% for elective and nonelective procedures, respectively. All these studies suggest increased preoperative risk in patients presenting with acute exacerbation, particularly those with underlying IPF.

Mortality in patients undergoing TBCB may be underestimated. Although procedure-related complications such as pneumothorax and bleeding are well documented in multiple TBCB studies,[10,15] reports of 30-day deaths appear limited to those deemed related to the procedure.[2,3,5,16,39] This limitation may explain the very low 0.3% mortality in the meta-analysis by Sethi et al.[10] The true mortality risk may be higher as indicated in our study and the 2% 30-day mortality rate in the recent prospective study by Hagmeyer et al.[40] More recently, Pannu et al[41] also reported a 30-day mortality rate of 2.0% in 187 patients undergoing TBCB.

The complication rate was otherwise low in our study.[15] The low bleeding rate may be attributed to the routine use of an endobronchial blocker, and the procedure-related escalation of care was low and did not differ between groups. Selective balloon occlusion of the predetermined side for biopsy, to predict ventilatory reserve in the event of bleeding

or pneumothorax, may explain the low rate of procedure-related respiratory compromise. The pneumothorax rate was higher for TBCB than for TBFB, but the need for chest tube insertion did not differ significantly between groups. Notably, the TBCB pneumothorax rate was lower in our study than in previous TBCB studies, which report higher histopathologic yield.[2,15,16,32,39]

The decision to pursue bronchoscopy and which sampling methods to use (ie, BAL and biopsy modality) should be made on the basis of the nature of the diagnostic dilemma at hand. The desire for increased diagnostic certainty may be achieved with biopsy, and thus TBCB appears to have increased utility compared with TBFB. In certain cases, however, increased confidence for a treatment decision may be achieved with BAL alone. For example, 7 of 10 cases in this study were deemed "clinically useful despite nondiagnostic histology" because the procedure enabled immunosuppressive therapy on the basis of the exclusion of infection and alternative diagnoses; all histologic samples contained adequate lung tissue but nondiagnostic histologic patterns.

Limitations

Limitations in our study include those inherent in the retrospective design. In particular, the preferential selection of suspected UIP cases and non-UIP fibrotic ILD for TBCB may have reduced the comparative efficacy of TBCB over TBFB. Because of the lack of randomization, the study does not address whether TBFB and TBCB reveal comparable yield in diseases with bronchocentric and perilymphatic distribution, such as sarcoidosis and lymphangitic carcinomatosis, although this premise is suggested by previous studies and experience.[19,42-44] The applicability of our findings to the spectrum of DPLD is supported by the wide range of prebiopsy clinical impressions and final diagnoses distributed between both groups.

CONCLUSION

Transbronchial cryobiopsy revealed increased diagnostic yield and clinical utility in the diagnostic evaluation of DPLD in clinical practice despite selection for more challenging cases. Both procedures were associated with low complication rates, but 2 deaths occurred in the TBCB group during the 30-day postprocedural period; both patients underwent bronchoscopy during the acute worsening of lung disease. For patients with nondiagnostic bronchoscopic biopsy results, the clinical utility of an additional biopsy procedure for diagnostic clarification needs to be decided on a case-by-case basis. Future studies of TBCB should include systematic reporting of 30-day mortality to identify patients at an increased risk of delayed complications and mortality.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BAL** = bronchoalveolar lavage; **CT** = computed tomography; **CTD** = connective tissue disease; **DAH** = diffuse alveolar hemorrhage; **HP** = hypersensitivity pneumonitis; **ILD** = interstitial lung disease; **IPF** = idiopathic pulmonary fibrosis; **OR** = odds ratio; **SLB** = surgical lung biopsy; **TBCB** = transbronchial cryobiopsy; **TBFB** = transbronchial forceps biopsy; **UIP** = usual interstitial pneumonia

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