Transbronchial Lung Cryobiopsy for Diagnosing Interstitial Lung Disease: A Retrospective Single-Center Experience

Jin Han Park, M.D. 1, Ji Hoon Jang 1, Hyun Kuk Kim, Ph.D. 1, Hang-Jea Jang, M.D. 1, Sunggun Lee, Ph.D. 2, Seong-Ho Kim, Ph.D. 3, Ji Yeon Kim, Ph.D. 4, Hee Eun Choi, M.D. 5, Ji-yeon Han, Ph.D. 6, Da Som Kim, M.D. 7, Sunggun Lee, Ph.D. 2, Seong-Ho Kim, Ph.D. 2, Ji Yeon Kim, Ph.D. 4, Hee Eun Choi, M.D. 5, Ji-yeon Han, Ph.D. 6, Da Som Kim, M.D. 7, Min Kyun Kang, M.D. 6, Eunsu Kang, M.D. 6, II Hwan Kim, Ph.D. 8, Jae Ha Lee, Ph.D. 1

1 Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, 2 Division of Rheumatology, Department of Internal Medicine, 3 Department of Pathology, 4 Department of Physical Medicine and Rehabilitation, Haeundae Paik Hospital, Inje University College of Medicine, Busan, 5 Department of Radiology, Busan Paik Hospital, Inje University College of Medicine, Busan, 6 Department of Thoracic and Cardiovascular Surgery, 7 Department of Anesthesiology, 8 Division of Oncology, Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea

Abstract

Background: An accurate diagnosis in patients with interstitial lung diseases (ILDs) by multidisciplinary discussion (MDD) based on histopathologic information is essential for optimal treatment. Transbronchial lung cryobiopsy (TBLC) has increasingly been used as a diagnostic alternative to surgical lung biopsy. This study aimed to evaluate the appropriate methods of TBLC in patients with ILD in Korea.

Methods: A total of 27 patients who underwent TBLC were included. TBLC procedure details and clinical MDD diagnosis using TBLC histopathologic information were retrospectively analyzed.

Results: All procedures were performed under general anesthesia with the fluoroscopic guidance in the operation room using flexible bronchoscopy and endobronchial balloon blocker. The median procedure duration was less than 30 minutes, and the median number of biopsies per participant was 2. Most of the bleeding after TBLC was not severe, and the rate of pneumothorax was 25.9%. The most common histopathologic pattern was alternative (48.2%), followed by indeterminate (33.3%) and usual interstitial pneumonia (UIP)/probable UIP (18.5%). In the MDD after TBLC, the most common diagnosis was idiopathic pulmonary fibrosis (33.3%), followed by smoking-related ILD (25.9%), nonspecific interstitial pneumonia (18.6%), unclassifiable-ILD (14.8%), and others (7.4%).

Conclusion: This first single-center experience showed that TBLC using a flexible bronchoscopy and endobronchial balloon blocker with the fluoroscopic guidance under general anesthesia may be a safe and adequate diagnostic method for ILD patients in Korea. The diagnostic yield of MDD was 85.2%. Further studies are needed to evaluate the diagnostic yield and confidence of TBLC.

Keywords: Interstitial Lung Disease; Diagnosis; Transbronchial Lung Cryobiopsy; Multidisciplinary Discussion

Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of chronic, progressive, diffuse parenchymal lung diseases with different prognostic and therapeutic implications. An accurate diagnosis of ILD is necessary...
Materials and Methods

1. Study population
This was a retrospective, descriptive, single-center study that included 27 patients with ILD who underwent TBLC at Haeundae Paik Hospital, Busan, Republic of Korea from July 2019 to December 2021. All subjects were evaluated and diagnosed by international guidelines by the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Society. Decision of performing the pathologic exam and final diagnosis was made in the MDD comprising two pulmonologists, one pathologist, two radiologists, and two rheumatologists. TBLC was performed only in patients with preference following informed consent after explanation of TBLC and SLB. The study protocol was approved by the Institutional Review Board of Haeundae Paik Hospital (approval number: 2019-08-007). The requirement for written informed consent was waived due to the retrospective nature of this study.

2. Clinical information
Clinical data for all patients were retrospectively obtained from medical records. The results of pulmonary function test and six-minute walk test (6MWT) within three months were collected. Spirometry, measurement of diffusing capacity of the lung for carbon monoxide (DLco), and plethysmography for the measurement of total lung capacity were performed according to the recommendations of the ATS/ERS; the results were expressed as percentages of normal predicted values. The 6MWT was performed according to ATS guidelines. Bronchoalveolar lavage was performed at the same time of TBLC or within three months in accordance with ATS guidelines. Serum laboratory tests including autoimmune panel were collected.

3. TBLC procedure
TBLC was performed by one pulmonologist and one experienced interventional pulmonologist. All procedures were performed under general anesthesia with spontaneous ventilation through an endotracheal tube using fluoroscopy in the operation room. A flexible bronchoscope (BF-P290, 4 mm scope, Olympus, Tokyo, Japan) and a 1.7-mm or 1.9-mm cryoprobe (ERBECRYO, Erbe Elektromedizin GmbH, Tuebingen, Germany) were used. To locate the target lesion, the cryoprobe via bronchoscopy was advanced into a segmental bronchus and a target site 1–2 cm away from the pleura was confirmed under fluoroscopic guidance. After freezing of the cryoprobe for six seconds, the bronchoscope and cryoprobe were simultaneously pulled back, followed by immediately inflation of the endobronchial balloon for hemostasis. For the endobronchial blocker, the Fogarty catheter (4Fr, Edwards Lifesciences, Irvine, CA, USA) and the Univent tube (TCB type, Fuji Systems, Tokyo, Japan) were used. The obtained specimens were thawed in saline and pressured negatively with a syringe for one minute to prevent crush artifact and then transferred gently to formalin for fixation. The classification of bleeding severity based on the four-point scale suggested by Hetzel et al. as follows: grade 0, no bleeding; grade 1, mild bleeding with self-limiting, manageable with suction alone; grade 2, moderate bleeding requiring additional intervention such as instillation of saline or transient balloon tamponade to stop bleeding; and grade 3, severe bleeding requiring additional prolonged monitoring or intensive care therapy after the procedure or if the bleeding was fatal. Detection of pneumothorax was investigated using fluoroscopy during the procedure and by chest X-ray after the procedure.

4. Statistical analysis
Data are presented as frequency with percentages for categorical variables and median and interquartile
range values for continuous variables. Some categorical variables ("Bleeding" and "Treatment") include one or more values per patient, and the percentages of those variables are presented as the percentage of patients represented by each value. All statistical analyses were carried out using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

### Results

#### 1. Baseline clinical characteristics

A total of 27 ILD patients who underwent TBLC were included in this study. The median patient age was 65.1 years (range, 63.0–71.0), and 74.1% were male. Among

| Table 1. Baseline clinical characteristics of the patients |
|----------------------------------------------------------|
| **Characteristic** | **Value (n=27)** |
| Age, yr | 65.1 (63.0–71.0) |
| Male sex | 20 (74.1) |
| Weight, kg | 67.0 (58.0–75.0) |
| Height, cm | 1.67 (1.59–1.70) |
| Body mass index, kg/m² | 25.1 (22.5–28.4) |
| Ever-smokers | 20 (74.1) |
| Pack-years | 40.0 (26.3–48.8) |
| BAL WBC, cell/μL | 1,100.0 (400.0–1,900.0) |
| Macrophage, % | 69.5 (48.0–90.0) |
| Neutrophil, % | 5.5 (2.3–26.3) |
| Lymphocyte, % | 8.0 (4.0–22.3) |
| Pulmonary function test FVC, % predicted | 78.0 (66.0–92.0) |
| FEV₁, % predicted | 84.0 (76.0–100.0) |
| DLco, % predicted | 63.0 (48.0–69.0) |
| Six-minute walk test Distance, m | 480.0 (445.5–544.5) |
| Initial SpO₂, % | 96.0 (95.5–97.5) |
| Nadir SpO₂, % | 92.0 (87.0–95.0) |
| Arterial oxygen pressure, mm Hg | 92.0 (66.9–99.8) |
| ProBNP, pg/mL | 73.4 (17.4–101.1) |
| LDH, U/L | 236.5 (197.5–304.8) |
| CRP, mg/dL | 0.17 (0.1–0.4) |
| IL-6, pg/mL | 4.4 (2.3–7.9) |

Values are presented as median (interquartile range) or number (%).

| Table 2. Details of transbronchial lung cryobiopsy |
|---------------------------------------------------|
| **Characteristic** | **Value** |
| Hospital length of stay, day | 3.0 (3.0–4.0) |
| Fogarty catheter | 2 (7.4) |
| Univent endobronchial tube | 25 (92.6) |
| 7.0 Fr | 10 (40.0) |
| 7.5 Fr | 15 (60.0) |
| Flexible bronchoscopy | 27 (100) |
| Cryoprobe | |
| 1.7 mm (disposable) | 15 (55.6) |
| 1.9 mm (reusable) | 12 (44.4) |
| Duration of procedure, min | 20.0 (15.0–30.0) |
| Biopsy location | |
| RLL | 17 (62.9) |
| LLL | 10 (37.1) |
| B8* | 33 (63.5) |
| B9 | 18 (34.6) |
| B6 | 1 (1.9) |
| No. of specimens | 2.0 (2.0–2.0) |
| Biopsy size, cm | |
| Smallest axis diameter | 0.3 (0.2–0.3) |
| Largest axis diameter | 0.5 (0.5–0.7) |
| Bleeding | |
| No bleeding | 10 (19.2) |
| Mild bleeding | 19 (36.5) |
| Moderate bleeding | 20 (38.5) |
| Severe bleeding | 3 (5.8) |
| Pneumothorax | 7 (25.9) |
| Chest tube drain (+) | 2 (7.4) |
| Chest tube drain (–) | 5 (18.5) |
| Pneumonia | 0 (0) |
| Acute exacerbation | 1 (3.7) |
| Death | 0 (0) |

Values are presented as median (interquartile range) or number (%).

*B was defined as segmental bronchus classification according to Japanese system.

RLL: right lower lobe; LLL: left lower lobe; B8: anterior basal in Rt. or anteromedial; B9: lateral basal segment; B6: superior segment.
the patients, 74.1% were ever smokers, and the median pack-years was 40.0 (range, 26.3–48.8). Most patients (88.9%) showed a reduced DLco and more than half of the patients revealed a mild restrictive ventilatory defect. In the MDD prior to TBLC, there were no relevant underlying conditions associated with ILD, except in two patients who were diagnosed with interstitial pneumonia with autoimmune features. The clinical characteristics of the patients are summarized in Table 1.

2. TBLC details
In most patients (81.5%), the median duration of the procedure was less than 30 min, and the median number of biopsies per participant was two (Table 2). All TBLC were performed at the lower lobe (right lobe, 62.9% and left lobe, 37.1%), and the most common level of segmental bronchus was anterior basal (right) or anteromedial (left) (63.5%), followed by lateral basal bronchus (34.6%) according to the Jack-Huber nomenclature of the tracheobronchial tree.23 The median of the largest axis diameter and smallest axis diameter of the specimens were 0.5 cm (range, 0.5–0.7 cm) and 0.3 cm (range, 0.2–0.3 cm), respectively.

Regarding complications, most bleeding after TBLC was not severe and manageable. Among three patients of severe bleeding requiring additional monitoring with use of endobronchial blockers or vasopressor, all patients were recovered without intensive care unit (ICU) admission or surgery. Seven patients (25.9%) had pneumothorax, and two patients recovered after percutaneous chest tube drain during 3 or 4 days. One patient exhibited acute exacerbation after 5 days of the procedure. There was no adverse event of pneumonia and death.

3. Histopathologic assessment and MDD
The most common pattern observed was alternative (48.2%), followed by indeterminate (33.3%) and usual interstitial pneumonia (UIP)/probable UIP (18.5%) (Table 3, Figure 1). Among the alternative patterns, the smoking-related pattern was most common (22.2%), followed by nonspecific interstitial pneumonia (NSIP) (11.1%), inhalation injury (7.4%), and others (7.4%). One patient met the histopathologic criteria of pleuroparenchymal fibroelastosis suggested by Reddy et al., and one patient was diagnosed with malignancy (adenocarcinoma). In the MDD after TBLC, the most common consensus diagnoses were idiopathic pulmonary fibrosis (IPF) (33.3%) and smoking-related ILD (25.9%); four patients (14.8%) did not fulfill diagnostic criteria and were classified as unclassifiable-ILD. Among nine patient diagnosed with IPF on final MDD, four patients were diagnosed with IPF according to the radiologic results (1 UIP and 3 probable UIP), not based on the histopathological result (4 indeterminate). Among eight patients for with non-diagnostic on clinic-radiologic evaluation (4 indeterminate for UIP, 2 probable UIP and 1 alternative pattern on high-resolution computed

### Table 3. Results of radiologic, histopathologic and multidisciplinary diagnosis

| Characteristic                        | No. (%) |
|--------------------------------------|---------|
| **Radiologic pattern**               |         |
| UIP                                  | 1 (3.7) |
| Probable                             | 9 (33.3)|
| Indeterminate UIP                    | 9 (33.3)|
| Alternative UIP                      | 8 (29.7)|
| **Histopathologic pattern**          |         |
| UIP                                  | 0 (0)   |
| Probable UIP                         | 5 (18.5)|
| Indeterminate                        | 9 (33.3)|
| Alternative                          | 13 (48.2)|
| **Specific alternative pattern**     |         |
| Smoking-related ILD                  | 6 (22.2)|
| NSIP                                 | 3 (11.1)|
| Inhalation injury                    | 2 (7.4) |
| PPFE                                 | 1 (3.7) |
| Lung cancer                          | 1 (3.7) |
| **Final MDD diagnosis**              |         |
| IPF                                  | 9 (33.3)|
| Smoking-related ILD*                 | 7 (25.9)|
| NSIP                                 | 5 (18.6)|
| Unclassifiable ILD†                  | 4 (14.8)|
| PPFE                                 | 1 (3.7) |
| Lung cancer                          | 1 (3.7) |
| **Treatment**                        |         |
| Pirfenidone                          | 11 (40.7)|
| Steroid                              | 11 (40.7)|
| Immunosuppressive drug               | 4 (14.8)|
| No treatment                         | 5 (18.5)|

*Smoking-related ILD was defined as the distinct but heterogeneous group of parenchymal lung diseases which can be grouped into those that likely have a causal association with tobacco exposure. Unclassifiable ILD was defined as the absence of a specific diagnosis following a multidisciplinary discussion and review of clinical, radiological, and pathological information.

UIP: usual interstitial pneumonia; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; PPFE: pleuroparenchymal fibroelastosis; MDD: multidisciplinary discussion; IPF: idiopathic pulmonary fibrosis.

https://doi.org/10.4046/trd.2022.0031
tomography [HRCT]), final consensus of MDD (4 smoking-related ILD, 1 inhalation injury, 1 NSIP, and 1 lung cancer) were archived on based on histopathologic results. The final diagnostic yield of MDD based on histopathologic specimens by TBLC was 85.2%, and most patients (81.5%) received anti-fibrotic agent or steroid combined with immunosuppressive agents.

**Discussion**

In our study, TBLC was performed under general anesthesia using flexible bronchoscopy and an endobronchial balloon blocker with the guidance of fluoroscopy. There were no severe complications requiring ICU admission or surgery. Most bleeding events were manageable with an endobronchial balloon blocker, and the incidence of pneumothorax was 25.9%. The diagnostic yield of MDD based on TBLC specimens was 85.2%.

Although TBLC was performed in a small number of patients in the current study, the complications of TBLC were mild and similar to those in previous reports. In this study, we used the endobronchial balloon blocker in all patients, and there was no severe bleeding resulting in ICU admission or death. In a previous study addressing the influence of prophylactic bronchial blocker balloon use, the incidence of moderate to severe bleeding was significantly lower in patients who underwent TBLC with prophylactic balloon placement than those without (35.7% vs. 1.8%, p<0.001). In this study, the incidence of pneumothorax was 25.9%, and 7.4% of patients required percutaneous chest tube drain. We suggest that the guidance of fluoroscopy had an important role of reducing the incidence and severity of pneumothorax. In a study by Dhooria et al. of 128 ILD patients, the incidence of pneumothorax was also significantly lower in patients who underwent the procedure with fluoroscopy compared with those without fluoroscopy (5.9% vs. 20.9%, p=0.01).

Although a standardized practice for TBLC has not yet been established, a learning curve has been suggested in previous studies. Almeida et al. reported that proficiency in TBLC is achieved at approximately 70 procedures using logarithmic regression of diagnostic yield, sample length, and area for groups of consecutive patients. In a study of 512 patients with TBLC, Niwa et al. reported that the incidence of pneumo-
thorax and bleeding decreased after the 79th and 69th experiences, respectively, suggesting a learning curve of TBLC of 79 experiences. In a recent online survey on the practice of TBLC, most TBLC training (43%) was performed by self-training, followed by fellowship training and procedure course/workshops. We have been preparing the setting of TBLC for one year and underwent a short-term training course at an experienced ILD center abroad twice. Therefore, we suggest that in starting TBLC, a direct training course from an experienced center or systematic training course considering specific environmental factors might be helpful to reduce the learning curve and improve patient safety.

The diagnostic yield of TBLC and classification rate of unclassifiable-ILD in this study were similar to those in previous studies. Histopathologic classification of probable UIP was diagnosed in 18.5% of patients, and there was no UIP pattern. And four patients were diagnosed with IPF according to the radiologic pattern, not based on the histological result. We assumed that the absence of UIP in histopathologic analysis might be explained because patients with relatively early stage and who do not have UIP pattern on HRCT were included in this study. Also, it might be the result reflecting the limitations of TBLC in this study, which were related to the small number and size of histopathologic samples, and lack of experiences in histopathological analysis. Among nine patients finally diagnosed with IPF, four patients (44.4%) were diagnosed with four histologic classifications of indeterminate including three probable UIP and one indeterminate on radiologic diagnosis using HRCT. In line with previous studies addressing the important role of MDD, MDD was necessary to increase the diagnostic confidence and yield of TBLC in patients with ILD.

This study has some limitations. First, this was a retrospective study conducted in a single center with a small number of patients. However, the safety profiles of TBLC and diagnostic yield of MDD in this study were similar to those in previous reports. Second, the diagnostic yield using TBLC histopathologic diagnosis in this study was not sufficiently powered because there was no control group of SLB and the MDD did not have sufficient expertise with TBLC. Further study is warranted to prove the diagnostic yield of TBLC by interdisciplinary diagnosis with a more experienced MDD group, considering the ethical concerns of performing SLB and TBLC simultaneously. Third, all procedures were performed at the lower lobe and same lobe with a relatively small number of specimens. However, the recommended minimum number of biopsy is two, and all biopsies were conducted at a different site even in the same lobe. If the safety of the procedure is secured, more numbers of biopsies might be useful to improve the diagnostic yield. Fourth, all the procedures were performed with relatively smaller size of cryoprobe. However, the diameter of TBLC specimens in this study was not small, and in previous study to compare the diagnostic yield according to cryoprobe size between 1.9 mm and 2.4 mm, no significant differences were observed with respect to the diagnostic yield and safety profile.

In conclusion, our study indicates that the TBLC method under general anesthesia with flexible bronchoscopy and endobronchial balloon blocker with the guidance of fluoroscopy might be safe and adequate for patients with ILDs in Korea. The diagnostic yield of MDD based on histopathologic diagnosis by TBLC was 85.2%.

Authors’ Contributions

Conceptualization: Park JH, Jang HJ, Lee JH. Methodology: Park JH, Kim HK, Jang HJ. Formal analysis: Park JH, Choi HE, Kim IH. Data curation: Jang JH, Kim JY, Han JY, Kim DS, Kang E. Validation: Kim HK, Choi HE, Han JY, Kang MK. Investigation: Park JH, Kang MK, Han JY, Kim DS, Lee JH. Writing - original draft preparation: Park JH, Jang HJ. Writing - review and editing: Park JH, Jang JH, Kim HK, Jang HJ, Lee S, Kim SH, Kim JY, Choi HE, Han JY, Kim DS, Kang MK, Kang E, Kim IH, Lee JH. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

The authors would like to thank Da Som Lee and Eun Gyeong Tak (clinical nurse specialists in the Department of Critical Care and Pulmonology in Haeundae Paik Hospital) and Young Ju Heo (Coordinator of the Haeundae Paik Hospital Interstitial Lung Disease Center) for their contributions and efforts.

Funding

No funding to declare.

References

1. American Thoracic Society; European Respiratory Soci-
1. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002;165:277-304.

2. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733-48.

3. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824.

4. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2010;370:2083-92.

5. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. Am J Respir Crit Care Med 2016;193:1161-7.

6. Lee YC, Wu CT, Hsu HH, Huang PM, Chang YL. Surgical lung biopsy for diffuse pulmonary disease: experience of 196 patients. J Thorac Cardiovasc Surg 2005;129:984-90.

7. Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, et al. Transbronchial cryobiopsy: a new tool for lung biopsies. Respiration 2009;78:203-8.

8. Raparia K, Aisner DL, Allen TC, Beasley MB, Borczuk A, Cagle PT, et al. Transbronchial lung cryobiopsy for interstitial lung disease diagnosis: a perspective from members of the Pulmonary Pathology Society. Arch Pathol Lab Med 2016;140:1281-4.

9. Hernandez-Gonzalez F, Lucena CM, Ramirez J, Sanchez M, Jimenez MJ, Xaubet A, et al. Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost-effectiveness analysis. Arch Bronconeumol 2015;51:261-7.

10. Ravaglia C, Wells AU, Tommasetti S, Gurioli C, Gurioli C, Dubini A, et al. Diagnostic yield and risk/benefit analysis of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients. BMC Pulm Med 2019;19:16.

11. Troy LK, Grainge C, Corte TJ, Williamson JP, Valley MP, Cooper WA, et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir Med 2020;8:171-81.

12. Cho R, Zamora F, Gibson H, Dincer HE. Transbronchial lung cryobiopsy in the diagnosis of interstitial lung disease: a retrospective single-center experience. J Bronchology Interp Pulmonol 2019;26:15-21.

13. Cooley J, Balsestra R, Aragaki-Nakahodo AA, Caudell Stamper DN, Sriprasad T, Swank Z, et al. Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. Respir Med 2018;140:71-6.

14. Guenther A, Krauss E, Tello S, Wagner J, Paul B, Kuhn S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respir Res 2018;19:141.

15. Maldonado F, Danoff SK, Wells AU, Colby TV, Ryu JH, Liberman M, et al. Transbronchial cryobiopsy for the diagnosis of interstitial lung diseases: CHEST guideline and expert panel report. Chest 2020;157:1030-42.

16. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198:e44-68.

17. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511-22.

18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

19. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720-35.

20. Holland AE, Spruit MA, Troosters T, Puhman MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428-46.

21. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, et al. 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 2012;185:1004-14.

22. 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.

23. Bienias GB, Polisar IA. Anatomy of the bronchial tree: a presentation of an extension of the Jackson-Huber nomenclature of the tracheobronchial tree. AMA Arch Otolaryngol 1958;68:454-9.

24. Reddy TL, Tominaga M, Hansell DM, von der Thensen J, Rasal D, Parfrey H, et al. Pleuroparenchymal fibroelasto-
sis: a spectrum of histopathological and imaging phenotypes. Eur Respir J 2012;40:377-85.
25. Hyldgaard C, Bendstrup E, Wells AU, Hilberg O. Unclassifiable interstitial lung diseases: clinical characteristics and survival. Respirology 2017;22:494-500.
26. Ryerson CJ, Urbania TH, Richeldi L, Mooney JJ, Lee JS, Jones KD, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. Eur Respir J 2013;42:750-7.
27. Kumar A, Cherian SV, Vassallo R, Yi ES, Ryu JH. Current concepts in pathogenesis, diagnosis, and management of smoking-related interstitial lung diseases. Chest 2018;154:394-408.
28. Kronborg-White S, Sritharan SS, Madsen LB, Folkersen B, Voldby N, Poletti V, et al. Integration of cryobiopsies for interstitial lung disease diagnosis is a valid and safe diagnostic strategy-experiences based on 250 biopsy procedures. J Thorac Dis 2021;13:1455-65.
29. Walscher 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;97:348-54.
30. Sethi J, Ali MS, Mohananey D, Nanchal R, Maldonado F, Musani A. Are transbronchial cryobiopsies ready for prime time?: a systematic review and meta-analysis. J Bronchology Interv Pulmonol 2019;26:22-32.
31. 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;12:1711-20.
32. Almeida LM, Lima B, Mota PC, Melo N, Magalhaes A, Pereira JM, et al. Learning curve for transbronchial lung cryobiopsy in diffuse lung disease. Pumonology 2018;24:23-31.
33. Niwa T, Baba T, Murotani K, Tabata E, Shintani R, Ikeda S, et al. Safety and learning curve for transbronchial lung cryobiopsy. Eur Respir J 2019;54:PA1323.
34. Seashore J, Nishi SP. Ice capades: skating around current practice of cryobiopsy for ILD. J Bronchology Interv Pulmonol 2021;28:53-9.
35. Davidsen JR, Skov IR, Louw IG, Laursen CB. Implementation of transbronchial lung cryobiopsy in a tertiary referral center for interstitial lung diseases: a cohort study on diagnostic yield, complications, and learning curves. BMC Pulm Med 2021;21:67.
36. Wang W, Xu J, Liu C, Feng R, Zhao J, Gao N, et al. The significance of multidisciplinary classifications based on transbronchial pathology in possible idiopathic interstitial pneumonias. Medicine (Baltimore) 2020;99:e20930.
37. Hagmeyer L, Matthes S, Frank K, Randerath W. Diagnosis in interstitial lung disease: highly confident histopathological results from transbronchial cryobiopsy are reliable. Ann Transl Med 2020;8:1328.
38. Zhou G, Ren Y, Li J, Yang T, Su N, Zhao L, et al. The effect of 1.9-mm versus 2.4-mm probes in transbronchial cryobiopsies for interstitial lung diseases: a prospective analysis. Ann Transl Med 2021;9:20.