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Transbronchial lung cryobiopsy for diagnosing interstitial lung disease: a cross-sectional, comparative study

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Abstract

Objectives Transbronchial lung cryobiopsy (TBLC) has been identified to be a new technique to diagnosis interstitial lung disease (ILD). The study was conducted to investigate the safety and the diagnostic accuracy of TBLC contrast with transbronchial lung biosy (TBLB) in patients with ILD.

Methods In a cross-sectional and comparative study, patients with suspected ILD who underwent TBLC or TBLB were evaluated from June 2018 to September 2022 in Nanjing drum tower hospital. TBLC and TBLB procedure details and clinical multidisciplinary discussion (MDD) diagnosis based on clinical, radiological, and histopathological information were retrospectively analyzed. Diagnostic yield and complications of TBLC and TBLB were evaluated.

Results 187 patients who underwent TBLC and 176 patients who underwent TBLB following a standardized protocol were enrolled. The diagnostic yield of TBLC and TBLB in patients with ILD were 85.0% and 63.1%, respectively. In TBLC, 162 patients (86.6%) had no or mild bleeding and 25 patients (13.4%) had moderate bleeding. None of the patients had severe bleeding and the rate of pneumothorax was 14.4%. Comparatively, pooled incidences of complications were 91.5% for no or mild bleeding, 8.5% for moderate bleeding and 5.1% for pneumothorax after TBLB. There was no difference in the occurrence of bleeding among TBLC group and TBLB group.

Conclusions This study indicated that the clinical applicability of TBLC in ILD diagnostic algorithms, with a diagnostic yield of 85.0% and an acceptable safety profile.

Keywords Interstitial lung disease, Diagnostic accuracy, Transbronchial lung cryobiopsy, Transbronchial lung biosy, Complication

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Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases that cause inflammation and scarring in the lung parenchyma [1]. These distinct histopathologic patterns are associated with different prognostic and therapeutic implications [2]. In patients with suspected ILD, a multidisciplinary discussion (MDD) which contains pulmonologist, pathologists, and radiologists is essential to identify an underlying interstitial lung disease subtype [3]. However, histopathological evaluation that helps figure out the specific cause of the disease is demanding to diagnosis ILD in up to 30% of cases [4]. Techniques available for lung tissue samples include transbronchial lung biosy (TBLB), transbronchial lung cryobiopsy (TBLC), and surgical lung biopsy (SLB). Surgical lung biopsy has been considered the gold standard for obtaining lung tissues to identify histopathologic pattern of a definitive type of ILD. However, SLB is invasive and has the possibility of severe procedure-associated complications and fatality. A retrospective study reported an inpatient mortality rate after SLB for ILD of 1.7% for elective procedures [5]. TBLB is very useful in some situations including granulomatous diseases and cryptogenic organizing pneumonia; however, it has not been considered sufficient to allow for confident histopathological diagnosis.

In recent years, TBLC is increasingly recognized to obtain specimens (as biopsies are larger than TBLB and without crush artifact which often hinders pattern recognition) and has been explored as an alternative to SLB for ILD diagnosis [6]. A cryoprobe is entered into the bronchus, then it is freezing at − 79 °C that working with carbon dioxide or − 89 °C that working with nitrous oxide within seconds, and finally pulled back with the frozen biopsy specimen [7]. A recent meta-analysis reported a diagnostic yield for an identifiable histopathological pattern in 83.7% of TBLC specimens, compared with around 92.7% for SLB specimens in the assessment of diffuse parenchymal lung disease [8]. Although it is obvious that the diagnostic accuracy of TBLC is lower than SLB, TBLC would be novel due to the lower rate of operation-associated complications and fatality [9].

Therefore, in the present article, we retrospectively investigated the accuracy and safety of TBLC vs. TBLB for patients with suspected ILD in our clinical practice.

Materials and methods

Study population

In a retrospective, single-center study, patients with suspected ILD who underwent TBLC or TBLB were enrolled from June 2018 to September 2022 at the Affiliated Drum Tower Hospital of Nanjing University Medical School in China. All subjects were evaluated and diagnosed by the guidelines published by the official American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS) and the Latin American Thoracic Society(LAT) in 2018 [10]. Patients with suspected ILD who underwent TBLC or TBLB should meet the inclusion criteria: (1) age between 18 and 80 years; (2) arterial oxygen partial pressure(PaO2) over 60 mmHg when breathing room air; (3) percent predicted forced vital capacity (FVC) over 40%; and (4) percent predicted diffusion capacity for carbon monoxide (DLCO) over 30%. Patients were ineligible if they met the following exclusion criteria: (1) excessive or uncorrectable bleeding risk; (2) severe cardiopulmonary insufficiency; and (3) pulmonary hypertension (right ventricular systolic pressure (RVSP) over 40 mmHg).

The study protocol was approved by Ethics Committee of Nanjing Drum Tower Hospital. The requirement for written informed consent was waived because of the retrospective nature of the study.

TBLC procedure

The procedure which needed regular ventilation through an endotracheal tube was performed under general anesthesia. A flexible bronchoscope (BF-1T260, Olympus, Tokyo, Japan) and a 1.9 mm cryoprobe (ERBE, Germany) were used. Under the bronchoscopy working channel, cryoprobe was inserted into the target bronchial segment which was determined by the interventional pulmonologist in view of high-resolution computed tomography (HRCT) scanning. The cryoprobe was inserted with 2 cm away from the pleura, then cooled the cryoprobe for 3–6 s and eventually pulled back with the attached frozen biopsy specimen followed by immediately placement of endobronchial balloon for hemostasis. The frozen lung tissue was defrosted in saline at room temperature and then moved to formalin for tissue fixation. The bronchoscope was re-inserted the airway to check that there was no active bleeding, and then the endotracheal tube was pulled back. Cold saline solution, adrenaline or thrombin can be used when there was any active bleeding.

TBLB procedure

Under general anesthesia, a flexible bronchoscopy (BF-260 or BF-1T260, Olympus, Tokyo, Japan) was inserted into the target bronchus. Once the location was determined, a biopsy forceps was used. The biopsy forceps should be retrieved by 1–2 cm, when it met resistance. The biopsy forceps was opened and pushed forward 1–2 cm, and then closed and slowly pulled back at the end of the breath.

Definition of complications

The bleeding severity scores were defined by Hetzel et al. as follows [11]: grade 0, no bleeding between the procedure; grade 1, mild bleeding which could stop bleeding without other interventions or workable just with suction; grade 2, moderate bleeding which may need additional practices including instillation of cold physiological saline or an endobronchial balloon to control bleeding; and grade 3, severe bleeding which may require other aggressive methods to manage the patient, including blood transfusion, intubation and spontaneous ventilation, parenteral tranexamic acid and so on. Detection of pneumothorax was investigated by chest X-ray after TBLC or TBLB.

Clinical information

Clinical data including gender, age, smoking history, body–mass index, comorbid conditions, pulmonary function testing results and PaO2 at admission for all patients were retrospectively gathered from electronic medical record database of affiliated hospital of medical school, Nanjing University. Procedural details were extracted for analysis, such as the practice of general anesthesia, number of biopsy lobes, and biopsy lung segments. The eventual diagnostic results of MDD referred to clinical, radiological, and histopathological information. A MDD team was comprised of expert pulmonologists, pathologists, radiologists and immunologists.

Statistical analysis

Numeric results were expressed as either mean ± standard deviation (SD), or the median and inter-quartile range. The *t* test and Mann–Whitney *U* test were used to evaluate the differences in distributed variables. Categorical results were given as percentages and X^2 test was applied to analyze proportions of variables. Statistical analyses were performed using SPSS 26.0 statistical software. All *P* values reported were two-sided.

Results

Baseline clinical characteristics of study participants

A total of 187 patients who underwent TBLC and 176 patients who underwent TBLB for the evaluation of interstitial lung diseases at the Nanjing drum tower hospital, from June 2018 to September 2022 were included in this study. The patient characteristics of the TBLC group were compared with TBLB group, as presented in Table 1. Male gender, smoking history and younger age were more familiar in the TBLC group (all $P<0.001$). Compared to the TBLB group, patients who underwent TBLC had higher level of FVC%pred (82.15 ± 19.27 vs. 75.81 ± 19.55, $P=0.043$). However, there were no differences of body–mass index, PaO2 and DLCO%pred between the two groups.

Table 1 Demographic and clinical characteristics of the patients undergoing TBLC or TBLB for the diagnosis of suspected ILD

Variables	TBLB (*n* = 176)	TBLC (*n* = 187)	*P* value
Age (years)	57.02 ± 10.90	48.41 ± 11.10	< 0.001
Sex (female), *n* (%)	89(50.6)	59(31.6)	< 0.001
Smoking history (yes), *n* (%)	43 (24.4)	83 (44.4)	< 0.001
Body-mass index, kg/m2	23.63 ± 3.31	23.22 ± 3.09	0.221
Comorbid conditions			
Gastro-oesophageal reflux disease, *n* (%)	2 (1.1)	4 (2.1)	0.736
Hypertension, *n* (%)	49 (27.8)	27 (14.4)	0.002
Cardiac disease, *n* (%)	8 (4.5)	2 (1.1)	0.089
Airways disease, *n* (%)	10 (5.7)	4 (2.1)	0.103
PaO2 (mmHg)	78.00 ± 16.52	80.17 ± 17.97	0.414
Lung function measurements			
FVC%pred	75.81 ± 19.55	82.15 ± 19.27	0.043
DLCO%pred	65.45 ± 20.54	72.72 ± 24.76	0.054

FVC forced vital capacity, *DLCO* carbon monoxide diffusion capacity

Table 2 Details of TBLC and TBLB procedures

Procedure characteristics	TBLB (*n* = 176)	TBLC (*n* = 187)	*P* value
No. biopsies	4.82 ± 1.52	4.54 ± 1.42	0.073
> 1 lobe biopsied, *n* (%)	20 (11.4)	58 (31.0)	< 0.001
> 1 segment biopsied, *n* (%)	22 (12.5)	62 (33.2)	< 0.001

TBLC or TBLB details

During the TBLC procedures, the cryoprobe was inserted with 2 cm away from the pleura. TBLC procedures were performed under general anesthesia using rigid bronchoscopy or endotracheal tube. Further procedural details are shown in Table 2. There was no difference in average specimens obtained from patients among TBLC group and TBLB group.

Procedure-related complications

Regarding complications, TBLC was mostly safe with none or just mild bleeding happening in 162 patients (86.6%). There was no difference of the occurrence of bleeding between TBLC group and TBLB group. In relation to TBLC, the frequency for none or mild bleeding was 86.6%, moderate bleeding 13.4% and severe bleeding 0%. As shown in Table 3, 27(14.4%) patients who underwent TBLC had the incidence of pneumothorax, while pneumothorax occurred in 9(5.1%) patients who

Table 3 Complications of TBLC and TBLB procedures

Adverse events	TBLB ($n=176$)	TBLC ($n=187$)	*P* value
Bleeding			0.179
Grade 0 or grade 1, *n* (%)	161 (91.5)	162 (86.6)	
Grade 2, *n* (%)	15 (8.5)	25 (13.4)	
Grade 3, *n* (%)	0 (0.0)	0 (0.0)	
Pneumothorax, *n* (%)	9 (5.1)	27 (14.4)	0.004
Exacerbation of ILD, *n* (%)	0 (0.0)	1(0.5)	0.331

underwent TBLB ($P=0.004$). In addition, one patient exhibited acute exacerbation of ILD post-transbronchial cryobiopsy was shown in this study. The aggregated frequency of respiratory infections was negligible (0%) in patients undergoing TBLC and TBLB.

Histopathologic assessment and MDD

TBLC yielded a general histologic diagnosis in 159 patients (85.0%). The final clinical diagnoses are presented in Table 4. Of the 187 cases who had undergone TBLC in the present study, the most common histopathologic pattern observed was pulmonary granulomatous diseases (21.4%), followed by occupational and environmental lung diseases (21.4%) and idiopathic interstitial pneumonia (15.0%). Among 40 patients diagnosed with pulmonary granulomatous diseases, the most common diagnose was hypersensitivity pneumonitis (16.6%). As for the occupational and environmental lung diseases patterns, the most common histopathologic pattern observed was welder's pneumoconiosis. Among 28 patients with idiopathic interstitial pneumonia, nonspecific interstitial pneumonia (NSIP) was most common (7.5%), followed by organizing pneumonia (3.2%), respiratory bronchiolitis–ILD or desquamative interstitial pneumonia (2.1%), and idiopathic pulmonary fibrosis/usual interstitial pneumonia (1.6%). Histopathologic findings of two patients who underwent TBLC are shown in Fig. 1. Considering TBLB, 111 patients had definite histopathologic diagnosis, with a pooled diagnostic yield of 63.1%.

Table 4 Final histopathologic diagnoses in patients undergoing TBLC or TBLB for the diagnosis of interstitial lung infiltrates

Histopathological patterns	TBLB ($n=176$)	TBLC ($n=187$)
IPF/UIP	4 (2.3%)	3 (1.6%)
Organizing pneumonia	9 (5.1%)	6 (3.2%)
Non-specific interstitial pneumonia	14 (8.0%)	14 (7.5%)
Respiratory bronchiolitis-ILD or desquamative interstitial pneumonia	0 (0.0%)	4 (2.1%)
Idiopathic airway-centered interstitial fibrosis	0 (0.0%)	1 (0.5%)
CTD-ILD	2 (1.1%)	1 (0.5%)
Hypersensitivity pneumonitis	11 (6.3%)	31 (16.6%)
Sarcoidosis	1 (0.6%)	9 (4.8%)
Pulmonary langerhans cell histiocytosis	2 (1.1%)	3 (1.6%)
Pulmonary alveolar proteinosis	21 (11.9%)	17 (9.1%)
Pulmonary alveolar microlithiasis	0 (0.0%)	2 (1.1%)
Lymphangioleiomyomatosis	1 (0.6%)	0 (0.0%)
Granulomatosis with polyangiitis	1 (0.6%)	0 (0.0%)
IgG4-related lung disease	0 (0.0%)	1 (0.5%)
Diffuse alveolar hemorrhage	0 (0.0%)	1 (0.5%)
Idiopathic pulmonary hemosiderosis	0 (0.0%)	2 (1.1%)
Idiopathic pleuroparenchymal fibroelastosis	0 (0.0%)	1 (0.5%)
Primary lung malignancy	3 (1.7%)	6 (3.2%)
Pulmonary hamartoma	2 (1.1%)	0 (0.0%)
Diffuse panbronchiolitis	1 (0.6%)	1 (0.5%)
Follicular bronchiolitis	0 (0.0%)	1 (0.5%)
Erdheim-Chester disease	0 (0.0%)	1 (0.5%)
Silicosis	0 (0.0%)	1 (0.5%)
Welder's pneumoconiosis	8 (4.5%)	37 (19.8%)
Giant cell interstitial pneumonia	0 (0.0%)	2 (1.1%)
Infection	31 (17.6%)	11 (5.9%)
Eosinophilic pneumonia	0 (0.0%)	1 (0.5%)
Exogenous lipid pneumonia	0 (0.0%)	1 (0.5%)
Emphysema	0 (0.0%)	1 (0.5%)
Undiagnosed	65 (36.9%)	28 (15.0%)
Diagnostic yield	63.1%	85.0%

IPF idiopathic pulmonary fibrosis, *UIP* usual interstitial pneumonia, *ILD* interstitial lung disease, *CTD* connective tissue disease

Discussion

In this study, the final diagnosis was reached in 85.0% of the TBLC and 63.1% of TBLB. Contrast with TBLC, the comparatively small biopsy specimen is the main restriction of TBLB in the histopathologic diagnosis of suspected ILD. According to the published expert statement, TBLC procedure which needed flexible bronchoscopy and an endobronchial balloon was performed under general anesthesia [12]. In the current study, there were no severe procedure-associated complications requiring further aggressive measures, with rates of bleeding (none or mild bleeding 86.6%, moderate bleeding 13.4%, severe bleeding 0%) and pneumothorax (14.4%), which was similar to previous reports [13–15].

Histopathologic specimens were critical in the diagnosis of ILD. Although international guidelines propose that SLB is still the standard method to obtain biopsy tissue if the compounding of the clinical features and HRCT patterns cannot determine a specific diagnosis [10], clinicians still chose the clinical use of TBLC, with the advantages of lower invasiveness than SLB, shorter hospitalisation stay, less mortality, and lower cost. TBLC

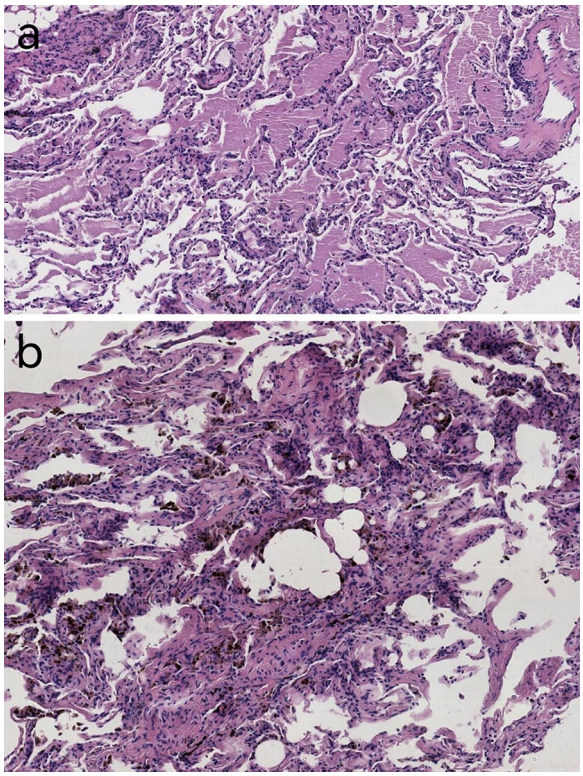

Fig. 1 Histopathologic findings of TBLC specimens. **a** PAP pattern. HE stained tissue demonstrated alveolar filling with eosinophilic material which was positive in periodic acid stain (PAS). (magnification × 100). **b** Welder's pneumoconiosis pattern.HE stained tissue demonstrated hyperplasia of alveolar epithelial cells and welding dust deposition. *TBLC* transbronchial lung cryobiopsy, *PAP* pulmonary alveolar proteinosis, *HE* hematoxylin and eosin (magnification × 100)

is a novel technique which could obtain suitable biopsy specimen for ILD diagnosis [16]. Although pathological diagnostic yield is one measure of biopsy efficacy, more direct measures should be considered when compared between different biopsy techniques, including accessing biopsy specimen adequacy and biopsy specimen with a definite histological pattern. TBLC can obtain biopsy specimens with the size of almost 10–30 mm^2 that is enough large to recognize the pattern of lung lobules [17]. In a study by Ravaglia et al., TBLC has been reported to have a diagnostic yield of 87.8% among 699 patients from a high-volume and experienced center [18]. In this study, a pathological diagnosis was reached in 85.0% consistent with the literature report. Moreover, it is noteworthy that the most common final diagnoses were hypersensitivity pneumonitis (HP) and welder's pneumoconiosis in this study. Previous studies had noted that TBLC provided larger biopsy specimens than TBLB and, therefore, might improve the diagnostic yield of pathological diagnosis of HP [19, 20]. However, the ATS/JRS/ALAT clinical practice guideline for HP suggests that pathology findings should refer to biopsy specimens obtaining from SLB, but do not consider whether this is equally applicable to TBLC [21].

Possible factors for diagnostic yield and complications of TBLC include number of biopsy specimens and biopsy location, probe size, freezing time, guidance of fluoroscopy, approach of anesthesia, and flexible or rigid bronchoscopy. Compared with 1.9 mm size of probe, a larger probe size of 2.4 mm could have greater diagnostic yield but a higher rate of pneumothorax (2.7% vs. 21.2%)[18]. In 2018, an expert statement recommended that a frozen time of 7 s with a 1.9 mm size of probe were suitable when performed the procedure of TBLC [12]. In our cohort, a 1.9 mm size of probe was used with a mean frozen time of 3–6 s, using carbon dioxide as the cryogen. Moreover, the cryoprobe was been inserted to a suitable placement away from the pleura with the guidance of fluoroscopy was considered to be a critical factor which minimized procedure-associated complications including pneumothorax and bleeding. Dhooria et al. reported that the occurrence of pneumothorax was significantly higher in patients who were performed the TBLC procedure without the guidance of fluoroscopy contrast with those with using fluoroscopy (20.9% and 5.9%, $P=0.01$) among 128 ILD patients [22]. In addition, it has been reported the occurrence of moderate to severe bleeding was definitely higher in patients who were preformed TBLC procedure without prophylactic endobronchial balloon placement than those with prophylactic endobronchial balloon placement(35.7% and 1.8%, $P<0.001$) [22]. In the present study, we used fluoroscopy and endobronchial balloon blocker in all patients based on the standardized protocol.

Bleeding and pneumothorax was the most common complication after TBLC. The occurrences of procedure-associated complications including bleeding and pneumothorax were considered acceptable (4.9% and 9.5%, comparatively) [8]. However, the range of substantial bleeding was reported to be wide, with the range of 0.3–26.6% in meta-analyses of TBLC procedures [15, 19]. The difference may be associated with the lack of a prophylactic balloon placement in a number of studies. In the present study, there were none patients who had severe hemorrhage after transbronchial cryobiopsy. We encountered moderate bleeding in 25 patients (13.4%), which required to be immediately treated by endoscopic measures. Pneumothorax was observed in 27 patients (14.4%), consistent with previous reports [23–25].

A previous study indicated that the rate of procedure-associated complications was modest in terms of experienced operators [6]. According to a survey which was investigate the procedure of TBLC, most of TBLC practice training (43%) was completed by self-training, other

TBLC training was completed by fellowship training and practice course [26]. A standard TBLC training course which was performed by an experienced center was considered to be an important role in starting TBLC, with the advantages of convenience and ease of accessibility. With less procedure-associated complications including bleeding and pneumothorax, patients who underwent TBLC had a shorter hospital stay and better cost-effectiveness profile, making TBLC technique growing attractive in clinical procedures.

This study has several limitations. First of all, this is a retrospective and cross-sectional study conducted in a single center with a small study cohort. Second, final diagnoses were not always made within a MDD team. Further studies are needed to prove the diagnostic accuracy of TBLC by definite diagnosis with a more experienced MDD team.

Conclusions

This study demonstrates that TBLC can be identified as an efficient technique to obtain biopsy tissue in a great number of patients with suspected ILD, with less invasion, higher accuracy and lower rates of complications. Therefore, it should be considered as a valid first-line diagnostic technique in patients with suspected ILD.

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Author contributions
MY, X-FX, X-YX, S-YS and X-BF were involved in conception and design. MY, X-FX, X-YX, S-YS and X-BF were involved in analysis and interpretation. MY, S-YS, S-WY and Y-HW were involved in acquisition of data. MY, X-FX, X-YX, S-YS and X-BF were involved in writing and revisions.

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Availability of data and materials
The data are available upon request. No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was consented by Ethics Committee of Nanjing Drum Tower Hospital. The Ethics Committee waived the need for informed consent as the study was retrospective and the data were analyzed anonymously.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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