Original Article

Impact of biopsy number and radiologic pattern on diagnostic yield and complications of transbronchial lung cryobiopsy in interstitial lung diseases: a multi-center retrospective study

Ranxun Chen[1#], Lulu Chen[1#], Hui Ge[2#], Qingqing Xu[1], Qi Zhao[1], Yingwei Zhang[1], Fanqing Meng[3], Hourong Cai[1], Shuhong Guan[4], Chong Li[4], Lingfeng Min[2], Bi Chen[5], Jinghong Dai[1]

[1]Department of Pulmonary and Critical Care Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China; [2]Department of Respiratory and Critical Care Medicine, Northern Jiangsu People's Hospital, Clinical Medical College, Yangzhou University, Yangzhou, China; [3]Department of Pathology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China; [4]Department of Respiratory and Critical Care Medicine, Changzhou First People's Hospital, Changzhou, China; [5]Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China

Contributions: (I) Conception and design: J Dai; (II) Administrative support: C Li, L Min, B Chen, J Dai; (III) Provision of study materials or patients: C Li, L Min, B Chen, J Dai; (IV) Collection and assembly of data: R Chen, L Chen, H Ge, S Guan; (V) Data analysis and interpretation: R Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Lingfeng Min, PhD. Department of Respiratory and Critical Care Medicine, Northern Jiangsu People's Hospital, Clinical Medical College, Yangzhou University, 98 West Nantong Rd, Yangzhou 225001, China. Email: minlingfeng@126.com; Bi Chen, PhD. Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Xuzhou Medical University, 99 West Huaihai Road, Xuzhou 221000, China. Email: chenbi207@126.com; Jinghong Dai, PhD. Department of Pulmonary and Critical Care Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, No. 321 Zhongshan Road, Nanjing 210008, China. Email: daijinghong@nju.edu.cn.

Background: Given that transbronchial lung cryobiopsy (TBLC) is recommended as a surrogate for surgical lung biopsy (SLB) in the diagnosis of interstitial lung disease (ILD), few studies have evaluated the optimal number of biopsy sample or the impact of radiologic pattern on the diagnostic yield and postoperative complications. This study aimed to investigate how biopsy sample number and radiologic patterns affect diagnostic yield and complications.

Methods: We conducted a multi-center retrospective study including 334 consecutive ILD patients who underwent TBLC. The impact of number of biopsy sample and radiologic pattern on diagnosis yields and postoperative complications was assessed. Logistic regression analyses were used to explore the risk factors for complications.

Results: The histopathologic and multidisciplinary discussion (MDD) diagnostic yields were 70.06% (234/334) and 86.23% (288/334). Moderate-severe bleeding and pneumothorax occurred in 39 (11.68%) and 29 (8.68%) cases, respectively. The MDD diagnostic yield was higher in patients with non-fibrotic pattern on high-resolution computed tomography (HRCT) compared to those with a fibrotic pattern (88.11% *vs.* 75.00%, P=0.02). However, the diagnostic yields or postoperative complications were comparable when obtaining three or more than three biopsy samples. Multiple lobe biopsy and number of biopsy samples were associated with bleeding [odds ratio (OR) =3.675, 95% confidence interval (CI): 1.414–9.553, P=0.008; OR =0.649, 95% CI: 0.470–0.895, P=0.009], while a fibrotic pattern increased the risk of pneumothorax (OR =3.479, 95% CI: 1.210–10.005, P=0.02).

Conclusions: This study showed that obtaining three biopsy samples is appropriate to achieve an adequate diagnostic yield, while procedure methods are associated with complications. Further well-designed studies are required to standardize TBLC procedures.

Keywords: Transbronchial lung cryobiopsy (TBLC); interstitial lung disease (ILD); diagnostic yield; complications

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Introduction

The diagnosis of interstitial lung disease (ILD) involves a comprehensive assessment and frequently requires a multidisciplinary discussion (MDD) (1). A multidisciplinary approach combined with clinical-radiologic-histopathological data is now considered the gold standard for the diagnosis of ILD (2). Surgical lung biopsy (SLB) and transbronchial lung biopsy (TBLB) are two established methodologies for procuring lung tissue to establish the histopathological diagnosis of ILD. Though SLB is acknowledged as the standard method for achieving a definitive histopathological diagnosis, its widespread application is constrained by the considerable risk of postoperative complications (3,4). Compared to TBLB, transbronchial lung cryobiopsy (TBLC) represents a novel technique permitting the acquisition of more substantial lung parenchymal biopsy samples (5). Moreover, TBLC has a commendable diagnostic yield, a reasonable safety profile, and a lower mortality rate than SLB, which is considered an alternative to SLB (6,7). The recent guideline suggests conditional recommendation to consider TBLC as an alternative method to SLB for making a histopathological diagnosis in patients with indeterminate ILD in medical centers with experience performing and interpreting TBLC (8).

Studies have explored the diagnostic yield and safety of TBLC for ILD (9-11). However, some key questions remain unanswered. For example, considering the diagnostic yield and safety, what is the appropriate number of biopsy samples to achieve the diagnosis? Few studies have assessed the optimal number of TBLC samples for diagnosing ILD or whether the radiologic patterns affect the diagnostic yield. Therefore, we conducted this multi-center study to investigate the impact of biopsy sample number and radiologic patterns on diagnostic yield and complications. Furthermore, we evaluate risk factors associated with the occurrence of postoperative complications. This manuscript is presented in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-1933/rc).

Highlight box

Key findings

- The diagnostic yields were comparable when obtaining three or more than three biopsy samples in transbronchial lung cryobiopsy (TBLC) for interstitial lung diseases (ILD).
- TBLC had higher diagnostic yields in non-fibrotic radiologic patterns.

What is known and what is new?

- Multiple lobe biopsy and the number of biopsy sample increased the risk of bleeding, and fibrotic pattern was associated with pneumothorax.
- Diagnostic yield was higher in patients with a non-fibrotic pattern on high-resolution computed tomography. No significant differences in diagnostic yield or postoperative complications were observed between obtaining three and more than three biopsy samples.

What is the implication, and what should change now?

- The study highlights the need to standardize TBLC protocols and optimize patient selection. Obtaining three biopsy samples is appropriate to achieve a satisfactory diagnostic yield and cryobiopsy plays a crucial role in the early diagnosis of ILD.

Methods

Study design

This retrospective study included patients with ILD who underwent TBLC from four tertiary hospitals in China between December 1, 2017, and January 1, 2023. Inclusion criteria were patients aged 18 years or above whose diagnosis could not be determined based on clinical, serological, and radiological information. Anticoagulants and antiplatelet agents were discontinued for at least 72 hours before the biopsy procedure. Clinical and biopsy-associated data for each patient were extracted from the electronic medical record. Complications following the procedure and mortality rates at one month and six months post-procedure were recorded. The histopathological analysis of tissue samples was reviewed by two proficient pathologists in ILD. The multidisciplinary diagnosis was achieved by a multidisciplinary team comprising pathologists, radiologists, and clinicians. If the clinical and pathological information is complied with ILD but cannot be classified into a specific type of ILD, it was defined as

"unclassifiable idiopathic interstitial pneumonia (IIP)". Diagnostic yield was defined as the ratio of procedures that resulted in a histopathological or MDD diagnosis to the total number of procedures performed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Nanjing Drum Tower Hospital (No. 2022-067-02, March 28, 2022). Written informed consent was waived because of the retrospective nature of the study.

High-resolution computed tomography (HRCT) pattern

HRCT was performed within one month before the TBLC procedure. A fibrotic pattern was defined according to the ATS/ERS/JRS/ALAT guidelines as usual interstitial pneumonia (UIP) or probable UIP: the presence of honeycombing and/or reticular pattern with or without peripheral traction bronchiectasis (4). Other radiologic findings that did not meet the criteria of UIP or probable UIP including the presence of predominant ground-glass opacity (GGO), profuse micronodules, centrilobular nodules, nodules and consolidation were classified as non-fibrotic pattern. Two radiologists collectively reviewed the HRCT features of each patient.

TBLC procedure

TBLC was performed according to 2018 expert statement from the Cryobiopsy Working Group (12). The TBLC procedure was carried out by experienced clinical pulmonologists. Patients were under general anesthesia, and TBLC was performed using a combination of rigid bronchoscopy (7.5 or 8.5 F; Karl Storz, Tuttlingen, Germany) and flexible bronchoscopy (BF-1T260; Olympus, Japan). A flexible cryoprobe with a diameter of 1.9 mm (ERBE, Germany) was advanced into the representative lesion through the rigid bronchoscopy based on HRCT scans.

Biopsies were performed under fluoroscopic guidance. The cryoprobe was advanced to the target bronchial segment and, the probe was frozen for approximately 3–6 seconds during each procedure. A Fogarty balloon was prophylactically placed in the lobar bronchus near the biopsy segment and routinely inflated after sampling to minimize the consequence of bleeding. Cold physiological saline, hemostatic drugs, or adrenaline may be sprayed through the bronchoscope, if necessary. A chest X-ray was performed to investigate the occurrence of pneumothorax after the procedure.

Complications

The assessment of bleeding and pneumothorax severity was based on previous literature (9,13,14). The severity of bleeding is graded as follows—no bleeding; mild bleeding: characterized by bleeding that did not disrupt the procedural trajectory and solely required continuous suctioning; moderate bleeding: requiring additional bronchoscopic measures beyond routine procedures such as the use of cold saline, epinephrine or thrombin; severe bleeding: the occurrence of hemodynamic or respiratory instability, requiring bronchial artery embolization or surgical intervention, intensive care unit (ICU) admission, or death. The classification of pneumothorax was as follows—no pneumothorax; mild pneumothorax: spontaneous absorption without special treatment; moderate pneumothorax: requiring a needle aspiration or a chest drain insertion; severe pneumothorax: demanding surgical interventions, ICU admission or death.

Statistical analysis

All continuous variables were tested for normality. Data were presented as means and standard deviations (SDs) for normally distributed variables, or as medians and interquartile ranges (IQRs) for non-normally distributed variables. Categorical variables were expressed as frequencies with percentages. The Chi-squared test (or Fisher's exact test when appropriate) was used to compare the differences in diagnostic yield and complications between the number of biopsy sample >3 group and the number of biopsy sample ≤3 group. Logistic regression analyses were used to explore the risk factors for moderate-severe bleeding and moderate-severe pneumothorax. Variables with a P value of less than 0.2 in univariate analysis were included in the multivariate analysis. All data were analyzed using SPSS Software version 26.0 (IBM Corp., New York, NY, USA). A P value of <0.05 was considered statistically significant.

Results

Patient characteristics and complications

The study cohort consisted of 334 patients. Their median age was 51 years (range, 42–58 years), and 212 (63.47%) of them were male. Among these patients, 44 individuals (13.17%) had hypertension, and 11 individuals (3.29%) had diabetes. Eight patients (2.40%) had a history of malignancy. Two subjects had previously used anticoagulants, and eight

Table 1 Demographic and clinical characteristics of subjects

Characteristics	Value (N=334)
Gender	
Male	212 (63.47)
Female	122 (36.53)
Age (years)	51 [42–58]
Smoking history	
Never	204 (61.08)
Current	83 (24.85)
Former	47 (14.07)
Patients with comorbidities	
Hypertension	44 (13.17)
Diabetes	11 (3.29)
Malignancies	8 (2.40)
Anticoagulants	2 (0.60)
Antiplatelet agents	8 (2.40)
BMI (kg/m^2)	23.43±3.11
FVC% pred	83.86±21.98
FEV_1% pred	82.84±21.72
DLCO% pred	71.59±25.83
HRCT pattern	
Fibrotic	48 (14.37)
Non-fibrotic	286 (85.63)
Bleeding	
No or mild	295 (88.32)
Moderate	37 (11.08)
Severe	2 (0.60)
Pneumothorax	
No or mild	305 (91.32)
Moderate	28 (8.38)
Severe	1 (0.30)
Death	
1-month mortality	5 (1.50)
6-month mortality	2 (0.60)

Data are presented as n (%), median [range], or mean ± SD. BMI, body mass index; DLCO, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; SD, standard deviation.

had used antiplatelet agents, all of whom had discontinued for at least 72 hours before TBLC. The mean body mass index (BMI) was 23.43±3.11 kg/m^2. Forty-eight patients showed a fibrotic pattern on HRCT, while 286 presented a non-fibrotic pattern.

Moderate-severe bleeding was identified in 39 cases (11.68%), while moderate-severe pneumothorax occurred in 29 cases (8.68%) of the 334 subjects. Five patients died within one month after undergoing TBLC. Four patients died due to acute exacerbation of ILD, and one patient died from cerebral hemorrhage unrelated to ILD. Additionally, within six months after the procedure, two patients died from acute exacerbation of ILD. The demographic characteristics and complications after the procedure are summarized in *Table 1*.

Procedure details of TBLC

The median number of biopsies performed was 4 (range, 3–5), with a maximum diameter of 3 mm (range, 2–5 mm). The predominant biopsy site was the right upper lobe (33.53%), followed by the right lower lobe (28.44%), right upper and lower lobe (20.96%), left lower lobe (7.78%) and left upper lobe (5.69%). Overall, 253 subjects underwent single lobe biopsy, while 81 subjects underwent multiple lobes biopsy. Biopsy-related information is presented in *Table 2*.

Histopathological diagnosis and multidisciplinary diagnosis

A specific histopathological diagnosis was achieved in 234 out of 334 cases (70.06%), while an MDD diagnosis was achieved in 288 cases (86.23%). The detailed histopathological and MDD diagnosis for all subjects, stratified by fibrotic and non-fibrotic radiologic patterns, are outlined in *Tables 3*,*4*. The histopathological diagnoses included 57 (17.07%) occupational lung disease, 44 (13.17%) hypersensitivity pneumonitis (HP), 24 (7.19%) organizing pneumonia (OP), 21 (6.29%) non-specific interstitial pneumonia (NSIP), 20 (5.99%) pulmonary alveolar proteinosis (PAP), 11 (3.29%) sarcoidosis, 10 (2.99%) malignancy, 10 (2.99%) smoking-related ILD, 10 (2.99%) infection, 5 (1.50%) UIP, 3 (0.90%) aspiration pneumonia, 3 (0.90%) alveolar hemorrhage, 2 (0.60%) pulmonary alveolar microlithiasis (PAM), 2 (0.60%) diffuse pulmonary ossification, and 12 (3.59%) alternative diagnoses. Additionally, 100 (29.94%) patients were diagnosed with unclassifiable IIP. The MDD

Table 2 Procedure details of patients undergoing TBLC

Variables	Value
Biopsy site	
Single lobe	253 (75.75)
Multiple lobes	81 (24.25)
Biopsy location	
Right upper lobe	112 (33.53)
Right lower lobe	95 (28.44)
Right middle lobe	1 (0.30)
Right upper and lower lobe	70 (20.96)
Right middle and lower lobe	1 (0.30)
Right upper lobe, middle and lower lobe	2 (0.60)
Left upper lobe	19 (5.69)
Left lower lobe	26 (7.78)
Left upper and lower lobe	7 (2.10)
Right upper and left upper lobe	1 (0.30)
Number of biopsy samples	4 [3–5]
Number of samples ≤3	85 (25.45)
Number of samples >3	249 (74.55)
Cryobiopsy maximum diameter (mm)	3 [2–5]

Data are presented as n (%) or median [range]. TBLC, transbronchial lung cryobiopsy.

diagnoses included 69 (20.66%) occupational lung disease, 54 (16.17%) HP, 29 (8.68%) connective tissue disease-associated ILD (CTD-ILD), 23 (6.89%) PAP, 20 (5.99%) infection, 15 (4.49%) cryptogenic OP (COP), 13 (3.89%) idiopathic NSIP (iNSIP), 11 (3.29%) sarcoidosis, 10 (2.99%) malignancy, 10 (2.99%) smoking-related ILD, 9 (2.69%) idiopathic pulmonary fibrosis (IPF), 4 (1.20%) idiopathic pulmonary hemosiderosis (IPH), 4 (1.20%) Langerhans cell histiocytosis (LCH), 3 (0.90%) PAM, 2 (0.60%) diffuse pulmonary ossification, 12 (3.59%) alternative diagnoses, and 46 (13.77%) patients were diagnosed with unclassifiable IIP.

Association between number of biopsy samples, diagnostic yield, and complications

The number of biopsy samples ranged from 1 to 10, with the respective counts of 3, 21, 61, 94, 82, 49, 14, 7, 1, and 2. Patients were divided into two groups based on the number of biopsy samples: ≤3 group and >3 group. Analysis revealed no significant differences in histopathological diagnostic yields (71.76% *vs.* 69.48%, P=0.69) or MDD diagnostic yields (87.06% *vs.* 86.35%, P=0.87) between the two groups. Additionally, there was no significant difference in the incidence of moderate-severe bleeding (16.47% *vs.* 10.04%, P=0.11) and moderate-severe pneumothorax (9.41% *vs.* 8.43%, P=0.78) between the two groups (*Table 5*). The majority in our study had 3 to 7 biopsy samples. The histopathologic diagnostic yields for 3, 4, 5, 6, and 7 samples were 77.05% (47/61), 71.28% (67/94), 65.85% (54/82), 69.39% (34/49), and 64.29% (9/14), with no significant differences among the groups (P=0.66). The MDD diagnostic yields were 90.16% (55/61), 85.11% (80/94), 87.80% (72/82), 85.71% (42/49), and 92.86% (13/14), also with no significant differences (P=0.85).

In the subgroup analysis, patients were categorized into fibrotic group and non-fibrotic group. The histopathologic diagnostic yields were 62.50% (30/48) for patients with a fibrotic pattern on HRCT and 71.33% (204/286) for those with non-fibrotic pattern, with no significant difference between the two groups (P=0.22). However, the MDD diagnostic yields were significantly higher in patients with non-fibrotic pattern (252/286) compared to those with a fibrotic pattern (36/48) (88.11% *vs.* 75.00%, P=0.02). In both the fibrotic and non-fibrotic subgroups, there remained no significant differences in diagnostic yields or postoperative complications between patients with ≤3 biopsy samples and those with >3 biopsy samples (*Table 5*). We analyzed the risk factors for postoperative bleeding and pneumothorax in 249 patients with pre-procedural lung function (*Table 6*). Multiple lobes biopsy [odds ratio (OR) =3.675, 95% confidence interval (CI): 1.414–9.553, P=0.008] and a lower number of biopsy samples (OR =0.649, 95% CI: 0.470–0.895, P=0.009) were associated with an increased risk of moderate-severe bleeding. The fibrotic pattern on HRCT was an independent risk factor for moderate-severe pneumothorax (OR =3.479, 95% CI: 1.210–10.005, P=0.02).

Discussion

Our multi-center study demonstrated that the histopathological diagnostic yields of TBLC in ILD were 70.06%, and after MDD reaching 86.23%. When stratified by HRCT pattern, patients presenting as non-fibrotic radiologic features had a higher diagnostic yield compared to those as fibrotic radiologic features. There

Table 3 Histopathological diagnosis in patients stratified by radiologic fibrotic and non-fibrotic pattern

Histopathological diagnosis	Overall, n (%)	Fibrotic group, n (%)	Non-fibrotic group, n (%)
UIP	5 (1.50)	5 (10.42)	0
NSIP	21 (6.29)	4 (8.33)	17 (5.94)
Occupational lung disease	57 (17.07)	3 (6.25)	54 (18.88)
HP	44 (13.17)	8 (16.67)	36 (12.59)
OP	24 (7.19)	1 (2.08)	23 (8.04)
PAP	20 (5.99)	0	20 (6.99)
Sarcoidosis	11 (3.29)	1 (2.08)	10 (3.50)
Malignancy	10 (2.99)	1 (2.08)	9 (3.15)
Smoking-related ILD	10 (2.99)	1 (2.08)	9 (3.15)
Infection	10 (2.99)	2 (4.17)	8 (2.80)
Aspiration pneumonia	3 (0.90)	0	3 (1.05)
Alveolar hemorrhage	3 (0.90)	0	3 (1.05)
PAM	2 (0.60)	1 (2.08)	1 (0.35)
Diffuse pulmonary ossification	2 (0.60)	0	2 (0.70)
Alternative diagnosis	12 (3.59)	3 (6.25)	9 (3.15)
Total	234 (70.06)	30 (62.50)	204 (71.33)

HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; PAM, pulmonary alveolar microlithiasis; PAP, pulmonary alveolar proteinosis; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

Table 4 MDD diagnosis in patients stratified by radiologic fibrotic and non-fibrotic pattern

MDD diagnosis	Overall, n (%)	Fibrotic group, n (%)	Non-fibrotic group, n (%)
IPF	9 (2.69)	5 (10.42)	4 (1.40)
iNSIP	13 (3.89)	4 (8.33)	9 (3.15)
Occupational lung disease	69 (20.66)	3 (6.25)	66 (23.08)
HP	54 (16.17)	8 (16.67)	46 (16.08)
CTD-ILD	29 (8.68)	8 (16.67)	21 (7.34)
PAP	23 (6.89)	0	23 (8.04)
Infection	20 (5.99)	0	20 (6.99)
COP	15 (4.49)	1 (2.08)	14 (4.90)
Sarcoidosis	11 (3.29)	0	11 (3.85)
Malignancy	10 (2.99)	1 (2.08)	9 (3.15)
Smoking-related ILD	10 (2.99)	3 (6.25)	7 (2.45)
IPH	4 (1.20)	0	4 (1.40)
PAM	3 (0.90)	1 (2.08)	2 (0.70)
LCH	4 (1.20)	0	4 (1.40)
Diffuse pulmonary ossification	2 (0.60)	0	2 (0.70)
Alternative diagnosis	12 (3.59)	2 (4.17)	10 (3.50)
Total	288 (86.23)	36 (75.00)	252 (88.11)

COP, cryptogenic organizing pneumonia; CTD-ILD, connective tissue disease-associated interstitial lung disease; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; iNSIP, idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; IPH, idiopathic pulmonary hemosiderosis; LCH, Langerhans cell histiocytosis; MDD, multidisciplinary discussion; PAM, pulmonary alveolar microlithiasis; PAP, pulmonary alveolar proteinosis.

Table 5 The relationship between the number of biopsies and postoperative complications and diagnosis

Variables	Overall			Fibrotic group			Non-fibrotic group		
	Number of samples ≤3 (N=85)	Number of samples >3 (N=249)	P value	Number of samples ≤3 (N=17)	Number of samples >3 (N=31)	P value	Number of samples ≤3 (N=68)	Number of samples >3 (N=218)	P value
Moderate-severe bleeding	14	25	0.11	3	1	0.12	11	24	0.26
Moderate-severe pneumothorax	8	21	0.78	3	4	0.69	5	17	0.90
Histopathological diagnosis	61	173	0.69	8	21	0.16	52	152	0.28
MDD diagnosis	74	215	0.87	13	23	>0.99	61	192	0.71

MDD, multidisciplinary discussion.

were no significant differences in diagnostic yield or complication rates when obtaining three or more biopsy samples. Research has indicated that both multiple lobes biopsy and the biopsy sample number were associated with postoperative bleeding, while a fibrotic pattern on HRCT was associated with postoperative pneumothorax (12). These findings suggested the importance of radiologic patterns and implementation methods in diagnostic yield and postoperative complications.

TBLC has considerable value in the evaluation of ILD diagnosis. The reported MDD diagnostic yield ranged from 83.5% to 94% (9,13,15-18). In our study, the most common multidisciplinary diagnosis was occupational lung disease, followed by HP, CTD-ILD, PAP, and others. The discrepancy in the patient composition between our center and previous reports (9,10,13,19,20) was due to the selection of patients performed for TBLC. The 2022 guideline emphasized that TBLC may not be appropriate for all patients (8). Further study is still required to formulate the physiological criteria or radiologic features for considering patient's suitability for TBLC or SLB. Our research revealed that compared to having fewer than three biopsy samples, having more than three biopsy samples was not associated with a significantly increased diagnostic yield. Similarly, a systematic review indicated that the number of biopsies did not influence diagnostic yield (21). Another study showed that the diagnostic yield of ILD improves when the second biopsy sample is obtained from two different segments within the same lobe (22). Our study only explores the diagnostic yield of TBLC in ILD patients, without addressing the diagnostic concordance with SLB. Cooper *et al.* found that the diagnostic agreement with SLB was higher when five TBLC samples were obtained compared to four TBLC samples, but the majority of the patients (60%) were IPF patients (23). Interestingly, our study showed that a lower number of biopsy samples were associated with the occurrence of bleeding. Consistently, Zhou *et al.* found that having fewer than three specimens was associated with an increased risk of moderate bleeding, but did not affect the incidence of pneumothorax or diagnostic yields (17). We attributed this result to that, the occurrence of bleeding limited further obtaining biopsy samples. Moreover, the size of our specimens was smaller than that reported in previous studies (13,24), which may be related to the shorter cryobiopsy duration (3–6 seconds) and the use of a 1.9 mm cryoprobe in our study. Taken together, balancing diagnostic yield and safety, obtaining three samples appears to be appropriate for diagnosing ILD. Our results needed further external validation.

Bleeding and pneumothorax are common complications in TBLC. The reported incidences of bleeding and pneumothorax ranging from 3.8% to 28.4%, and 8.2% to 28%, respectively (9-11,13,15,17,24,25). This wide variability is likely due to inconsistent criteria for bleeding and pneumothorax in different study designs (10,17,25). In our study, Fogarty balloons were prophylactically inserted, which might have contributed to the lower incidence of bleeding. A prospective randomized controlled study demonstrated that the pre-placed bronchial balloon can reduce the incidence of moderate bleeding (26). Additionally, the rapid on-site evaluation (ROSE) has the potential to reduce repeat procedures (27). Multiple lobes biopsy was also identified as a risk factor for bleeding, suggesting that it was important to select the most representative lesion in HRCT before the procedure.

Our study showed the fibrotic pattern is an independent risk factor for pneumothorax. This is supported by another study in which among patients undergoing transbronchial biopsy, the proportion of individuals with pulmonary fibrosis was found to be higher in the pneumothorax

Table 6 Univariate and multivariate logistic regression analysis on risk factors for complications

Variables	Univariate regression			Multivariate regression		
	OR	95% CI	P value	OR	95% CI	P value
Moderate-severe bleeding						
Male	0.695	0.321–1.507	0.36			
Age	0.988	0.956–1.021	0.48			
Smoking	0.862	0.391–1.899	0.71			
Anticoagulants	7.737	0.474–126.257	0.15			
Antiplatelet agents	1.083	0.130–9.042	0.94			
BMI	0.985	0.871–1.114	0.81			
FVC% pred	1.000	0.983–1.018	0.96			
FEV_1% pred	0.997	0.979–1.014	0.71			
DLCO% pred	1.011	0.996–1.026	0.16	1.012	0.997–1.028	0.12
Multiple lobes biopsy	1.957	0.873–4.385	0.10	3.675	1.414–9.553	0.008
Number of biopsy samples	0.779	0.590–1.029	0.08	0.649	0.470–0.895	0.009
Number of samples >3	0.745	0.322–1.725	0.49			
Cryobiopsy maximum diameter	0.954	0.796–1.143	0.61			
Fibrotic pattern	0.626	0.180–2.184	0.46			
Moderate-severe pneumothorax						
Male	1.738	0.610–4.952	0.30			
Age	0.996	0.957–1.036	0.84			
Smoking	0.802	0.308–2.086	0.65			
Anticoagulants	10.857	0.661–178.311	0.10			
Antiplatelet agents	<0.001		0.99			
BMI	1.032	0.893–1.193	0.67			
FVC% pred	0.985	0.964–1.006	0.15	1.013	0.962–1.067	0.62
FEV_1% pred	0.983	0.963–1.004	0.12	0.976	0.926–1.028	0.36
DLCO% pred	0.993	0.975–1.011	0.43			
Multiple lobes biopsy	0.754	0.242–2.349	0.63			
Number of biopsy samples	0.968	0.709–1.323	0.84			
Number of samples >3	0.755	0.277–2.059	0.58			
Cryobiopsy maximum diameter	0.986	0.803–1.210	0.89			
Fibrotic pattern	3.714	1.369–10.074	0.01	3.479	1.210–10.005	0.02

BMI, body mass index; CI, confidence interval; DLCO, carbon monoxide diffusing capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; OR, odds ratio.

group compared to the non-pneumothorax group, suggesting a potential link between fibrotic patterns and postoperative pneumothorax (28). The cryoprobe located less than 1 cm from the pleura significantly increase the risk of pneumothorax, while biopsies obtained too proximally from the middle third of the lung increase the risk of severe bleeding (12). Avoiding biopsies in fibrotic areas may reduce the incidence of pneumothorax, and

fluoroscopic guidance to determine the position of the probe ensure the safety.

Interestingly, our study indicates that non-fibrotic radiologic patterns yielded a higher diagnostic rate compared to fibrotic radiologic patterns. TBLC may offer more valuable information in the diagnosis of patients with non-fibrotic patterns. In the 2020 guidelines for HP, for newly identified ILD where the differential diagnosis includes fibrotic HP, TBLC was recommended with very low confidence in estimated effects (29). Of note, in our study, among the patients with an initial histopathological diagnosis of unclassifiable IIP, 54% of patients received a final specific diagnosis after MDD. Following MDD, 29 patients were diagnosed with CTD-ILD, highlighting the critical role of a multidisciplinary team comprising pulmonologists, rheumatologists, radiologists, and pathologists in the diagnosis of ILD. A large retrospective study involving 938 patients compared the diagnoses before and after MDD, a definitive diagnosis was made for 755 (80.5%) patients, and 191(41.9%) patients with pre-MDD diagnoses were revised after MDD (30). In another study, MDD led to 53% of patients changing the diagnosis, with 8% reducing steroid use, 7% starting immunosuppressants, and 18% receiving antifibrotic therapy (31). In our study, after MDD, even 13.77% of patients were still diagnosed with unclassifiable IIP. The diagnosis of ILD requires long-term, dynamic management by a multidisciplinary team and TBLC is a key component of the diagnostic criteria considered during MDD.

The present study reported five deaths at one month and two at six months of follow-up. The causes of death were likely attributed to the acute exacerbation of ILD. Previous studies have indicated that 1-month mortality ranged from 0.37–2.0% (10,13,16,32), and 3-month mortality 0.4–2.5% (9,16,19,24,32). These findings demonstrated that TBLC is a safe biopsy method. TBLC can also be applied to patients with acute respiratory failure to obtain lung pathology (33).

There are some limitations in this study. Firstly, it is a retrospective study, and the possibility of selection bias cannot be excluded. Secondly, the absence of lung function data for some subjects prevented a comprehensive logistic regression analysis of risk factors for complications for the whole cohort. Thirdly, we were unable to obtain data on the number of patients for whom the number of biopsies was reduced due to bleeding, which limits our ability to further assess the relationship between fewer biopsies and a higher risk of bleeding. The exact cryobiopsy duration for each sample was also not available, so we could not evaluate the impact of cryobiopsy duration on the diagnostic yield. Fourthly, we did not routinely perform bronchoalveolar lavage for every patient, which limited the ability to analyze the combined diagnostic value of bronchoalveolar lavage and TBLC in ILDs.

Conclusions

Our study revealed that the utilization of TBLC in ILD to establish a definitive diagnosis offers high diagnostic yield with low incidence of complications. There was no significant increase in the diagnostic yield when comparing biopsy sample numbers more than three to those of three or fewer. The diagnostic yield for non-fibrotic radiographic patterns was significantly higher compared to that of fibrotic patterns. Fibrotic patterns were associated with postoperative pneumothorax, while multiple lobes biopsy and the number of biopsy samples were linked to the risk of bleeding. Further well-designed study is urgently required to standardize the TBLC protocols and patient selections to minimize risk and maximize diagnostic yield.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (No. 2022-067-02, March 28, 2022). Written informed consent was waived because of the retrospective nature of the study.

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